THE EFFECT OF SUBSTITUENTS UPON THE ALKALINE HYDROLYSIS OF ESTERS

A Thesis
presented for the
Ph.D. Degree
in the
Faculty of Science
of the
University of London

by

JAMES JOSEPH GORDON

The Technical College,
CARDIFF.
July, 1938.

STATEMENT

All the experimental work herein described has been carried out by the author in the laboratories of the Cardiff Technical College between September 1936 and the present date.

The work has not been presented, and is not being concurrently presented, in candidature for any other degree.

The substance of the work has been published in a series of papers communicated to the Journal of the Chemical Society, 1937 (pp. 1421 and 1430); a further two papers have also been submitted for publication by the same journal.

J. J. Gordon.

CARDIFF TECHNICAL COLLEGE.

Department of
Chemistry and Industrial Chemistry.

H B Watson
HEAD OF DEPARTMENT.

The author wishes to record his indebtedness to Dr. H. B. Watson for suggesting the study of the hydrolysis of substituted benzoic esters and supervising the experimental work. Thanks are also due to Dr. D. P. Evans for suggesting and directing the further work on the effects of alkyl groups upon reactivity.

The photographic reproduction of the diagrams in this thesis were made by Mr. George Strickson, A.R.P.S., to whom the author expresses his thanks.

Statement of the Proposed Scope and Method of Treatment of the Thesis, approved by the Council for External Students

Special attention will be given to the effect of (a) groups in the *ortho* position, and (b) alkyl groups. It is hoped that the results may throw some further light on the peculiarities of benzene derivatives with *o*-substituents, and results of a rather significant nature have already been obtained. The influence of alkyl groups upon the reactivities of aliphatic and aromatic compounds will also be considered in the light of results relating to the hydrolysis of esters.

ABSTRACT

The velocity coefficient of a reaction in solution may be written $k = PZe^{-E/RT}$, where E is the energy of activation, Z is the collision frequency as calculated for a gaseous system, and P is the proportion of energised collisions which actually leads to the formation of products. The thesis describes a kinetic studyof the alkaline hydrolysis of (a) a series of substituted benzoic esters and (b) a series of aliphatic esters; a similar study of the base-catalysed prototropy of a number of phenyl alkyl ketones had been carried out for purposes of comparison. The results are analysed in accordance with the above equation, and their significance is considered in its relationship to two problems, viz., that of the *ortho* effect and that of the influence of alkyl groups upon reactivity.

Previous workers have shown that the introduction of substituents into the *m*- or *p*-position in the aromatic nucleus influences reaction velocity almost entirely by changing the energy of activation, the variations in the P factor being relatively unimportant. This was shown, for example, in the case of the alkaline hydrolysis of

p-substituted ethyl benzoates (Ingold and Nathan, J.C.S., 1936, 222). In the present work a similar constancy of P has been demonstrated for *m*-substituted benzoic esters. When the substituent is in the *o*-position, however, it reduces the reaction velocity by decreasing P. This is discussed in connection with other data relating to the *ortho* effect, and the conclusion is drawn that the changes in P are due to a "chelation" process.

In the alkaline hydrolysis of normal aliphatic esters from ethyl acetate to ethyl octoate, the changes in velocity are due to variations in the energy of activation, which are in harmony with the known order of inductive effects of alkyl groups. Esters having a branched chain show, in addition, variations in the P factor, while this factor also changes appreciably in passing from the prototropy of acetophenone to that of propiophenone. These changes in P are interpreted in the light of an interaction between β-hydrogen and carbonyl oxygen, already postulated by Evans (J.C.S., 1936, 785) in interpreting his results on the acid-catalysed prototropy of phenyl alkyl ketones. Peculiarities observed by other workers in the effects of alkyl groups upon reaction velocities are considered in the light of the new results.

CONTENTS

SECTION I.

THE USE OF KINETIC MEASUREMENTS IN DETERMINING THE POLAR EFFECTS OF SUBSTITUENTS

The study of chemical kinetics offers one of the most useful and interesting means of determining the mechanisms underlying the interactions of various substances, and as Hinshelwood (Ann.Reports, 1927, 24, 314) writes: "the interpretation in physically intelligible terms of the inner mechanism of chemical reactions" forms the "central problem" of chemical kinetics. The first important studies of Wilhelmy (Pogg.Annalen, 1850, 81, 413, 499) on reaction velocity, and the enunciation of the Law of Mass Action by Guldberg and Waage (Etudes sur les affinités chemiques, Christiania, 1867) were soon followed by Arrhenius' interpretation (Z.Physikal Chem., 1889, 4, 226) of the large temperature coefficients of chemical reactions, and the recognition of the importance of the activated state required for the completion of a chemical change. In spite of the large collection of experimental data on reactions in solution, the paucity of our knowledge regarding the liquid state has made the study of gaseous reactions most useful in elucidating the mechanism of chemical processes. In this field a marked advance was made in 1918 by Lewis (J.C.S., 1918, 113, 471) who extended the Arrhenius conception of reaction velocity in the case of homogeneous bimolecular changes. In more recent years the work of many chemists has made clear the distinction between homogeneous and heterogeneous reactions, whilst Lindemann (Trans. Faraday Soc., 1922, 17, 598), Hinshelwood (Proc. Roy. Soc., 1926, A, 111, 245 et seq.) and others, in their studies of unimolecular processes, have confirmed the utility and truth of the Activation Theory. A clearer picture of the inner mechanism of a chemical change has been made possible by the theories and calculations of Polanyi (Atomic Reactions, London, 1932) and his co-workers, and the Activation Theory is now recognised as completely established.

The simple assumption that in bimolecular changes, reaction occurs at each collision of reactant molecules, does not lead to an explanation of the velocity coefficients of gaseous bimolecular reactions, which are smaller by several powers of ten than the number of collisions as calculated by application of the kinetic theory. This assumption would also lead to similar velocities in all bimolecular processes in the gas phase - a result which is quite contrary to the experimental data, for almost any two different bimolecular reactions, e.g.

$$H_2 + I_2 = 2HI$$

and $$2HI = H_2 + I_2$$

possess very different speeds, whilst in the case of unimolecular changes (which actually proceed with measurable velocity) reaction should occur instantaneously or not at all. Finally, the increase of reaction velocity with rise in temperature is very much larger than the increase in the number of collisions, a fact which points clearly to the necessity for the attainment of an exceptional condition before molecules may react; increase of temperature being strongly conducive to the attainment of this state. Since during chemical change there is always a transfer of energy, it appears that the exceptional state which molecules must reach before reaction can occur is merely one of high energy content.

This was the conclusion of Arrhenius, who showed that the variation with temperature of the velocity coefficients of a number of reactions could be represented by an equation of the form

$$\log k = B - \frac{A}{T}$$

where A and B are constants specific to each reaction and T is the absolute temperature. If the constant A is replaced by the fraction $\frac{E}{R}$ (R being the gas constant), the equation may be written:

$$\log k = B - \frac{E}{RT}$$

or $$\frac{d \log k}{dT} = \frac{E}{RT^2} \quad \ldots\ldots\ldots\ldots \quad (1)$$

Equation (1), when compared with the van't Hoff Isochare expression (which expresses the variation of the equilibrium constant with temperature, and the relationship between the heat of reaction and the equilibrium constant)

$$\frac{d \log_e K}{dT} = \frac{Q}{RT^2}$$

led Arrhenius to suggest the existence of an equilibrium between "normal" and "active" molecules of which only the latter were capable of reacting. This comparison indicates also that if E denotes the energy absorbed in the formation of an active from a normal molecule (i.e. a molecule with energy = $\frac{3}{2}$ RT), then the change in the equilibrium

$$\text{normal molecules} \rightleftharpoons \text{active molecules}$$

is represented by equation (1) in accordance with the principles of thermodynamics. E is termed the "energy of activation" and the "critical increment of energy" and is evaluated experimentally from the plot of log K against the reciprocal of the absolute temperature; this straight line has slope $\frac{E}{R}$. It will be shown (below) that the value of E so obtained is too large by the factor ½RT, but usually this correction is small compared with the actual value of E, e.g. 300 calories in 20,000.

The extension of the Arrhenius concept of activation by Lewis (loc.cit.) marked the next notable step in the problem of reaction kinetics. Lewis calculated the absolute velocities of homogeneous bimolecular reactions in the gas phase by application of the kinetic theory and Arrhenius' hypothesis of activation. Integration of equation (1) gives

$$\log_e k = \frac{-E}{RT} + I \text{ (constant of integration)}$$

which may be written

$$k = Ae^{\frac{-E}{RT}} \quad \ldots\ldots\ldots\ldots\ldots \quad (2)$$

According to the Maxwell-Boltzmann principle, the term $e^{\frac{-E}{RT}}$ in the expression represents the fraction of the total number of molecules (A) which possess energy E in excess of the average energy of all the molecules. If A is assumed to represent the number of collisions per second of the reacting molecules, then k is given by the number of collisions which take place with the energy E. The number of collisions per second for a bimolecular gas reaction is readily calculated by means of the kinetic theory, and thus Lewis obtained the expression

$$k = Ze^{\frac{-E}{RT}} \quad \ldots\ldots\ldots\ldots\ldots \quad (2a)$$

where Z = total number of collisions of the reacting molecules per second. This factor, Z, is readily calculated on the basis of the kinetic theory by the following expressions.

(a) When the reacting species are identical, e.g. in the bimolecular decomposition of hydrogen iodide in the gas phase

$$Z = \sqrt{2}.\pi\sigma^2 cn^2 \quad \cdots\cdots\cdots \quad (3)$$

where σ = the effective molecular diameter,

c = the root mean square velocity,

n = the number of molecules per c.c.

(b) When the reacting species are unlike, e.g. in the bimolecular formation of hydrogen iodide from hydrogen and iodine vapour.

$$Z = n_1 n_2\left(\frac{\sigma1 + \sigma2}{2}\right)^2\left[8\pi RT\left(\frac{1}{M_1} + \frac{1}{M_2}\right)\right]^{\frac{1}{2}} \qquad (4)$$

(compare Moelwyn-Hughes, Kinetics of Reactions in Solution, Oxford, 1933, p.73).

In case (a) the velocity coefficient is given by the equation

$$k = 2\sqrt{2}.\pi\sigma^2 cn^2 e^{-\frac{E}{RT}} \quad \cdots\cdots \quad (5)$$

and from the data recorded by Bodenstein (Z.Physikal Chem., 1899, 29, 295) for the thermal decomposition of hydrogen iodide, Lewis calculated the value of E from the temperature coefficients of k, and then computed the values of the velocity coefficients at various temperatures by substituting in expression (5). The remarkable agreement between the calculated velocities and the experimental values was sufficient to allow Lewis (loc.cit., p.490) to state that "the rate of a bimolecular reaction is identical with the number of collisions which occur per second between active molecules." Further evidence for this view was obtained by employing Bodenstein's results of the rate of union of hydrogen and iodine. From equations (2a) and (4) the velocity coefficient is given by the expression

$$k = \frac{N}{1000}\left(\frac{\sigma_1 + \sigma_2}{2}\right)^2 \left[8\pi RT\left(\frac{1}{M_1} + \frac{1}{M_2}\right)\right]^{\frac{1}{2}} e^{-\frac{E}{RT}} \qquad (6)$$

in which N = Avogadro's number. Lewis again obtained excellent agreement between observed and calculated velocity coefficients. Differentiation of equation (6) leads to the expression

$$\frac{d \log_e k}{dT} = \frac{E + \frac{1}{2}RT}{RT^2}$$

which indicates the necessity for subtracting $\frac{1}{2}RT$ from the Arrhenius value of E in order to obtain the more correct value of the "Critical Increment of Energy." Similar agreement has been observed in several other simple bimolecular gaseous reactions, and in fact the velocity coefficients of the majority of such reactions can be calculated by the equation $k = Z.e^{-\frac{E}{RT}}$ with very close approximation (cf. Hinshelwood, Kinetics of Chemical Change in Gaseous Systems, Oxford, 1933).

In 1922 Lindemann (loc.cit.) extended the theory of activation by collision to unimolecular reactions on the assumption that a time lag occurs between activation and reaction, during which time the energy is communicated to the bond or bonds undergoing breakdown. This view was soon amply confirmed by the study of several gaseous decompositions, e.g. nitrogen pentoxide, acetone and propionic aldehyde, by Hinshelwood and his co-workers (see Kinetics, Chap. V) and Ramsperger (J.A.C.S., 1927, 49, 1495 et seq.). In certain cases, however, there is little doubt that reactions proceed by a chain mechanism (Christiansen and Kramers, Z. Physikal.Chem., 1923, 104, 451), and in recent years several workers have found many examples of such changes (see, e.g. Stavely and Hinshelwood, J.C.S., 1937, 1568).

It is therefore evident that the energy of activation is a factor of fundamental importance in determining the speed of a homogeneous gas reaction, and the striking "parallelism between E and the absolute temperature at which the reaction attains an assigned speed" affords strong additional evidence in favour of this view (Hinshelwood, Kinetics, p.120). For reactions which proceed at measurable rates within temperature ranges suitable for experiment, the value of the energy of activation varies between 15,000 and 60,000 calories. Such an increase in the energy content of a molecule is completely in harmony with the modern views of molecular structure, since the molecule may possess varying amounts of electronic, vibrational, rotational and translational energy, and any one or more of these types of energy may be increased far above the value obtaining in a normal molecule.

The Energy Changes in a Simple Reaction between Two Molecules.

Polanyi (Atomic Reactions, London, 1932, Chap. 1) has described in a simple form the possible energy changes which a molecule undergoes on dissociation.

A polyatomic molecule possesses minimum potential energy when the atoms are at certain "equilibrium" distances apart. Owing to the internal vibrations, the distances sometimes decrease below, and increase beyond, their equilibrium values, and at the same time the potential energy of the system varies. To consider the simplest case, take a diatomic molecule. If, starting from the equilibrium distances apart, the atoms approach each other, they meet an opposing force which increases rapidly and resists compression, causing a rise in the energy of the molecules; on the other hand, if the atoms move away from each other, work is done against the forces of attraction (electrostatic and exchange) and again the energy rises, first rapidly and then more slowly. As the distance apart increases so also the forces of attraction decrease to a limiting value at which dissociation of the molecule occurs. Figure (1) illustrates clearly these variations in energy content of the molecule, o represents the equilibrium state and the height d corresponds to the energy of complete dissociation of the molecule. The breakdown of a chemical link, as visualised above, is termed an "adiabatic" process, because it is assumed that no electronic

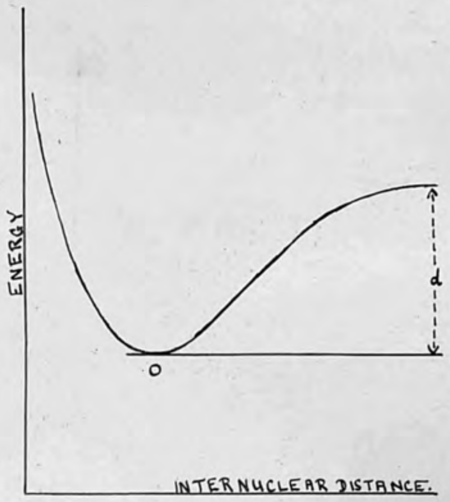


FIG.1.

energy is given to or taken from the system.

Sufficient energy to cause dissociation may in certain cases be communicated to the molecule by the absorption of a light quantum. Thus the dissociation of hydrogen iodide involves the absorption of about 70,000 calories per gram-molecule (see Hinshelwood, op.cit., p.134). The marked contrast between this value and the energy of activation for the thermal decomposition of hydrogen iodide, which is about 44,000 calories, indicates that chemical reactions do not primarily involve the complete dissociation of the molecule, and a different mechanism must be postulated.

Polanyi (J.C.S., 1937, 629) has recently given a very clear picture of the possible mechanism of certain simple reactions. He considers the change

$$2O_3 \rightleftharpoons 3O_2$$

as an illustrative example and represents the two ozone molecules, as in Figure (2a), with a gap between the two molecules. The change $2O_3 \longrightarrow 3O_2$ involves the stretching of two bonds of each ozone molecule to give a "halfway" or transition state (2b) in which the distinction between gap and bond is lost, and then the further lengthening of the "bonds" holding the oxygen atoms to the ozone molecules results in dissociation and formation of three oxygen molecules separated from one another by two gaps (2c). The stretching of the bonds requires an expenditure of work

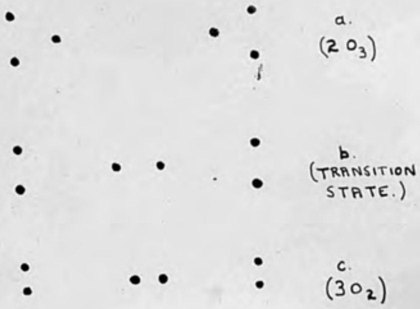


FIG. 2.

(increase in potential energy), and hence in passing from (a) to (b) the potential energy of the whole system increases; the transition state is therefore associated with high energy content and represents the active condition of the Arrhenius concept of activation. Further lengthening (b) to (c) causes a decrease in energy because in this change the system is approaching the state of three stable oxygen molecules (with normal energy). These variations of energy are represented in the graph, Fig.(3) where the potential energy is plotted against a function of the intermolecular distances. The minima at R and P represent the normal (unexcited) states of the reactants ($2O_3$) and products ($3O_2$) respectively, while the maximum at T denotes the energy at the transition state. The height of T above R represents the energy of activation in the "energy barrier" for the reaction $2O_3 \longrightarrow 3O_2$.

Eyring and Polanyi (Z.Physikal.Chem., 1931, 12, 279) have given a similar picture of the mechanism of a simple substitution of the type

$$Z + XY \longrightarrow ZX + Y$$

In those cases where it is less easy to visualise the formation of a definite complex, ZXY, as an intermediate, the modern view of the mechanism, first given by London (Z. Electrochem., 1929, 35, 552) is that the approach of Z takes place simultaneously with removal of Y, and along the line of centres represented below.

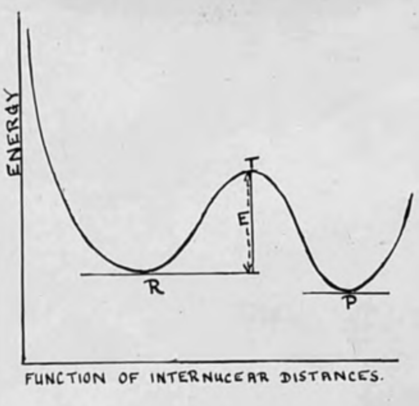
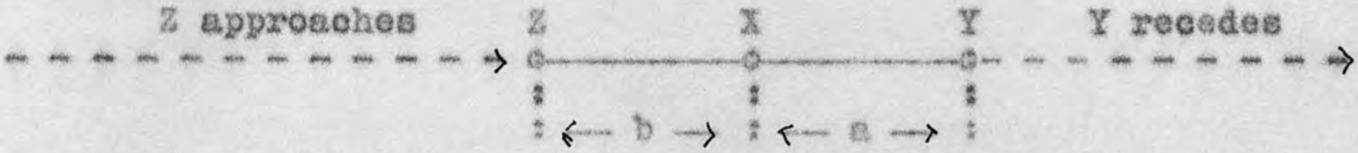


FIG. 3.



By plotting lines of equal energy for different values of internuclear distances ZX and XY, Eyring obtained a contour diagram of the type shown in Fig.(4).

The dotted lines are energy contours, the heights of which increase in three directions from the minima at, R and P and rise to an energy pass at T. When Z is at infinite distance from XY the internuclear distance, XY, is normal and equal to a and the energy of the system is at a minimum. As Z approaches the distance XY increases and the energy of the system rises up the valley RT to the pass at T, where the system is in the transition state. Here the relations of Z and Y to X are identical, and the transition complex can either return along the path TR, when Z will recede and Y will return to its original state, or Y may recede further away from X, when the energy of the system will descend the valley TP, and Z will approach to the equilibrium distance from X in the compound ZX, as represented by the distance b. Here the energy of the system (products) lies at a minimum in the bottom of the valley at P. The height of the pass at T above that minimum at R represents the energy of activation for the reaction. These two illustrations give a simple and very helpful picture of the inner mechanism underlying chemical reactions, more especially those which proceed

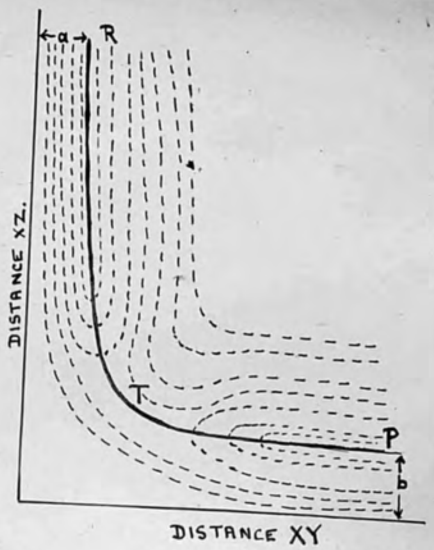


FIG. 4.

according to the simple equation, $k = Ze^{-\frac{E}{RT}}$.

Reactions in Solution.

The application of the Arrhenius concept of activation has proved of remarkable utility in elucidating the nature of reaction mechanisms in the gaseous phase, but owing to our lack of knowledge regarding the conditions obtaining in the liquid state, such simple application in this field is hardly to be expected. It is indeed surprising that any similarity is found between reactions in the gaseous and liquid phases. Whereas in the former the reacting molecules are usually the only types of matter concerned, in solution several factors may work together to make the progress of the reaction more complicated. It is well known from the experiments of Menschutkin (Z.Physikal.Chem., 1890, 6, 41) that the solvent has a very marked influence upon the velocity of a reaction (for example, the rate of interaction of ethyl iodide and trimethylamine is almost a thousand times as fast in benzyl alcohol as in hexane) and no satisfactory explanation of this solvent effect has yet been put forward. We are also at a loss regarding the applicability of the kinetic theory for calculating the number of collisions between molecules in solution, whilst further difficulties may arise owing to energy transfers between solute and solvent, polar effects of the solvent and solvation phenomena, in addition to other causes.

It has been the custom in recent years, however, to make a comparison of the reaction velocities in solution with either those of the same reaction in the gas phase or with those calculated on the basis of the equation

$$k = Ze^{-\frac{E}{RT}}$$

In the case of unimolecular reactions, several examples are known which take place with equal velocity in the gaseous and liquid phases. The unimolecular decomposition of nitrogen pentoxide in chloroform, carbon tetrachloride, nitromethane and certain other solvents proceeds with the same speed as in the gaseous phase, but in nitric acid or propylene dichloride the energy of activation is increased, causing a marked reduction in velocity (Lueck, J.A.C.S., 1922, 44, 757; Eyring and Daniels, ibid, 1930, 52, 1473). The change of d-pinene to dipentene also proceeds at about the same rate in solution, in the liquid and in the gaseous state (Smith, J.A.C.S., 1927, 49, 43), whilst the rate of racemisation of 2:2'-diamino-6:6'-dimethyldiphenyl is the same in the gas state as in solution in diphenyl ether (Kistiakowsky and Smith, J.A.C.S., 1936, 58, 1042; cf. Ann. Reports, 1936, 33, 94).

It has been pointed out by Hinshelwood (Kinetics of Chemical Change in Gaseous Systems, Oxford, 1933, p.233) that for unimolecular reactions the results imply that "large solvent influence is exceptional." It may be possible, however, that if a wider range of solvents were employed we might obtain further divergences from the "normal" behaviour. One instance has been quoted and another is indicated by the results of Moelwyn-Hughes and Hinshelwood (Proc.Roy.Soc., 1931, A, 131, 186) who showed that the decomposition of trinitrobenzoic acid takes place at very different rates in water, acetophenone, toluene and anisole.

A similar state of affairs is also found in the case of bimolecular reactions. Moelwyn-Hughes (loc.cit.) has made a comprehensive survey of the literature, describing 181 bimolecular reactions in solution, and finds that more than 40% of these proceed with almost normal velocity, i.e. the velocity calculated on the assumption that Z in the expression, $k = Ze^{-\frac{E}{RT}}$, is given by equations (3) or (4) page 6. Of the remainder, some have velocities higher and others lower than normal, but on the whole the greatest probability is for Z to be about 2.8×10^{11}, the value approximately required for normal velocity. The decomposition of chlorine monoxide (Eyring and Daniels, loc.cit., Smith, ibid, 1927, 49, 43; Moelwyn-Hughes and Hinshelwood, loc.cit., p.177) has the same rate and energy of activation in the gas phase as in certain solvents, whilst the bimolecular addition of acraldehyde to cyclopentadiene (diene synthesis) studied recently by Wassermann (J.C.S., 1936, 1028) also proceeds with almost the same rate and activation energy in the gas phase as in solution. Of these two reactions the former is important since it has "normal" velocity, and hence suggests that the collision frequency in solution is the same as in the gaseous state, whilst the latter is a "slow" reaction, having a speed about 10^6 times slower than normal. Hinshelwood and Winkler (J.C.S., 1936, 371), in a statistical survey of the data, summarised the position obtaining for bimolecular reactions in solution and showed that the value of the velocity coefficient can vary in different reactions between the limits $Ze^{-\frac{E}{RT}}$ and $10^{-8}Ze^{-\frac{E}{RT}}$. It is now generally accepted that the collision frequencies between solvent molecules in dilute solution are approximately equal to those in the gas phase at the same concentration (cf. Bowen, Ann.Reports, 1934, <u>31</u>, 51), and it is therefore convenient to express the velocity coefficient of a reaction in solution by the equation

$$k = PZe^{-\frac{E}{RT}}$$

in which Z is the collision number and P is a factor independent of temperature which may have any value between the limits ~~between~~ unity and 10^{-8}. The factor P is a measure of the probability that collisions with energy E shall result in reaction, and hence is often termed the "probability factor." The nature of this factor will now be considered.

In most organic bimolecular reactions in solution, variation of the substituents in the reacting molecules causes marked changes in the velocity coefficients (cf. Ann.Reports, 1933, 30, 42). Since the term Z varies very little from one similarly constituted compound to another it was not unreasonable to expect that these changes in k might be due to alteration in either E or P or in both. Actually in the few accurate studies of reactions of similarly constituted compounds the surprising fact has emerged that <u>in the main</u> the variation in velocity in passing from member to member of a series is due to the change in E, whilst the P factor remains almost constant. Thus Bradfield and B. Jones (J.C.S., 1928, 1106, 3073; 1931, 2903), Bradfield, W. O. Jones and Spencer (ibid, 1931, 2907) and Bradfield (Chem. & Ind., 1932, 51, 254) showed that the chlorination of phenolic ethers, p - ROC_6H_4X and  where R = alkyl and X = Cl, Br, COOH or NO_2, the P factor remains almost constant throughout the series and the changes in k are almost wholly accounted for by changes in E. Later, Williams and Hinshelwood (J.C.S., 1934, 1079) demonstrated that a similar constancy of P obtained in the reaction between *m*- or *p*-substituted anilines and benzoyl chlorides in benzene solution. These results were significant in view of the fact that the value of the P term was so small (about 10^{-7}). Again, the studies of Ingold and Nathan (J.C.S., 1936, 222) on the alkaline hydrolysis of p-substituted ethyl benzoates showed clearly that the probability factor was remarkably constant for this series, although the velocity coefficients of the slowest and fastest reactions are in the ratio 1:5000.

The variations in velocity in the above series of reactions, which are due almost entirely to the changes in the activation energy, arise from the polar effects of the substituents, the benzene nucleus acting as a ready means of transmitting the electronic displacements set up by the groups in the _m_- or _p_-positions in the ring. It is noteworthy that in each of the examples cited, the "induced polar effects of the substituents may be assumed to be isolated from local disturbances" (cf. Ingold and Nathan, loc.cit.) and as a result any "steric" influences are avoided. If, on the other hand, the substituent groups are so placed (e.g. in the _ortho_ position in the aromatic ring) that their bulk or steric effects might come into action, we should then not expect to have constancy of P. In certain instances, however, even when the substituent is relatively near the seat of reaction, the changes in k are due mainly to variations in E. Hinshelwood and Legard's study (J.C.S., 1935, 587) of the esterification of six different acids (acetic, benzoic, _o_-nitrobenzoic, diphenylacetic, 2:4:6-trimethylbenzoic and trichloracetic) in four alcohols (methyl, benzyl, isopropyl, _tert_-butyl) and Winkler and Hinshelwood's experiments (ibid, 1935, 1147) on the reaction between alkyl halides and tertiary bases showed that the differences in speed are due mainly to changes in activation energy, but certain variations in k were ascribed to the appreciable change in the probability factor P. In the acid catalysed bromination of m- and p-substituted acetophenones (Evans, Morgan and Watson, ibid, 1935, 1167) small variations in P were observed for different substituents (P changes by a factor, 2), whilst Evans (J.C.S., 1936, 785) has demonstrated that in the acid-catalysed prototropy of phenyl alkyl ketones the P factor rises by a power of ten in passing from acetophenone to propiophenone, and that further substitution in the n-alkyl chain causes a small but regular decrease in P. The results described in the later sections of this thesis also afford examples where the non-exponential factor changes on introducing a substituent near the seat of reaction.

A survey of the results of accurate kinetic investigations therefore leads to the conclusion that when the reacting substances are similarly constituted, compounds, in which the variable group is separated from the point of reaction by a conducting system (e.g. the benzene nucleus), the induced polar effects of the substituent will cause an alteration in the activation energy with little or no alteration in P. However, if the substituent is situated near the seat of reaction, changes in k are caused by variation in both E and P, of which the latter may be considerable. In connection with the former conclusion, it should be pointed out that it may be possible for P to be altered by the polar effect of a group, especially if the reaction takes place in more than one stage, as, for example, the acid-catalysed prototropy of nuclear substituted acetophenones studied by Evans, Morgan and Watson (loc.cit.). The changes in P recorded by these workers are small, but large variations cannot be expected in this reaction.

During the last three years the work of Hinshelwood and his collaborators on the nature of the P factor of the kinetic equation has led to some interesting and illuminating postulates. In conjunction with Winkler (loc.cit.) a number of effects were conceived which might reduce the probability factor below unity, and some which might tend to make P larger. In the reaction

$$A + B \;=\; \text{products},$$

occurring in solution, the P factor of the equation $k = PZe^{-\frac{E}{RT}}$, may be reduced for one or more of the following reasons:-

(a) The molecules may not collide with the correct orientations (reactive centres must come into contact in order to obtain reaction).

(b) The bond to be broken may not be sufficiently weakened (stretched) to allow of rupture after impact.

(c) If there are large substituent atoms or groups of atoms about the seat of reaction in the molecule A, the reactive centre of molecule B may not be able to collide with that of A unless their hindering groups during their oscillations are widely separated.

(d) Even when the molecules A and B have collided and formed the transition complex, the intervention of the solvent molecules may be necessary (e.g. to remove energy from the complex) in order to complete the reaction. In extension of this factor Watson (Modern Theories of Organic Chemistry, Oxford, 1937, p.161; cf. Evans, Morgan and Watson, loc.cit.) has pointed out that in a catlaysed reaction such as esterification or hydrolysis the probability of transformation of the activated complex (formed between A and the catalyst) to products is influenced by the presence or absence of molecule B in suitable orientation.

$$A + \text{catalyst} \rightleftharpoons A.\text{catalyst} \xrightarrow{B} \text{products}$$

On the other hand the unfavourable effect of these factors will be reduced by the operation of some or all of the following:-

(e) Simplicity of the reacting molecules will lead to more collisions with suitable orientation.

(f) Increase in the time during which the molecules A and B are together in the transition complex will favour the transmission of energy to the vulnerable bond. In the extreme case it is possible to have a definite addition complex between the reactants, which later breaks down to the products.

(g) Ionic charges on the reacting molecules tend to increase P; it is an experimental fact, pointed out by Grant and Hinshelwood (J.C.S., 1933, 258) that reactions in solution which involve an ion usually proceed with almost normal velocity (P = unity).

(h) If any specific energy transfers are concerned within the molecules (e.g. $C = O \longrightarrow \overset{+}{C} - \overset{-}{O}$) they will tend to behave as simpler structures.

According to Hinshelwood, these factors are sufficient to account in an empirical manner for the variation of P between unity and 10^{-8} in reactions of the type quoted.

The Effects of Substituents upon Reaction Velocities in Solution.

In considering the influence of various substituents upon the velocity of a given reaction in solution, it is important to determine whether the change in k is caused by variation in E or in P or in both. For simplicity of treatment attention may first be directed to those cases where the factor P is known to remain almost constant throughout a given series, even though the velocity coefficient varies over a considerable range. The three reactions for which this has been shown to be the case have been mentioned previously (page 17). Since P and Z are constant the equation $k = PZe^{-\frac{E}{RT}}$ readily gives the following relationship between log k and E; $\log k = \text{constant} - \frac{E}{2.303\,RT}$. Therefore, on plotting the values of log k for temperature

T against those of E, the points should lie on a straight line of slope −2.303 RT. The figures (5) and (6) below illustrate the extent of agreement obtained in the first two cases cited, and the third example is illustrated in Fig.(7), Section II, p.54. In the graphs the thick line has the slope 2.303 RT and it is seen that in Fig.(5) the points lie approximately on this line, whilst in the other two graphs the linearity is extraordinarily good for the *m*- and *p*-substituents. The order of magnitude of the P factor in each case is as follows: 10^{-5} for the chlorination of phenolic ethers, 10^{-7} for the benzoylation of anilines and 10^{-2} for the alkaline hydrolysis of the *m*- and *p*-substituted benzoic esters. That the polar effect of the substituent as transmitted through the aromatic nucleus from the *m*- and *p*-positions is sufficient to produce the marked changes in activation energy, is clearly shown by the relationships between E and the dipole moments of corresponding substituted benzenes which have recently been recorded (Watson, op.cit., p.169). The equations connecting E and μ have the form

$$E \;=\; E_0 \mp C(\mu - a\mu^2)$$

and it now appears quite likely that, when not affected by local disturbances in space, the change in the energy of activation of a reaction determines the variation in velocity from one member to another of a series of similarly constituted compounds taking part in the same reaction under identical

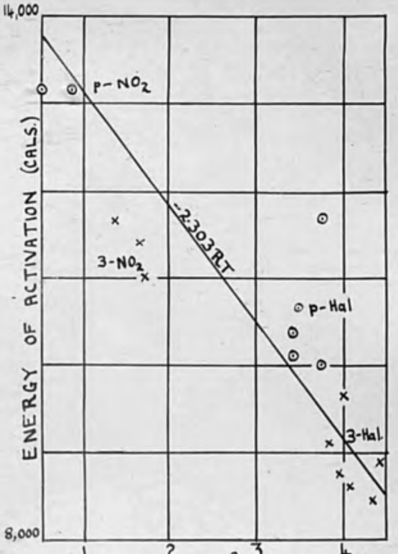


FIG. 5. REACTION I.

CHLORINATION OF PHENOLIC ETHERS.

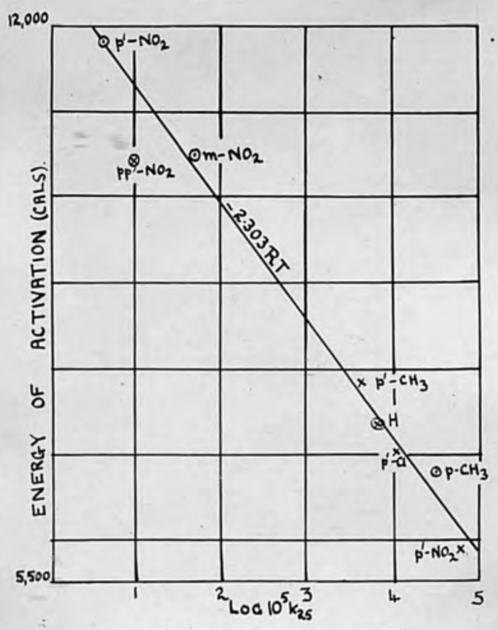


FIG. 6. REACTION II.
BENZOYLATION OF ANILINES.

conditions. The variation in activation-energy is caused by the change in the availability of electrons at the seat of reaction, and as long as this availability is not influenced by steric effects the P factor remains constant throughout the series.

In 1935 Winkler and Hinshelwood (J.C.S., 1935, 1147) showed that in the reaction between alkyl halides and tertiary nitrogen bases in benzene solution there existed certain regularities in the changes in P (between the limits 10^{-6} and 10^{-8}) produced by altering one or other of the reaction species. Thus the P factor was constant for the rates of interaction of NMe_3 with (a) methyl iodide and (b) ethyl iodide, but was much smaller for n-propyl iodide. The reaction between pyridine and methyl, ethyl and isopropyl iodides also possessed the same value of P but that for n-propyl iodide was considerably less. The change in the rate of reaction between pyridine and (a) an alkyl bromide and (b) the corresponding alkyl iodide was also found to be due almost entirely to the variation of P rather than of E. These alterations of the probability factor must have some explanation, and Hinshelwood suggested that the low P factor associated with the n-propyl radicle is probably due to the steric effect of the long chain. It seems quite evident that if regular variations in the P factor are found in a reaction on changing the substituents, then conclusions can safely be drawn regarding the particular effects of these groups.

It has been pointed out by Ingold and Nathan (cf. Hughes, Ingold and Shapiro, J.C.S., 1937, 1277) that, owing to the difficulty of obtaining accurate values of the parameters of the Arrhenius equation, small differences in the values of E and P have little significance. Certain reactions are known where there is appreciable change in both E and P with temperature, e.g. in the dealdolization of diacetone alcohol studied by La Mer and Miller (J.A.C.S., 1935, 57, 2674), whilst in others the small temperature variation of these factors sometimes lies within the limits of experimental error. These latter variations in the values of E and P have not yielded to theoretical interpretation, and it is possible "that large variations may be due to some change in reaction mechanism" (Watson, op.cit., p.166). Ingold and his co-workers have also implied that when, for different members of a series of similarly constituted compounds undergoing the same reaction, the differences in P and E are reasonably large, they are of real value in elucidating the reaction mechanism.

A case where the striking alteration of the factors P and E occurred was observed by Evans (loc.cit.) in the acid-catalysed bromination of phenyl alkyl ketones R.CH_2.CoPh. In passing from acetophenone to propiophenone the energy of activation increased from 20,000 to 22,000 calories and the

P factor increased by a power of 10, whilst further substitution of n-alkyl groups R in the side-chain caused a small but regular decrease in both E and P. The large changes referred to were not capable of interpretation on the basis of the polar effect of the alkyl substituent, and an interaction between the carbonyl oxygen and the β-carbon atom through the medium of a hydrogen bond was postulated (see Section III).

This suggestion gave a ready explanation of the changes in both the energy of activation and the probability factor. The work described in the following sections has thrown further light on this particular problem, and it has become apparent that the hydrogen bond is formed during the approach of the catalyst to the ketone molecule (see Section II), whilst the change $\mathrm{c} \overset{\curvearrowright}{=} \mathrm{o} \longrightarrow \overset{+}{\mathrm{c}} - \overset{-}{\mathrm{o}}$ occurs. This is in harmony with the absence of a hydrogen bond in the phenyl alkyl ketones in the free state.

The influence of the β-methyl or methylene group in the above reaction falls under the type which Ingold terms a "local disturbance" and a similar type of effect was anticipated in reactions involving benzene derivatives containing _ortho_-substituents. Reaction velocity experiments on substances containing a local disturbing group have formed the subject of the author's investigations. The results have been analysed by application of the kinetic equation k =

$PZe^{-\frac{E}{RT}}$, and the variations of P and of E have been capable of interpretation on the basis of the polar effects of substituents and of bond formation between the seat of reaction and a suitably placed substituent.

SECTION II.

THE ALKALINE HYDROLYSIS OF ORTHO-SUBSTITUTED BENZOIC ESTERS

(a) Peculiarities of ortho-Substituted Aromatic Compounds.

During the past sixty or seventy years it has frequently been observed that benzene derivatives having groups in ortho positions with respect to each other showed anomalous behaviour as compared with their isomeric compounds, where the groups occupy meta or para positions. The unusual nature of such compounds is often exhibited by a peculiar lack of reactivity, while many ortho-substituted acids are exceptionally strong and bases exceptionally weak. A number of typical observations relating to ortho and di-ortho-substituted compounds are summarised.below.

(a) As early as 1872 Hofmann found that the addition of methyl iodide to certain dialkylanilines having alkyl groups in both ortho-positions proceeded either extremely slowly or not at all (Ber., 1872, 5, 713, 718; 1875, 8, 61). Later, Fischer and Windaus (Ber., 1900, 33, 345, 1967) observed that of the six xylidenes only the 2:6-compound gave no quaternary salt, and a similar remark applied to the bromotoluidines and bromoxylidenes. An analogous observation, made by Decker (Ber., 1905, 38, 1144) was that of the unreactivity of o- and α-substituted quinolines with alkyl iodides; the second nucleus here behaves as an "ortho-substituent." The alkylation of amines is also retarded by one ortho-substituent (Thomas, J.C.S., 1913, 103, 594).

(b) The formation of oximes and phenylhydrazones by quinones and aromatic ketones is retarded by ortho-substituents (Kehrmann, Ber., 1888, 21, 3315, and later, Hantzsch, ibid, 1890, 23, 2773; V.Meyer, 1895, 28, 3207; 1896, 29, 836, 2564); ortho-substituted phenylhydrazines do not react with benzaldehyde, and benzylidene-anilines are not formed by s-tribromo and s-trinitro-anilines (Hantzsch, loc.cit.).

(c) In 1883 the stability of di-ortho-substituted benzonitriles towards hydrolysing agents was observed by Merz and Weith (Ber., 1883, 16, 2886, 2892) and by Hofmann (ibid, 1884, 17, 1915), and Claus (Annalen, 1891, 265, 378; 266, 225; 1892, 269, 212 et seq.), in a fuller examination of the subject, found that hydrolysis is rendered difficult by an alkyl group, halogen, and nitro group, in o-positions, and still more by two. Similar remarks apply to o-substituted benzamides (Jacobsen, Ber., 1889, 22, 1219; Claus, Annalen, 1891, 265, 364). Moreover, similar retardation of the formation of imino-ethers from ortho-substituted benzonitriles was noted by Pinner (Ber., 1890, 23, 2917); α-naphthonitriles refused to give imino-ethers, while with β-naphtho-nitriles the reaction was normal. A single _o_-substituent inhibits the esterification of benzonitriles by alcohol and hydrochloric acid (Pfeiffer et al., Annalen, 1928, _467_, 158).

The earlier observations were all independent, and the first attempt at a systematic study of the effect of _o_-substituents was due to Victor Meyer, Sudborough and their co-workers, who carried out a series of investigations on the progress of certain typical reactions involving benzene derivatives containing substituents in one or both _ortho_-positions. It was found that di-_ortho_ substituted benzoic acids were not perceptibly esterified when their alcoholic solutions were saturated with hydrogen chloride and allowed to remain at 0° for twelve hours or boiled with 3% hydrochloric acid for three hours. Under these conditions the groups CH_3, OH, F, Cl, Br, I and NO_2 all prevented the formation of ester. If hydrogen chloride was passed through a boiling alcoholic solution of the acid for several hours, the smaller groups (CH_3, OH, F) permitted the formation of some ester, but the larger groups (NO_2, Cl, Br, I) still inhibited the reaction completely (see Meyer and Sudborough, Ber., 1894, _27_, 510, 1580, 3146; 1895, _28_, 182, 1254, 2773, 3197; 1896, _29_, 830, 1397; van Loon and Meyer, Ber., 1896, _29_, 839).

The unusual stability of the esters of these di-_ortho_-substituted acids towards hydrolysis was also clearly demonstrated, and an examination of the esterification and hydrolysis processes in the case of mono-ortho-substituted acids and esters showed that the presence of one ortho-substituent also retarded the reaction (Goldschmidt, Ber., 1895, 28, 3224; Kellas, Zeit.Phys.Chem., 1897, 24, 221). Kindler (Annalen, 1928, 464, 278) has more recently obtained similar results. In addition, the inactivity of mono and di-ortho-substituted acid chlorides, amides and nitriles under the influence of hydrolysing agents, was dealt with in detail by Meyer, Sudborough, and their collaborators (Ber., 1894, 27, 3153; J.C.S., 1894, 65, 1030; 1895, 67, 587, 601; 1897, 71, 229). The results of all these investigations (see summary by Sudborough and Lloyd, J.C.S., 1899, 75, 580) led to the general conclusion that groups in the ortho-position are capable of exerting a peculiar influence on a compound, in addition to their usual polar effects which operate also from the m- and p-positions.

This conclusion is emphasised by the fact that the dissociation constants of o-substituted benzoic acids are higher than those of corresponding m- and p-acids. This is illustrated by a table of recent and accurate relative values for the dissociation constants of a number of substituted benzoic acids (referred to benzoic acid as unity) given by Dippy and Lewis (J.C.S., 1937, 1427) and reproduced below (10^5K for benzoic acid = 6.27):-

	o	*m*	*p*
CH_3	1.97	.867	.676
OH	15.9	1.26	.440
OCH_3	1.29	1.30	.538
OC_6H_5	4.74	1.79	.478
F	8.63	2.18	1.15
Cl	18.2	2.36	1.68
Br	22.3	2.46	1.71
I	21.9	2.25	—
NO_2	1077	5.19	6.00

The presence of a second *o*-substituent leads to a further increase in the dissociation constant, as in 2:6-dihydroxybenzoic acid ($10^2K = 5.0$, Ostwald, Z.Physikal.Chem., 1889, 3, 249), the 2:6-dinitro-acid ($10^2K = 8.15$, Sirks, Rec.Trav. Chim., 1908, 29, 221), and 3-nitro-*o*-toluic acid ($10^2K = 1.335$, Dippy and Page, J.C.S., 1938, 359). Groups in the *o*-position decrease the strength of anilines; Farmer and Worth (J.C.S., 1904, 85, 1726), for example, find the following values of K_b:-

aniline, 5.3×10^{-10}

p-toluidine	11.3×10^{-10}	*p*-nitro-aniline	1.24×10^{-13}
o-toluidine	$.73 \times 10^{-10}$	*o*-nitro-aniline	5.6×10^{-15}

Groups in the *o*-position also increase the stability of benzaldehyde-cyanohydrins (Lapworth and Manske, J.C.S., 1928, 2533).

There are analogies among aliphatic compounds. Thus, allocinnamic acid (the cis-isomeride) is considerably stronger than ordinary (trans) cinnamic ($10^5K = 13.2$ and 3.65 respectivelyDippy et al., J.C.S., 1937, 1008) and the substituted acrylic acids having the cis-configuration are esterified much more slowly than their trans-isomerides. Again, the order of velocities

$CH_3COOH > CH_2X.COOH > CHX_2.COOH > CX_3.COOH$

holds for the esterification of all series of aliphatic acids, independent of the nature of X (Lloyd and Sudborough, 1899, 75, 467).

(b) The Concept of Steric Hindrance.

The lack of reactivity of many o-substituted compounds was ascribed by Meyer to steric hindrance, arising from the proximity of the groups in the o-position to the reacting group. This view was justified by two main observations:-

(a) The ortho-effect is not observed if the reacting group is separated from the nucleus by at least one carbon atom. Thus, mesitylacetic acid is esterified at the normal speed (Meyer and Sudborough, Ber., 1894, 27, 1580) and the same remark applied to di-ortho-substituted β-phenyl-propionic acids (Meyer, ibid, 1895. 28, 1254). Kindler observed that there is no ortho-effect in the alkaline hydrolysis of o-substituted cinnamic esters (loc.cit.), and the recent dissociation constants obtained for o-substituted phenylacetic, β-phenylpropionic and cinnamic acids by Dippy, Lewis and Page (J.C.S., 1937, 1426; 1938, 357) indicate the absence of any factor which would make the acids abnormally strong.

(b) The ortho-effect appears to depend not upon the chemical nature of the group, but rather upon its size, as measured, according to Meyer, by the sum of the weights of the atoms. Thus, fluorine did not lead to any ortho-effect comparable with those given by the other halogens.

Flürscheim (J.C.S., 1909, 95, 725) showed how the high conductivities of o-substituted acids could be explained on the basis of steric hindrance; according to his view, as expressed in terms of modern views on ionisation, the undissociated acid is in continual contact with water molecules, so that in the equilibrium

$$R.COOH + H_2O \rightleftharpoons R.CO\bar{O} + H_3O^+$$

steric hindrance will exercise a retarding effect on the association of ions, but will not appreciably influence the ionisation.

A phenomenon which has been observed recently by Turner, Mills and Adams, and which is interpreted on the basis of steric hindrance (see Summary by Adams and Yuan, Chem.Reviews, 1933, 12, 261) is the optical activity of o-substituted diphenyls and certain naphthalene and even benzene derivatives (Mills et al., J.C.S., 1928, 1291; 1932, 2209; 1937, 274). The rotation of the nuclei of diphenyl about the bond joining them is restricted by sufficiently large groups in o-positions, and this leads to disymmetry of the molecule and therefore optical activity. The same explanation is accepted for the naphthalene and benzene derivatives studied by Mills.

There is evidence, however, that steric hindrance cannot by itself be responsible for the whole of the observed behaviour of <u>ortho</u>-substituted compounds. In the first place there is no definite relationship between the influence of a group in the <u>o</u>-position and its weight or volume; for example, the nitro group is more effective than bromine or iodine in spite of its smaller weight and volume, and <u>o</u>-hydroxyl increases the strength of benzoic acid far more than <u>o</u>-methoxyl does (10^5K for salicylic acid = 105 and for <u>o</u>-methoxybenzoic acid = 8; Branch and Yabroff, J.Amer. Chem.Soc., 1934, <u>56</u>, 2568). Then, if Flürscheim's postulate is applied to the equilibrium

$$R.NH_2 + H_2O \rightleftharpoons R.NH_3^+ + OH^-$$

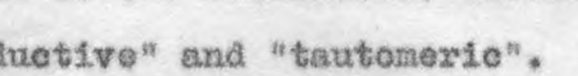
for the ionisation of anilines, it is easily seen that an increase in strength should be the result (since only the reverse change will be influenced unfavourably), whereas actually a marked decrease is observed. It is apparent, therefore, that, although steric hindrance may frequently be an important factor, the problem of the <u>ortho</u>-effect is a complex one, and it cannot be interpreted as a purely geometrical effect. This view was actually put forward by Feilmann and Sudborough (Proc.Chem.Soc., 1897, <u>13</u>, 241) by

Davis (J.C.S., 1900, 77, 33) and later by Kindler (loc.cit.). The nature of another factor which doubtless contributes to the total effect in many cases, and may sometimes be the principal cause of the "ortho-effect", is discussed below.

(c) The Polar Effects of Groups.

It is evident that whatever special factors may intervene when a group is placed ortho to the point of reaction, the polar influences which the group normally exerts when situated in the m- or p-positions will still operate. It has long been recognised that the replacement of hydrogen by another atom or group may have a very marked effect upon the properties and the reactivity of an organic compound. This is shown, for example, by the widely differing strengths of substituted acetic acids (10^5K for acetic acid is 1.82, for monochloracetic acid is 155, and for trichloracetic acid 121,000; Ostwald, Z.Physikal.Chem., 1889, 3, 418) and by the qualitatively similar effects of various groups upon the dissociation constants of benzoic acids. The facts of aromatic substitution, which divide groups more or less sharply into the two classes of "o-p-directive" and "m-directive", and a multitude of observations of tautomeric changes, addition reactions and many other chemical processes, have all contributed to the modern view of the polar characters of different atoms and groups. Measurements of dipole moments during recent years have also provided data upon which conclusions can be based.

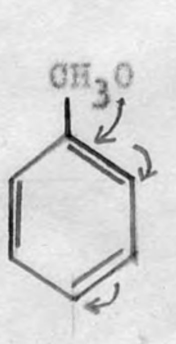
Relatively to hydrogen, an atom or group may be electron-attractive or electron-repelling. In the former case the introduction of a group will increase the strength of a carboxylic acid, weaken a base, retard the attack of an "electrophilic" reagent (i.e. a reagent which demands a high electron-availability, such as the ordinary reagents which bring about substitution in the benzene nucleus) and facilitate the reaction of the compound with a nucleophilic reagent (i.e. a positive centre-seeking reagent such as the hydroxide ion in alkaline hydrolysis). But either effect may operate by one of two mechanisms. These are distinguished by the terms "inductive" and "tautomeric". The inductive effect, which is denoted by +I when the group is electron-repulsive and by -I when it is electron attractive, represents a permanent condition of the molecule, and is measurable in the dipole moment of a saturated substance or the dissociation constant of a simple saturated aliphatic acid. It is synonymous with Flürscheim's "polar factor" and arises from the unequal sharing of the covalent pair linking the atom or group to the carbon chain as in

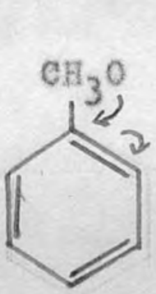


$$\mathrm{Cl} \longleftarrow \mathrm{C} \longleftarrow \mathrm{C}(=\mathrm{O}) \longleftarrow \mathrm{O} \longleftarrow \mathrm{H}$$

It may be transmitted through a carbon chain, whether saturated or unsaturated, or the medium. The electronic interpretation of the "polar factor" is due to G. N. Lewis

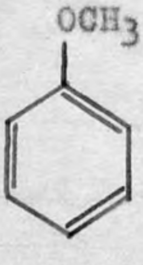
(Valence and the Structure of Atoms and Molecules, New York, 1923, p.83), and it has been incorporated in the electronic theories of Lapworth, Robinson and Ingold (see, for example, Robinson, "Outline of an Electrochemical Theory of the Course of Organic Reactions," Institute of Chemistry, 1932; Ingold, Chem.Reviews, 1934, 15, 225). But a group when linked to a suitable system may also give rise to electronic displacements by a tautomeric mechanism. This effect is the electronic successor to Flürscheim's "Quantitative Factor" and Lapworth's "alternate induced polarity" produced by a "Key Atom". Thus, a group such as methoxyl, which possesses unshared electrons, tends to increase its covalency with the neighbouring carbon atom when it is linked to a loose system such as the benzene nucleus. The following processes may then occur at the demand of an electron-seeking reagent:-

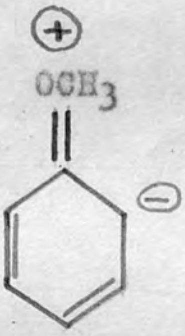


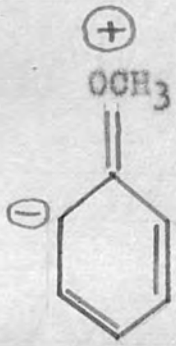


This is termed the electromeric effect, operative on d demand, and transmitted only through a "conjugated system". The effect has a permanent analogue, however, the mesomeric effect. The benzene nucleus is now believed to exist in a mesomeric state between the two Kekulé structures:

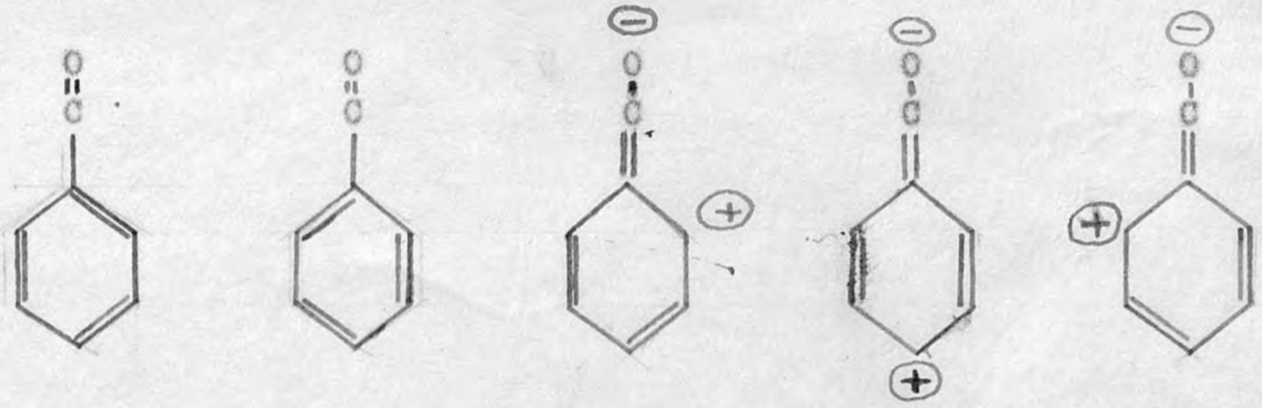
When methoxyl is linked to the nucleus, in addition to the benzenoid structures, the o- and p-quinonoid structures can participate in the mesomeric state, i.e. the compound is a resonance hybrid to which all of the following five structures contribute:







In a similar way, groups such as c = o or NO_2 when linked to the benzene nucleus can set up electromeric displacements <u>towards</u> <u>themselves</u>, and the mesomeric state of such a compound is "between" the following structures:-



The mesomeric effect is thus a permanent state of the molecule, and at the demand of a suitable reagent it can develop into the full electromeric effect. These effects are, of course, the cause of the powerful o-p-directive influence of hydroxyl or alkoxyl and of phenomena such as the low value observed for the dissociation constant of p-hydroxy-benzoic acid as compared with that of its m-isomeride.

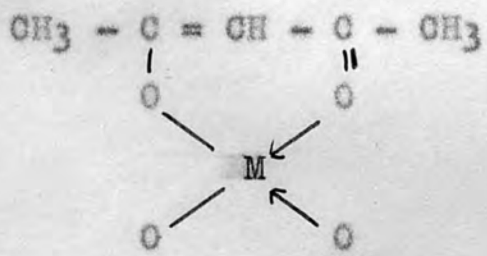
It has already been pointed out that the effects of groups in the m- or p-position to the point of reaction, whether they operate by the inductive mechanism (e.g. CH_3) or by the tautomeric mechanism (e.g. OCH_3), are reflected in the energy of activation and not to any extent in the probability factor of the equation $k = PZe^{\frac{-E}{RT}}$ for the velocity coefficient of a reaction. A kinetic study of the alkaline hydrolysis of ortho-substituted benzoic esters has now shown that the position is very different when the substituent is in the ortho-position, and the results have an important bearing upon the possible factors to which the *ortho*-effect is to be attributed. These are discussed in the paragraphs which follow.

(d) Chelation in ortho-Substituted Compounds.

In attempting to formulate a general theory of the nature of the *ortho*-effect it must be emphasised that the effect is not a general one and is not observed in all aromatic compounds where a substituent is situated *ortho* to the reacting group. In fact it appears to operate only in cases where the reacting group contains an atom which is known to be a powerful electron donor, such as $-COR$, $-COOR$ or $-NR_2$. This is illustrated by the fact that the velocities of hydrolysis of 2:6- and 3:5-dibromobenzoyl chlorides, as compared with the unsubstituted compound, are .0112 and 13.5 respectively, while for the corresponding benzyl chlorides the values are .12 and .07 (Olivier, Rec.Trav.Chim., 1929, *48*, 227). In fact the *ortho*-effect never seems to be detectable in the reactions of benzyl chlorides (cf. indem., ibid, 1930, *49*, 697, Bennett and Jones, J.C.S., 1935, 1815). Also Branch, Yabroff and Bettmann (J.Amer.Chem.Soc., 1934, *56*, 937, 1865) find no increase in the strength of *o*-substituted phenylboric acids $X.C_6H_4.B(OH)_2$ as compared with their isomerides, and this contrasts strongly with the relatively high dissociation constants of *o*-substituted benzoic acids (Dippy and Lewis, loc. cit.). Further, the characters of *o*-substituted phenols and their derivatives do not indicate any appreciable effect, for they are not more strongly acidic than their isomeric *m*- and *p*-substituted compounds nor are they appreciably less reactive (cf. Boyd et al., J.C.S., 1914, 105, 2117; 1915, 107, 538; 1919, 115, 1239; Burkhardt et al., J.C.S., 1936, 17).

The figures given on the next page illustrate the absence of an *ortho*-effect of the usual type in phenols and phenylboric acids.

The apparent connection between the *ortho*-effect and the presence of an electron-donating atom at once directs attention to "chelation" processes as a possible interpretation of the observations. The term "chelate ring" was introduced by Morgan and Drew (J.C.S., 1920, 1456) to describe rings such as those formed in the metallic ethylenediamine compounds, e.g. $[Co\ en_3]Cl_3$ and the acetylacetone derivatives which are formulated



In the production of such rings, the ethylenediamine or the acetylacetone residue forms two links with the metallic atom.

The conception of chelation was later extended to include ring closure through a hydrogen atom which acts as "acceptor".

Substituent	k for reaction of phenol with ethylene oxide (Boyd et al., loc.cit.).	K for phenols	10^{10}K for phenylboric acids (Branch et al., J.Amer.Chem.Soc., 1934, 56, 937, 1850, 1864.
H	.075	5.0×10^{-7}(a); 1.15×10^{-10}(b); $.32\times10^{-10}$(c)	1.97
p-CH_3	.101	$.67\times10^{-10}$ (b)	.608
o-CH_3	.078	$.63\times10^{-10}$ (b)	.910
p-Cl	.042	1.32×10^{-10} (c)	6.23
o-Cl	.050	10.2×10^{-10} (c)	14.0
2:4:6-3-Cl	.045	--	--
p-NO_2	.0075	96×10^{-7} (a)	9.8
o-NO_2	.0035	75×10^{-7} (a)	5.6

(a) Hantzsch, Ber., 1899, 32, 3066

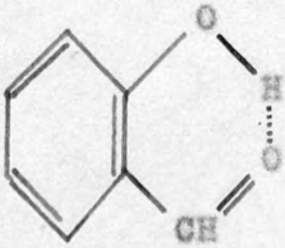
(b) Boyd, loc.cit.

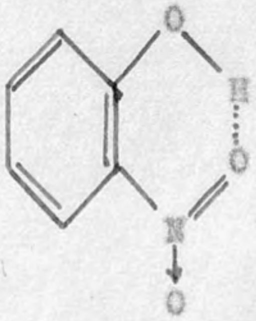
(c) Bennett et al., J.C.S., 1935, 1821.

This was originally described as "co-ordinated" or "two-covalent" hydrogen. The "divalency" of hydrogen was first postulated by Latimer and Rodebush (J.Amer.Chem.Soc., 1920, 42, 1431) and was considered also by G. N. Lewis ("Valence") and more fully by Sidgwick ("Electronic Theory of Valency", 1927). Such a postulate is necessary, for example, in order to account for the existence of the acid fluoride ion $HF_2^{\ominus}$, the polymerisation of hydrogen fluoride and the association of water and other hydroxylic liquids. The Pauli Exclusion Principle would be violated by a hydrogen atom having a four-electron valence group, however, since the existence of two electrons in the same quantum state would be involved, and the "hydrogen bond" is now regarded as a resonance phenomenon. A compound having two atoms linked through hydrogen is regarded as a resonance hybrid, the contributory structures having the hydrogen linked to one or the other of the atoms concerned (see Sidgwick, Annual Reports, 1934, 31, 40). Thus the HF_2 ion is written $[F \ldots\ldots H — F]^{\ominus}$ and the structures contributing to the resonance are $[F \quad H — F]^{\ominus}$ and $[F — H \quad F]^{\ominus}$. The stability of the "hydrogen bond" arises from the fact that the resonance states have less energy than either of the individual structures which contribute to it.

Reference has already been made to the existence of "chelate rings" completed by a co-ordinate bond in which a metallic atom acts as electron acceptor. In 1924 Sigwick and Callow (J.C.S., 1924, 125, 527) in order to explain the abnormalities noticed in certain physical properties of benzene derivatives, suggested the possibility of ring formation of this type in systems having hydrogen instead of a metal as the acceptor atom. A detailed examination of the physical properties of a number of phenols, chiefly the solubilities and volatilities, had been carried out by Sidgwick and his collaborators, and the conclusion was reached that *o*-substituted phenols in general showed very marked differences from their *m*- and *p*-isomerides, the most noticeable abnormalities being that they were (a) more volatile, (b) less miscible with water, and (c) more miscible with benzene. Sidgwick and Callow summarised their results in the statement that the *o*-derivatives are "less polar" than the *m*- and *p*-compounds, and pointed out that the abnormalities coincided with the presence of *two* substituents of a reactive nature (such as NO_2 or CHO *ortho* to OH). In the case of phenols containing such "active" substituents, in the *o*-positions, the polar characters due to the hydroxylic hydrogen are suppressed; this is easily illustrated by the analogy between *o*-substituted phenols and phenolic ethers. These facts appear to justify the belief that the hydrogen in such cases forms a link with an atom of the *o*-substituent.

Sidgwick and Callow's view may be illustrated by reference to salicylic aldehyde and *o*-nitro-phenol. These compounds are written:

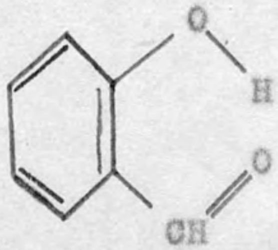


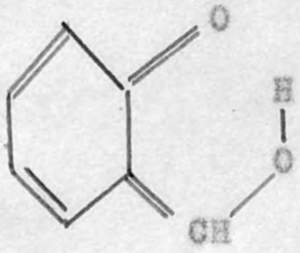


I.

II.

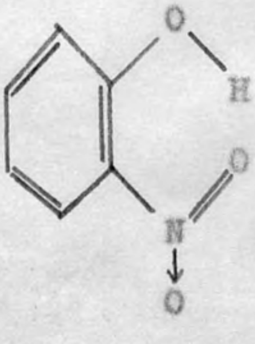
and in the light of the modern view regarding the hydrogen bond, they are in resonance between Ia and Ib and IIa and IIb.

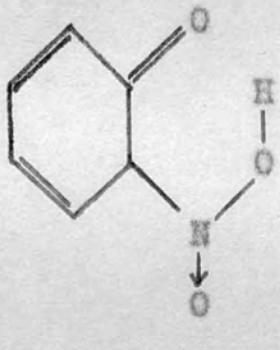




Ia.

Ib.



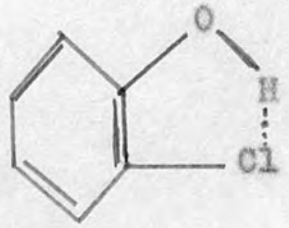


IIa.

IIb.

It will be noticed that the "chelate ring" completed by the hydrogen bond is six-membered and has two conjugated double bonds. Moreover, the appearance of electrical charges in the contributory structures is prevented by covalency changes.

In certain other o-substituted phenols Sidgwick and Callow postulate a ring of five members, e.g. in o-chlorophenol (III).



III.

The conditions which make possible "ring closure" of this kind appear to be the following:-

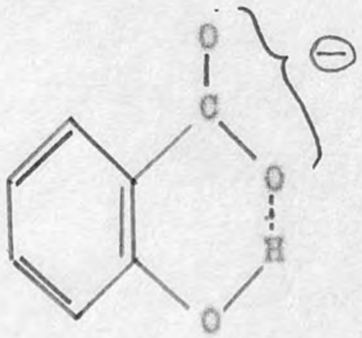
(a) The atoms to be linked through hydrogen must be so placed that the hydrogen can, without strain, become attached to either of the atoms concerned. In the phenols studied by Sidgwick and Callow the most favourable position seems to be that in which the "chelate ring" so completed is six-membered and contains two double bonds.

(b) The hydrogen must be so linked that the ionisation is not difficult. This is clearly the case in phenolic hydrogen, and Sidgwick and Callow suggest that a similar process might occur in o-nitrotoluene, where the powerfully electron-attracting nitro-group will render the hydrogens of the alkyl group "incipiently ionised".

(c) The atom to which the hydrogen is to become bound must be an electron donor.

(d) The process is facilitated if electronic rearrangements are possible to prevent the development of charges in the second contributory structure. This is perhaps not essential, however.

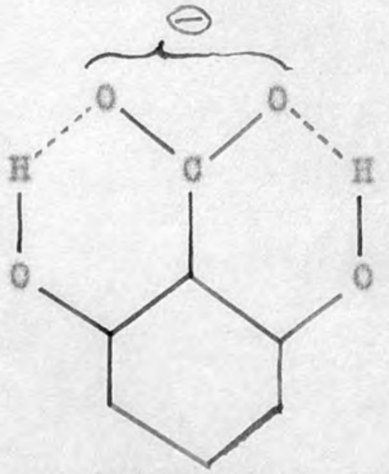
The explanation given by Sidgwick and Callow of the abnormal properties of certain o-substituted phenols naturally leads to the supposition that the ortho-effect observed in numerous chemical reactions might be capable of interpretation on similar lines. Kindler (loc.cit.) suggests, indeed, that since the ortho-effect cannot be interpreted as merely steric hindrance in the Victor Meyer sense, it may be connected with the "residual affinities" of the two groups. It has been pointed out above that an electron-donating atom appears to be necessary, and a definite suggestion that the effect is largely due to a chelation process was made by Branch and Yabroff (J.Amer.Chem.Soc., 1934, 56, 2568). They considered the dissociation constant of salicylic acid ($10^5K = 105$). The relatively high strength of this acid cannot be due to steric hindrance by so small a group as hydroxyl, particularly as the methoxyl group does not lead to any great increase in conductivity (10^5K for the methoxy acid = 8). They therefore interpreted the anomaly by postulating the formation of a hydrogen bond between carboxyl and hydroxyl groups, as in IV.



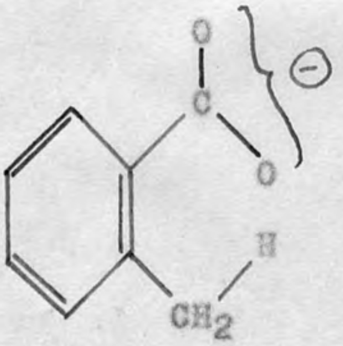
IV.

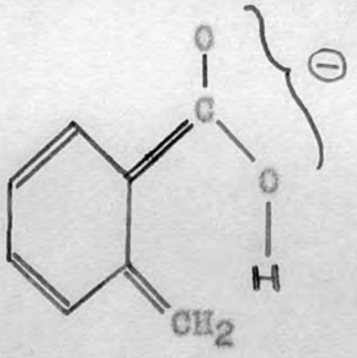
This is clearly an application of Sidgwick and Callow's ideas. Branch and Yabroff point out that such a process will be possible only if the phenolic and carboxylic oxygen atoms can approach so closely that a proton may be within easy "bonding distance" of both, in which case the change requires no more than ordinary bond rearrangements within the nucleus.

It is evident that such a process will occur in the anion far more easily than in the acid itself, for the negatively charged carboxylate group will exert a definite attraction for the phenolic hydrogen. The hydrogen bond will then decrease the electron-availability of the carboxylate oxygen, thus inhibiting reassociation and leading to a stronger acid. W. Baker (Nature, 1936, 137, 236) suggests that the further large increase in strength of 2:6 dihydroxybenzoic acid is due to the formation of hydrogen bonds by both oxygen atoms of the carboxyl group, this would obviously have an even more pronounced effect on the reassociation process.

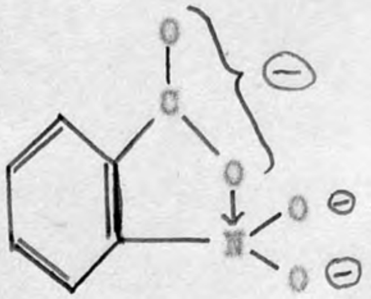


It is quite probable that under suitable conditions an alkyl group can form a hydrogen bond. It is necessary, of course, that a proton-accepting atom should be placed suitably with respect to it, and that some factor should operate favourably upon the production of the second contributory structure (e.g. the electron-attracting nitro-group in o-nitro-toluene referred to above). In the anion of o-toluic acid, the negative charge of the carboxylate group may be such a factor, and here the relatively high strength of this acid may be due to resonance between

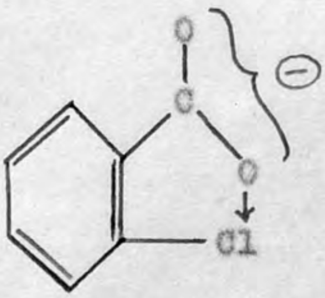




In o-nitro and o-halogeno-benzoic acids (excluding o-F) an oxygen of the carboxyl may act as an electron donor to form a co-ordinate bond of the normal type; this is possible because chlorine, bromine and iodine are all capable of expanding their valence groups beyond eight electrons and, according to Bennet and Willis (J.C.S., 1929, 256), the nitrogen atom of the nitro-group may have electron-acceptor properties. The following two structures, a and b, therefore, may be suggested for the ions of the o-chloro and o-nitrobenzoic acid respectively; the formation of a five-membered ring containing a normal co-ordinate bond is regarded as taking place.



a



b

If the ortho-effect can actually be attributed to this kind of phenomena, then it is easily seen why the reacting group should be of an electron-donating character, for the suggested chelation processes could not occur in o-substituted benzyl chlorides, for example, and the hydrogen bond formation suggested by Sidgwick and Callow in o-substituted phenols (loc.cit.) would not be expected to exert a very great influence on the electron-availability of the oxygen. It may be mentioned here, however, that, while the explanation put forward above is capable of interpreting many of the characteristics of ortho-compounds, steric hindrance of the Victor Meyer type cannot be altogether neglected as a possible cause; such hindrance may be at least a contributory factor in a large number of cases and may sometimes be the most important factor.

Hydrogen bond formation in certain o-substituted compounds is also indicated by the molecular weight measurements of V. Auwers (Ber., 1937, 70, 966; cf. Lassettre, Chem. Reviews, 1937, 20, 259) and of Chaplin and Hunter (J.C.S., 1937, 1114; 1938, 375). These indicate that many acid amides are associated in solution. Since the association is suppressed by substitution of the amide hydrogen (as in CH_3.-CO.NR_2, for example) it is logical to assume that the intermolecular linkage is formed by one of the hydrogens. Acetanilide is associated, as also are its m- and p-substituted derivatives, but if an electron-donating group, such as NO_2 or CHO, is introduced into the o-position, the association is very much reduced. Thus, while m-nitro-acetanilide is associated, o-nitro-acetanilide is not, nor is benzo-o-nitroanilide. A similar absence of association is found in o-acetamido-acetophenone and in ethyl o-acetamidobenzoate. The simplest interpretation is found by supposing that in the non-associated compound chelation occurs between the amide hydrogen and the electron-donating groups. The phenomena are, of course, quite comparable with those considered by Sidgwick and Callow.

(e) The Kinetics of the Alkaline Hydrolysis of Substituted Ethyl Benzoates.

The velocities of hydrolysis of a number of benzoic esters in 88% alcohol at 30° were determined by Kindler (Annalen, 1926, 450, 1; 1927, 452, 90; 1928, 464, 278), but it was made clear in Section I that the mere comparison of velocity coefficients at a single temperature may throw but little light upon the influences governing reaction velocity, and may, indeed, lead to incorrect conclusions. It has also been pointed out (p. 17) that substituents may influence reaction velocities by causing changes either in the energy of activation or the probability factor, P, of the equation $k = PZe^{-E/RT}$, or both. In at least three instances there is definite evidence that in benzene derivatives groups placed m- or p- to the point of reaction influence E to a marked extent but leave P almost unchanged. The primary object of the work described in this section was an analysis of the influence of ortho substituents upon the alkaline hydrolysis of ethyl benzoate into their effects upon the two parameters of the kinetic equation. It was hoped that such an analysis might serve to throw further light upon the question of the peculiar "ortho-effect", and this hope has been fulfilled.

Ingold and Nathan (J.C.S., 1936, 222) have conducted a careful investigation of the alkaline hydrolysis of p-substituted ethyl benzoates, and they find that the effect of the substituent is to change the energy of activation, variations in P being but small. In the course of the present work, four m-substituted benzoic esters were examined and the results were exactly similar to those of Ingold and Nathan for the corresponding p-compounds; the hydrolysis of ethyl p-fluorobenzoate was also measured. For all these cases the plot of E against log k gave a straight line of slope -2.303 RT; the results obtained, together with those of Ingold and Nathan, are shown graphically in Fig. 7 (p.   ), and the new figures are recorded in the table below.

Alkaline Hydrolysis of Substituted Benzoic Esters in 85% Alcohol

X	10^3k_{50}	10^3k_{35}	10^3k_{25}	E cals.	10^2P
H	6.28	1.68	.621	17,700	2.17
m-CH_2	4.57	1.18	.433	17,900	2.13
m-Cl	39.6	11.8	4.77	16,400	1.82
m-NH_2	3.21	.830	.308	18,100	2.15
m-NO_2	-	100	42.9	15,400	3.08
p-F	12.0	3.20	1.26	17,200	1.92
p-NO_2	-	162	72.0	14,800	1.86

[k is the bimolecular velocity coefficient expressed in l./g.-mol.-sec., and P is calculated from the kinetic equation on the assumption that $Z = 2.8 \times 10^{11}$]

As a matter of interest - though it is not relevant to the present discussion - all available values for m- and p-

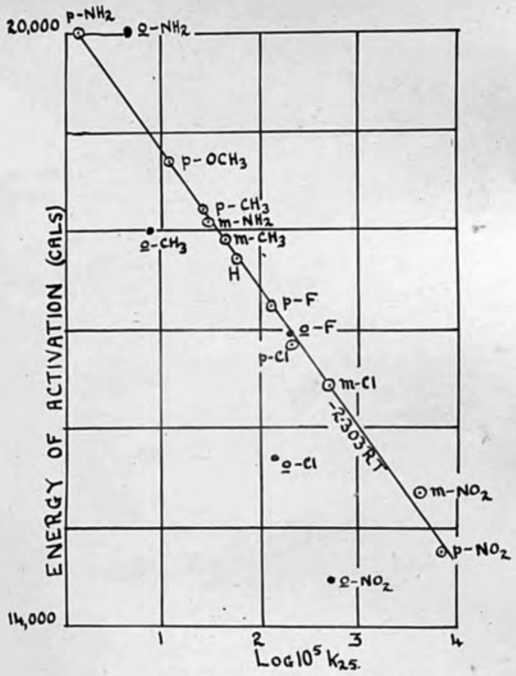
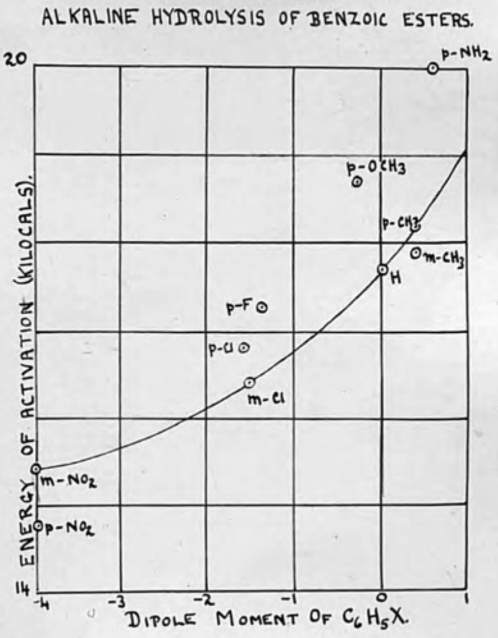


FIG. 7. REACTION III.

ALKALINE HYDROLYSIS OF ETHYL BENZOATES.

substituted ethyl benzoates have been used as a further test of the relationships observed by Nathan and Watson (J.C.S., 1933, 1248) and by Hammett (Chem.Reviews, 1935, 17, 125). In the former case values of E are plotted against the dipole moments of the appropriate substituted benzenes (Fig. 8), and the usual relationships are found (i.e. m-groups in general gave a smooth curve and p-groups show marked deviations owing to the effects operating by the tautomeric mechanism). The Hammett relationship is followed very well and the plot of E against log k for the corresponding benzoic acids (values due to Dippy et al.) is a good straight line, Fig. 9; this is to be expected since the two sets of compounds are so similar (cf. Dippy and Watson, J.C.S., 1936, 436).

It is evident therefore that no unusual factors are operative in the alkaline hydrolysis of m- and p-substituted benzoic esters. The main interest lies, however, in the behaviour of the esters having substituents in the o-position. Kindler (loc.cit.) showed that these were hydrolysed more slowly than their isomerides. The velocities of hydrolysis of five o-substituted ethyl benzoates have been measured at three temperatures and the results are shown below; unsubstituted ethyl benzoate is again recorded for purposes of reference.



ALKALINE HYDROLYSIS OF BENZOIC ESTERS.

FIG. 8

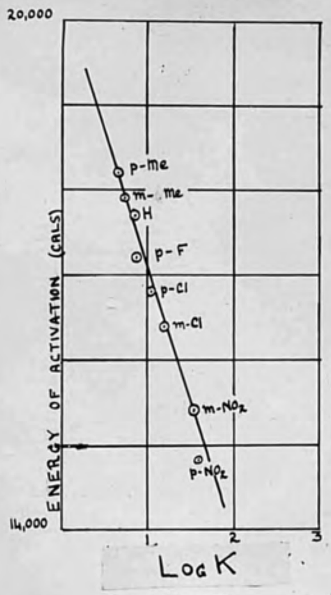

20,000
14,000
ENERGY OF ACTIVATION (CALS)
p-me
m- me
H
p-F
p-Cl
m-Cl
m-NO₂
p-NO₂
1
2
3
Log K

FIG. 9.

Alkaline Hydrolysis of o-Substituted Benzoic Esters in 85% Alcohol

X	$10^3 k_{50}$	$10^3 k_{35}$	$10^3 k_{25}$	E cals.	$10^2 P$
H	6.28	1.68	.621	17,700	2.17
O-CH_3	.809	.207	.0776	18,000	.45
O-F	21.0	5.81	2.32	16,900	2.13
O-Cl	11.0	3.38	1.39	15,700	.17
O-NO_2	38.8	12.75	5.41	14,500	.08
O-NH_2	.647	.146	.0476	20,000	8.32

The above values are also plotted on the E/log k graph in Fig. 7.

Three facts are at once apparent from an inspection of the results.

(a) Ethyl o-fluorobenzoate behaves in the same way as the m- and p-substituted esters; it gives a point on the theoretical line, indicating that o-F does not cause a change in P.

(b) The values of E for the remaining o-substituted esters approximate to those obtained for the m- and p-isomerides, but tend to be rather lower. The o-chloro ester gives a definitely lower value of E.

(c) With the exception of the o-amino and o-fluoro esters, the *ortho*-esters give values of P which are lower by roughly a power of 10 than those found for the other esters.

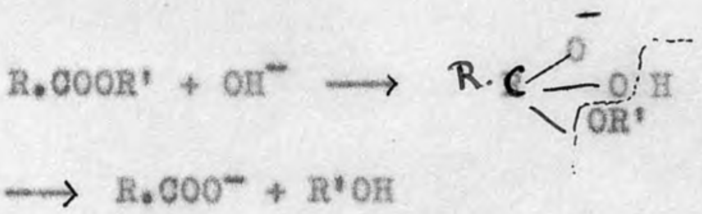
Ethyl o-amino-benzoate, however, gives a rather high P value.

It is clear, therefore, that a substituent in the o-position exerts a retarding effect on the hydrolysis by causing a decrease in the proportion of energised collisions which actually lead to the formation of reaction products. The possible causes which may reduce the value of P have already been discussed in Section I. It was there made clear that, even when the transition complex has been formed, it may yet be necessary for certain conditions to hold good in order that this complex may break down to give the final products. Thus, in a catalysed reaction, for example, P may largely depend upon the fulfilment or otherwise of the conditions necessary for the completion of the second stage in a scheme such as the following:-

$$A + \text{catalyst} \longrightarrow [A, \text{catalyst}]$$

$$\xrightarrow{B} \text{products} + \text{catalyst}$$

The mechanism of the alkaline hydrolysis of esters may be represented as the attack of hydroxyl ion followed by removal of a molecule of alcohol. Polanyi and Szabo (Trans. Faraday Soc., 1934, 30, 508) have shown that the alkoxyl group is eliminated in the final stage, and the simplest representation of the change is therefore as follows:-



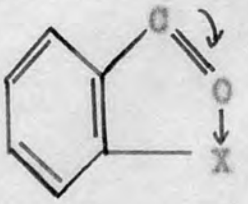
$$R.COOR' + OH^- \longrightarrow R.C\begin{matrix} O^- \\ O\,H \\ OR' \end{matrix}$$

$$\longrightarrow R.COO^- + R'OH$$

The velocity depends to a great extent, therefore, on the probability that the complex when formed will break down to give the anion and alcohol; the alternative, of course, is a return to the initial reagents.

The fairly large decreases in P observed in this investigation <u>might</u> be due to a decrease in the proportion of fruitful collisions between ester and OH^- ion, owing to stringent orientation conditions. Hinshelwood and Legard, however (J.C.S., 1935, 592), find that, in the acid-catalysed esterification of these esters, an increase in P actually occurs, and hence it appears improbable that the effect is exerted at the <u>first</u> stage of the reaction. It is more probable that the <u>ortho</u>-effect observed in these hydrolyses arises from the operation of some factor which reduces the facility with which the products are formed from the complex, and it remains to elucidate the probable nature of this factor.

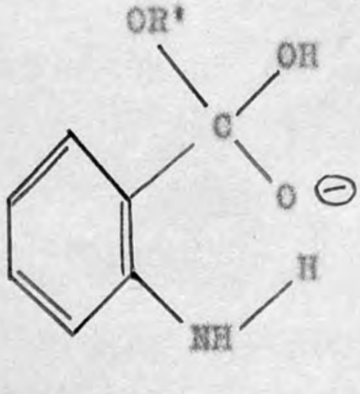
The interaction of the <u>ortho</u>-substituent with the negatively-charged carboxylate group of a carboxylic anion has already been postulated; this may be represented as involving the formation of a hydrogen bond (e.g. with <u>o</u>-methyl) or of an ordinary co-ordinate bond (e.g. <u>o</u>-Cl). It has already been assumed that the factor largely responsible for such interaction is the negative charge residing upon the oxygen atoms of $-COO^-$. In an ester there is, of course, no such charge. As the hydroxyl ion (or other reagent such as the hydrogen ion in an acid-catalysed reaction) approaches the ester molecule, however, the electromeric change, $\overset{\searrow}{\underset{\swarrow}{>}}C \overset{\curvearrowright}{=} O$, occurs, and the electrons of carboxyl oxygen move into higher energy levels, and thus become more reactive; the oxygen also acquires a negative charge. If, therefore, other atoms are suitably placed, chelation may perhaps occur simultaneously with the approach of the catalyst. It is suggested that this occurs in alkaline hydrolysis; the transition complex in the case of <u>o</u>-substituted benzoic esters being chelated as represented below:-



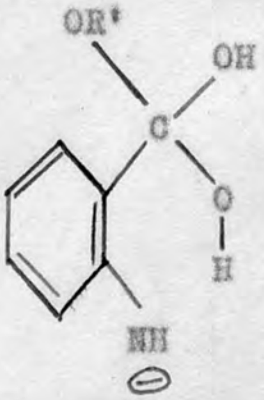
This is not likely to influence the energy of activation to any extent, however, except that the chelation process may tend to facilitate the electromeric change, $>C \overset{\curvearrowright}{=} O$, since it would encourage a movement of electrons in this direction. The slightly low values of E obtained are thus explained. In an esterification reaction, however, the first step is doubtless the co-ordination of a hydrogen ion at carboxyl oxygen; now if chelation takes place simultaneously with the approach of the catalyst, the resulting decrease in electron-availability of the oxygen will lead to a rise in E, as found by Hinshelwood and Legard (loc.cit.) for the esterification of s-trimethyl-benzoic acid. It will not influence E for alkaline hydrolysis very greatly, however.

It remains to account for the decrease in the P factor for the alkaline hydrolysis of o-substituted esters. The transformation of the complex to the final products involves removal of -OEt; this will be rendered more difficult by any process which causes a drift of electrons away from the carbon, and the suggested chelation is such a process. The observations are thus interpreted by postulating chelation, as in the anion of carboxyl, but occurring during the approach of hydroxide ion.

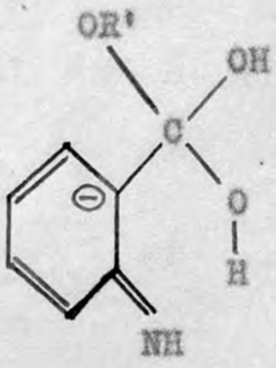
The case of ethyl o-amino-benzoate is peculiar, however. The relatively high value of E (20,000 calories) is identical with that found by Ingold and Nathan (loc.cit.) for the p-substituted isomeride; it is higher than the value for ethyl m-amino-benzoate on account of the mesomeric effect of the amino-group upon a reaction requiring recession of electrons from the point of attack (cf. ethyl anisate, which also gives a high E value). The o-amino group, however, also gives a value of P which is rather higher than that found for any of the other esters; it differs from the values for the other ethyl o-benzoates by considerably more than a power of 10 (two powers of 10 when compared with ethyl o-nitrobenzoate). It is clear that the actual condition of the complex will be greatly complicated by the powerful +T character of the nitrogen, and in the chelated form a number of structures such as the following will participate:-



(a)



(b)



(c)

The participation of a structure such as (c), with the negative charge situated at the ortho-carbon atom, may more than counteract the effect of the chelation and lead to a P factor higher than that for ethyl benzoate itself. Such a structure acquires additional importance on account of the hydrogen bond formation, since the transfer of the negative charge to the nitrogen in structure (b) sets up a demand for the electronic displacements to occur. The fact that P is somewhat higher for ethyl o-amino-benzoate than for ethyl p-amino-benzoate and m-aminobenzoate is thus understood.

Finally, a powerful argument in favour of the chelation processes is found in the behaviour of ethyl o-fluorobenzoate. Fluorine cannot expand its valence group beyond eight electrons and hence the formation of a co-ordinate bond with carboxyl oxygen is here impossible. In harmony with the theoretical requirements, the values of E and P are almost the same as for the isomeric *p*-substituted ester. On theoretical grounds chelation cannot occur, and all the criteria of the *ortho*-effect are absent.

The phenomena described may thus be interpreted in a satisfactory manner by employing the conceptions outlined above. At the same time, however, it is recognised that other factors will no doubt operate, and the complete solution of the problem of the *ortho*-effect is not as yet regarded as being in sight. Nevertheless it is felt that the investigation described in this section forms a definite contribution to our knowledge of the subject.

SECTION III.

THE BASE-CATALYSED PROTOTROPY OF PHENYL ALKYL KETONES AND THE ALKALINE HYDROLYSIS OF SATURATED ALIPHATIC ESTERS

Much attention has been directed towards the elucidation of the peculiar effects exerted by alkyl groups upon reactivity, and a large amount of experimental work relating to the subject has been reported from time to time. It cannot be said, however, that any theory which can account in a satisfactory manner for the whole of the observed facts has as yet been advanced. In this section an attempt is made to correlate the scattered experimental data and to systematise the various ideas which have been put forward to interpret the results. An account of some original experimental work carried out by the author, in order to throw further light on the behaviour of aliphatic compounds and to test the validity of existing postulates, is also given.

It has been recognised for a number of years that, relatively to hydrogen, alkyl groups repel electrons by an inductive mechanism. This was first pointed out by Lucas and Jameson (J.A.C.S., 1924, 46, 2475) after a study of the addition of hydrogen halides to propylene, acrylic acid and dimethyl allene, and later by Allan, Oxford, Robinson and Smith (J.C.S., 1926, 405) in a consideration of the relative directive powers of groups in aromatic substitution. The fact that the dipole moments of all saturated aliphatic hydrocarbons are zero makes it clear, however, that, as suggested by Ingold (Chem.Reviews, 1934, 15, 238) the inductive effect of an alkyl group operates only when it is stimulated by other groups.

It is a simple and logical deduction that the magnitude of the inductive effect of an alkyl group should increase with the length of the chain, and also in such series as

$$CH_3 < MeCH_2 < Me_2CH < Me_3C$$

since the higher radicles are all obtained by replacing hydrogen successively by methyl. Such an order of effects is observed in a number of cases to be found in the literature. For example, Stewart (J.C.S., 1905, 87, 185) showed that the rate of formation of bisulphite compounds of ketones, R.COR', decreased in a regular manner with increase in the length of the alkyl chain, R, whilst branching at the α-carbon caused a considerable decrease in velocity. A similar behaviour was observed in the formation of oximes from the same series of ketones (idem., ibid, p.410). Robinson and Smith (J.C.S., 1926, 392; 1927, 2647) recorded evidence which indicated that the directive influences of alkyl groups in the nitration of quinol methyl alkyl ethers varied in the expected order, and similar results were obtained for the nitration of phenyl alkyl sulphones (Baldwin and Robinson, J.C.S., 1932, 1445) and of a series of benzoic esters (Zaki, J.C.S., 1928, 983). In the latter study there were some small deviations from the normal order, but they appear to be insignificant. The ratios ${}^{kOH}/kH$ for the hydrolysis of alkyl glyceric esters (Ingold et al., J.C.S., 1930, 1057) also form an example where alkyl groups fall in the expected order of inductive influence, viz.,

$CH_3 < Et < n\text{-}Pr < n\text{-}Bu < n\text{-}Am \sim iso\text{-}Am < iso\text{-}Bu < iso\text{-}Pr$

The kinetic studies of the alkaline hydrolysis (Smith and Olsson, Z.Physikal.Chem., 1925, <u>118</u>, 99, 107) and ammonolysis (French and Wrightsman, J.A.C.S., 1938, <u>60</u>, 50) of a series of alkyl esters of acetic acid indicate no considerable departure from the predicted order of inductive effects of alkyl groups except for the low reactivity of the <u>sec</u>-butyl and the $-CMe_2Pr$ derivatives. The dissociation constants of <u>m</u>- and <u>p</u>-toluic acids are less than those of benzoic acid (Dippy and Lewis, J.C.S., 1936, 644), whilst the strengths of the alkyl substituted acetic acids fall in the order

$$CH_3COOH > MeCH_2COOH \sim Me_2CH.COOH > Me_3COOH$$

(Dippy, in the press). These results are in accordance with the +I effect of alkyl groups. The equality of the dissociation constants of propionic and isobutyric acids, however, is anomalous, and will be considered more fully later (p. 95).

Again, the theoretical order of inductive effects of alkyl groups has been noted in an investigation of the reaction of hydrochloric acid upon mixed dialkyl mercury compounds carried out by Kharasch and Flenner (J.A.C.S., 1932, 54, 674). These workers showed that in the reaction

$$HCl + R.Hg.R' \longrightarrow RH + R'HgCl$$

the alkyl group with the smaller inductive effect tended to form hydrocarbon, and by studying various mixed dialkyl derivatives they obtained the following order of electron-repulsive powers

$$\left.\begin{array}{r} n - C_7H_{15} > n - C_4H_9 > n - C_3H_7 \\ \text{tert-}C_4H_9 > \text{iso-}C_3H_7 \end{array}\right\rangle\ C_2H_5 > CH_3$$

Other experiments of this type, in which mixed lead tetra-alkyls and nitric acid were employed (Jones, Evans, Gulwell and Griffiths, J.C.S., 1935, 43) gave similar results.

Finally the theoretical order of inductive effects is illustrated very clearly by the dipole moments of the lower members in certain series of aliphatic compounds (Groves and Sugden, J.C.S., 1937, 158). In this connection also the influence of the group (or atom) attached to the alkyl radicle is very evident; thus n-alkyl chlorides show no increase in dipole moment beyond propyl, whereas in the iodides the limiting value is not reached at the butyl compound.

The alkyl bromides are intermediate in character, as would be expected from the varying polarizability of the halogens. On the other hand, in the nitriles and nitroparaffins the size of the alkyl radicle has little influence upon the dipole moment.

A search of the literature, however, shows that the instances where alkyl groups place themselves in the theoretical order are probably outnumbered by those where other influences become evident at some point in the series. These peculiar influences are mainly associated with branched chain alkyl groups, but frequent anomaly is found with the straight chain derivatives (especially in the higher members of the alkyl series). For example, the work of Dawson and his collaborators (J.C.S., 1910, 97, 2048; 1911, 99, 1740) on the rate of iodination of a series of dialkyl ketones R.Co.R' indicated no regular variation with length of the alkyl chain, whilst the measurements of Lapworth and Manske (J.C.S., 1930, 1976) of the stabilities of cyanohydrins of these ketones were not capable of a simple interpretation. The cyanohydrins of the alkyl phenyl ketones, $R.CO,C_6H_5$, also exhibited stabilities which varied in a peculiar manner.

In the reactions of hydrobromic acid with phenylalkyl ethers (Tronow and Ladigina, Ber., 1929, 64, 2844) with alkyl acetate (Tronow and Ssibgatullin, ibid, p.2850) and with aliphatic alcohols (Bennet and Reynolds, J.C.S., 1935, 134) which may be formulated,

$$R'OR \overset{H^{+}}{\rightleftharpoons} R-\overset{+}{O}H \,\vdots\!- R \xrightarrow{Br^{-}} R'OH + R.Br$$

(where R' = phenyl acetyl and hydrogen respectively), there is an appreciable fall in velocity from methyl to ethyl, followed by quite small differences between the higher n-alkyl derivatives, whereas the isobutyl compounds have a singularly small reactivity. Further, in the series primary, secondary and tertiary alkyl compounds, there is a very marked increase in velocity.

Baker and Nathan (J.C.S., 1935, 1844), in a recent study of the reaction between pyridine and p-alkyl-substituted benzyl bromides in acetone solution, found that the magnitude of the effect of the alkyl group upon the velocity varied in the order

$$\mathrm{Me} > \mathrm{Et} > \mathrm{Pr}^{\beta} > \mathrm{Bu}^{\gamma}$$

This indicates a complete reversal of the polar effects of the alkyl radicles, since the reaction is of class A. Observations closely related to this are found in the nitrations of p-isopropyl and tert-butyl toluenes (Le Févre et al., J.C.S., 1933, 980; 1934, 1501, 1697) and of p-ethyl toluene (Brady and Day, ibid, 1934, 114) where substitution occurs <u>ortho</u> to methyl, indicating a greater electron repulsion for methyl than for ethyl, isopropyl or tertiary butyl. Sufficient data has been given to illustrate the fact that many investigations have brought to light peculiar effects due to alkyl groups. Several other instances where anomalous effects are observed in the alkyl series will be discussed in the sequel.

In recent years the peculiarities in the relative influences of alkyl groups have received more detailed attention, and the work of different investigators leads to the conclusion that the anomalous orders of reactivity are to be ascribed to one or more of three distinct causes.

Substitution reactions such as

$$RX + YZ \longrightarrow RZ + XY$$

or

$$RX + Z \longrightarrow RZ + X$$

may proceed in one of two ways; (a) through the initial formation of an addition complex, or (b) by simultaneous addition of one group and removal of the other; the addition complex is possible only by co-ordination of one of the reactants with an unshared electron pair of the other. In substitution at a saturated carbon atom, however, such co-ordination is difficult to visualise, and hence the modern conception of London (Z.Electrochem., 1929, 35, 552) is applied in such cases. Either mechanism, however, makes the substitution a bimolecular process, the speed of which is proportional to the concentrations of both reactants, and the kinetics of the larger number of substitution reactions, both nucleophilic and electrophilic, are found to be in conformity with this view. There are, on the other hand, some examples where substitution occurs at a saturated carbon atom with unimolecular kinetics. The hydrolysis of benzyl chloride by alkali hydroxide depends upon the concentration of hydroxyl ion, whilst benzal chloride or benzotrichloride are hydrolysed at rates which are independent of the hydroxyl concentration (Olivier and Weber, Rec.Trav.Chim., 1934, <u>53</u>, 869). Recently, in a critical survey of the experimental data, Hughes and Ingold (J.C.S., 1935, 244) suggested that in such cases the measured velocity is probably that of a slow ionisation; this is followed by a rapid bimolecular process according to the scheme,

$$RX \xrightarrow[\text{(slow)}]{} R^{+} + X^{-}$$

$$\overset{+}{R} + \overset{-}{Y} \xrightarrow[\text{(fast)}]{} RY$$

These investigators brought forward strong evidence for such a theory by showing that the kinetics of hydrolysis of methyl and ethyl chlorides were bimolecular, whilst those of isopropyl and tert-butyl chloride were unimolecular in 60% aqueous alcohol. Further, the bimolecular velocity coefficient for ethyl chloride was less than that for methyl chloride, but the unimolecular velocity coefficient for tertiary-butyl was greater than that for isopropyl chloride. The following table summarises the data regarding the hydrolysis of alkyl halides (Hughes and Ingold, loc.cit.) in aqueous media:-

Mechanism	S_N2		S_N1	
Alkyl group	CH_3	CH_3CH_2	$\begin{matrix}CH_3\\CH_3\end{matrix}\!>CH$	$\begin{matrix}CH_3\\CH_3\\CH_3\end{matrix}\!>C$
Reaction order	2	2	1	1
Velocity change	—decrease→		—increase→	

The symbols S_N refer to the type of substitution - viz., in this case nucleophilic substitution - whilst the number indicates the order of the reaction mechanism.

Hughes, Ingold and Patel (loc.cit.) had previously predicted that if the variation in the inductive effect were sufficient, then in traversing the series, methyl, ethyl, iso-propyl and tert-butyl, the effect of progressively increasing the electron repulsion would impede the access of the attacking reagent for the bimolecular mechanism (S_N2) and facilitate the ionisation necessary for the unimolecular mechanism (S_N1). This should therefore, under suitable conditions, yield a change in mechanism in passing from CH_3X to Bu^rX. The variations in velocity shown above are also readily explained since the electron repulsion of methyl retards the bimolecular change, but accelerates the ionisation in the unimolecular process; hence ethyl chloride hydrolyses at a slower rate than does methyl chloride, but tert-butyl chloride is hydrolysed more readily than isopropyl chloride. Similar variations in velocity and kinetics were observed by Gleave, Hughes and Ingold (J.C.S., 1935, 236) in the degradation of sulphonium salts,

$$R_3S^+ + OH^- \longrightarrow R_2S + R.OH$$

Hughes and Ingold have more recently (see J.C.S., 1938, 881) developed other methods of distinguishing between S_N2 and S_N1 mechanisms.

The peculiar relationship between the velocities in the cases cited above, therefore, find a clear explanation in terms of the inductive effects of alkyl groups, and reaction kinetics. It may be noted, however, that, although the velocities of reactions of the various alkyl compounds are not in the order expected if the reactions were all bimolecular, the polar sequence

$$CH_3 < Et < Pr^{\beta} < Bu^{\gamma}$$

appears to be maintained.

It should also be mentioned that an alternative scheme has been postulated to explain the peculiar order of velocities of hydrolysis of alkyl halides in aqueous media (Taylor, J.C.S., 1937, 1965; 1938, 840), which is based upon the decreasing facility of attack of α-carbon by hydroxyl, and the increasing facility of addition of hydrogen (of water) to the halogen of the alkyl halide in the series Me, Et, Pr^{β}, Bu^{γ}.

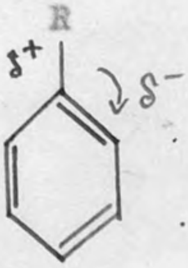
The second type of influence which leads to an irregular orderof effects in alkyl compounds was suggested by Baker and Nathan (loc.cit.) to explain the complete inversion of the polar influences of the series Me, Et, Pr^{β}, Bu^{γ}, in the reaction between pyridine and p-alkyl benzyl bromides. This reaction is of Class A, and the velocities of the p-alkyl compounds varied in the order

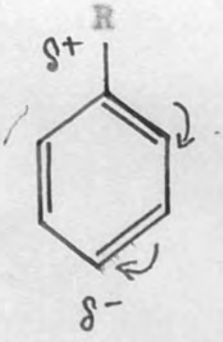
$$Me > Et > Pr^{\beta} > Bu^{\gamma}$$

In each case the reaction was shown to be completely bimolecular, so that the theories of Hughes and Ingold (loc. cit.) could not be applied to interpret the results. The variations of velocities indicate that in the system studied, the relative magnitude of the electron-release increases on passing from Bu^{γ} to Me; hence "the methyl group must permit additional electron-release by some mechanism which cannot function, or is greatly diminished, in the higher alkyl groups." The mechanism for this new type of electron-release was postulated for cases where methyl is attached to a conjugate system. The duplet of electrons binding hydrogen to the carbon atom of methyl was assumed to come under the control of the adjacent nucleus, giving rise to

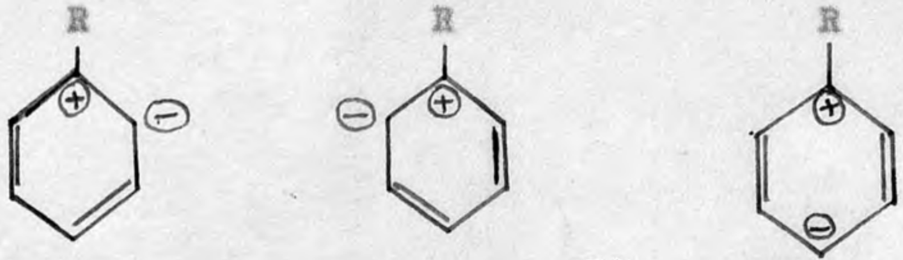
$$H - CH_2 - C = C - C = C -$$

a type of tautomeric effect which operates in addition to the normal inductive effect of methyl. The new type of electron repulsion is decreased when the hydrogen atoms of methyl are replaced by carbon; hence the fall in total electron-release in the series Bu^{γ} to Me. The electromeric displacements

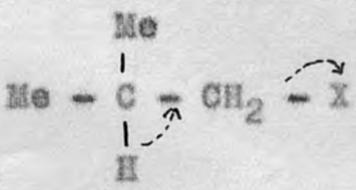




in the alkyl-substituted benzene are thus reinforced so as to favour the approach to the unperturbed structures



by the combined mechanisms  (cf. Watson, "Modern Theories of Organic Chemistry", p.75). Robinson (Chem. & Ind., 1936, 55, 962) has criticised this theory, since the dipole moment of tert-butylbenzene is greater than that of toluene, but the postulate of Baker and Nathan seems to afford a reasonable interpretation of several peculiar results. The most obvious is perhaps the nitration of p-ethyl, p-isopropyl and p-tertiary-butyl toluenes in the position ortho to the methyl group (see p. 68). The surprisingly low reactivity of isobutyl compared with that of sec-butyl compounds in reactions of alkyl halides (which requires anionisation of halogen) is ascribed to the possibility of the new type of electron-release from the three hydrogens in sec-butyl and from only one hydrogen in iso-butyl,



Examples where this order of effects is obtained are the interaction of alkyl iodides with triethylamine (Menschutkin, Z.Physikal.Chem., 1890, 5, 589) and with sodium

phenoxide (Segaller, J.C.S., 1913, 103, 1154, 1421). In the reaction of hydrobromic acid with alcohols (Bennet and Reynolds, loc.cit.), with phenyl alkyl ethers (Tronow and Ladigina, loc.cit.) and with alkyl acetates (Tronow and Ssibgatullin, loc.cit.) although the substitution of ethyl for methyl alcohol, which involves changing the group near the point of reaction, will probably have a much larger effect than will a further lengthening of the n-alkyl chain, the rupture of the R-O bond in the alcohol ($R \overset{\curvearrowright}{-} O$, see equation on p. 67) would be assisted by the tendency $\underset{\curvearrowright}{H - C -} O$.
Further examples of the applications of Baker and Nathan's postulates will be dealt with below.

A third type of influence, which causes alkyl groups to yield a curious order of effects, was postulated by Evans (J.C.S., 1936, 785) in a study of the acid-catalysed prototropy of phenyl alkyl ketones. It was found that the velocities of bromination of these ketones at constant temperature fall with increasing length of the alkyl chain up to n-butyrophenone and then remain almost constant up to n-caprophenone, but isobutyrophenone reacted much more slowly than any of the other ketones. When the energies of activation were evaluated, however, the surprising fact emerged that in passing from acetophenone to propiophenone there was a marked rise in E (2000 cals.) with a simultaneous increment (roughly ten-fold) in the probability factor, P (see Fig.10). Further lengthening of the n-alkyl chain caused a small and

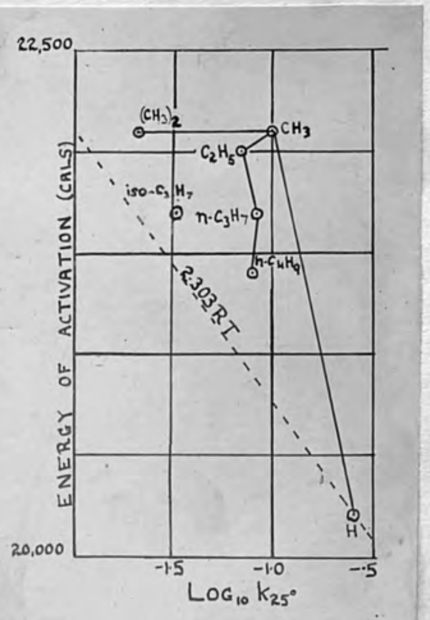
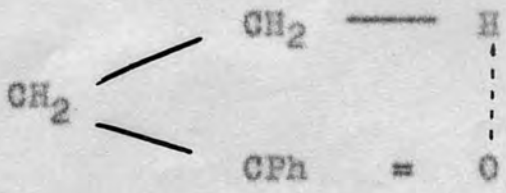
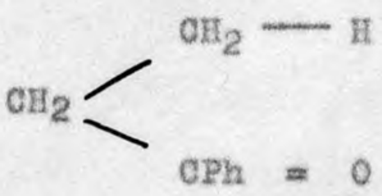

22,500
20,000
ENERGY OF ACTIVATION (CALS)
-1.5
-1.0
-.5
$Log_{10}\ k_{25°}$
$(CH_3)_2$
CH_3
C_2H_5
iso-C_3H_7
n-C_3H_7
n-C_4H_9
H
2.303RT

FIG. 10

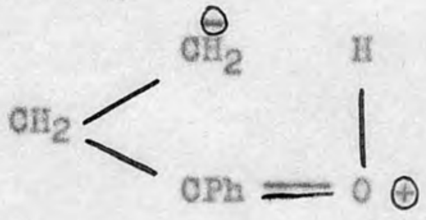
continuous decrease in E accompanied by a continuous decrease in P. The marked effect of the β-methyl in propiophenone upon the energy of activation could not be attributed to the ordinary polar effect of the alkyl group, since it was in the wrong direction and was much larger than expected [the nitro-group in the p-position of acetophenone causes an increase in E of only about 900 cals. (Evans, Morgan and Watson, J.C.S., 1935, 1167) above that for acetophenone]. Further, since the activation energy for isobutyrophenone was equal to that for propiophenone, it was argued that the high value of E was due to the introduction of the first methyl. A hydrogen bond was postulated to occur between the hydrogen of the β-methyl and carbonyl oxygen in propiophenone and the higher ketones, and evidence based upon interatomic distances was put forward to justify the view. A "direct" effect opposite in sign to the inductive effect has been ascribed to methyl by Bennet and Moses (J.C.S., 1930, 2366), and the view put forward by Evans was an attempt to give this direct effect some physical interpretation. The hydrogen bond causes an increase in the positive nature of carbonyl oxygen, which increases the energy necessary for the approach of the hydrogen ion.



The unperturbed forms are represented by



and



This view explains the high value of the activation energy in the higher ketones, since the electron-availability of the oxygen is decreased. Later it was realised (see Section II, p. 59) that this hydrogen bond was probably not present in the ketone itself,* but occurred simultaneously with the approach of catalyst during which the electromeric change, $C \overset{\curvearrowright}{=} O \longrightarrow C^{+}- O^{-}$, takes place, yielding a negative charge on the oxygen, which may then be supposed to "co-ordinate" with a suitably placed proton. The change in the probability factor, P, in passing from the acid-catalysed prototropy of acetophenone to that of propiophenone, is also interpreted on the basis of hydrogen bond formation, but this will be considered more fully in the later paragraphs.

Since the present work consisted mainly in a study of <u>alkaline</u> hydrolysis, it was clearly of interest to extend the investigation of the prototropy of phenyl alkyl ketones to include the <u>base</u>-catalysed reaction. This was done by bromination experiments upon the same series of ketones which had

---

* The infra-red spectra experiments of Gillette (J.A.C.S., 1936, <u>58</u>, 1143) on trimethylacetic acid and of Hilpert, Wulf, Hendricks and Liddel (ibid, p.548) on aldol, indicate the absence of hydrogen bond in these compounds.

been examined by Evans, the method being that of Morgan and Watson (J.C.S., 1935, 1173). The results have shown that the changes in energy of activation are quite different from those observed in the acid-catalysed change. They are ascribed (see below) to the rising inductive effects of the alkyl groups, whilst the fall in the probability factor, P, at one point only is interpreted on the basis of hydrogen bond formation. The author is indebted to Dr. D. P. Evans for permission to use his results for the acid-catalysed prototropy of isovalerophenone which yield further useful information regarding the effects of alkyl groups in this particular reaction.

The work of Lapworth (J.C.S., 1904, 85, 30) on the bromination of acetone showed that the speed of reaction was independent of the concentration of bromine, and he suggested that the reaction path consisted of a tautomeric change, followed by an instantaneous reaction with halogen. Later investigations (Dawson et al., J.C.S., 1909, 95, 1860, et seq.; K. H. Meyer, Annalen, 1911, 380, 212; Ber., 1912, 45, 2864; Watson et al., J.C.S., 1929, 1945 et seq.) have confirmed this view, which is general for all ketones, whilst the probability of this mechanism being correct has been demonstrated by the isolation of the ketonic and enolic forms of α- and β-diketones and β-ketonic esters (Knorr, Rothe and Averbeck, Ber., 1911, 44, 1138; Meyer and Schoeller, Ber., 1920, 53, 1410; Dufraisse and Moureu, Trans. Faraday Soc., 1928, 24, 562, and references there cited) and by the observations (Meyer, loc.cit.) that a number of these substances normally exist as equilibrium mixtures of keto and enol forms.

The acceleration of prototropic change by acids or bases has long been recognised, and a mechanism for the acid-catalysed change was put forward by Lapworth and Hann (J.C.S., 1902, 81, 1512), which may be expressed in the form:-

$$-\underset{|}{CH}-\underset{|}{C}=O \xrightarrow{+H^+} -\underset{|}{CH}-\underset{|}{C}=\overset{+}{O}H \longrightarrow -\underset{\underset{C}{|}}{C}=\underset{\underset{C}{|}}{C}-OH+H^+$$

Lapworth showed in 1903 (J.C.S., 1903, 83, 995) that cyanohydrin formation took place by the initial addition of cyanide ion to the carbonyl carbon.

$$>C=O \longrightarrow >C<^{CN}_{O-}$$

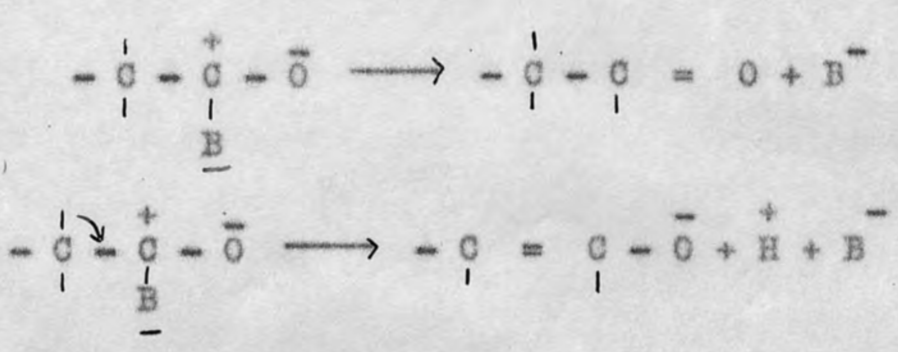
whilst Lowry postulated (J.C.S., 1923, 123, 822) that activation to the semipolar form $>\overset{+}{C}-\overset{-}{O}$ occurs previously to all reactions of double bonds. Later the modern conception of the carboxyl carbon-oxygen linkage was given a modern interpretation as a resonance form of the normal and semi-polar structures by Pauling and Sherman (J.Chem.Physics, 1933, 1, 606) and McKay (Chem. & Ind., 1934, 53, 870). In the absence of activating influences such as ultra-violet light or attacking molecules, the normal state of the ketone is represented as C = O with a very slight tendency towards $>\overset{+}{C}-\overset{-}{O}$. Follwoing this, a more precise physical picture was given to the mechanism of acid and base-catalysed prototropy by Watson, Nathan and Laurie (J.Chem.Physics, 1935, 3, 170) who, using the terms "acid" and "base" in the generalised sense of proton donators and acceptors respectively (Lowry, Chem. & Ind., 1923, 42, 43, 1048; Brönsted, Rec.Trav.Chim., 1923, 42, 718; J.Phys.Chem., 1926, 30, 777) suggested the following schemes.

An acid catalyst (H^+) forms a link with carbonyl oxygen which causes activation by the mechanism $>C=O \longrightarrow \overset{+}{C}-\overset{-}{O}$, yielding the semi-polar form. This may then either (a) revert to the original ketone or (b) be transformed to the enolic ion,

$$-\overset{|}{\underset{|}{C}}-\overset{+}{C}-\overset{-}{O}(H^+) \longrightarrow -\overset{|}{\underset{|}{C}}-\underset{|}{C}=O+H^+ \qquad (a)$$

$$-\overset{|}{\underset{|}{C}}-\overset{+}{\underset{|}{C}}-\overset{-\,+}{O}(H) \longrightarrow \overset{+}{H}+-\underset{|}{C}=\underset{|}{C}-\overset{-\,+}{O}(H) \qquad (b)$$

A basic catalyst ($\bar{B}$), however, is assumed to attach itself at the carbon and similarly cause activation into the semi-polar form, which may revert to ketone or be transformed to enol.



$$-\overset{|}{\underset{|}{C}}-\overset{+}{\underset{\underset{\bar{B}}{|}}{C}}-\overset{-}{O} \longrightarrow -\overset{|}{\underset{|}{C}}-\underset{|}{C}=O+\overset{-}{B}$$

$$-\overset{|}{\underset{|}{C}}-\overset{+}{\underset{\underset{\bar{B}}{|}}{C}}-\overset{-}{O} \longrightarrow -\underset{|}{C}=\underset{|}{C}-\overset{-}{O}+\overset{+}{H}+\overset{-}{B}$$

If these mechanisms are assumed, then the velocity of protropic change will depend upon two factors. (i) the rate of reaction of ketone and catalyst, and (ii) the proportion of semipolar form (which is now identified with the transition complex) which is transferred into enol or enolic ion. This view was confirmed by the experiments of Evans, Morgan and Watson (loc.cit.) on the acid-catalysed bromination of nuclear-substituted acetophenones, but the changes in the P factor were small and their value in theoretical discussion was questioned by Ingold and Nathan (J.C.S., 1936, 222). Unfortunately the system was one in which only small changes in E and P could be obtained, even on changing the p-substituent from CH_3 to NO_2.

The mechanisms put forward by Watson, Nathan and Laurie, however, seem to be the correct ones, and have been assumed in the present work.

The velocities of bromination of several phenyl alkyl ketones have been measured at temperatures of 45°, 55° and 65°, employing .1M solutions in 75% acetic acid in the presence of 20 g. per litre of sodium acetate. The speed of reaction between bromine and the ketones in 75% acetic acid is almost immeasurably slow in the absence of catalyst, and the addition of either hydrochloric acid or sodium acetate causes a very marked acceleration. There can be no doubtm therefore, that in the present work the results represent the speeds of the change by the "basic" mechanism. The results are recorded in Table I, where the velocity coefficients are expressed as fall of $\frac{N}{50}$ thiosulphate litre per minute for 20 c.c. of the reaction mixtures; they have not been reduced to the customary units (1./g.-mol./sec.), since the concentration of acetate ion is uncertain and the actual figures do not influence the arguments. Each figure recorded is the mean of at least two concordant determinations. The energies of activation are quoted in the last column of Table I and were determined from the slope of the line obtained by plotting log k against $\frac{1}{T}$, the small correction of $\frac{1}{2}RT$ (see Section 1, p. 7.) having been applied. In each case the linear relation between log k and $\frac{1}{T}$ was followed very closely.

TABLE I.

The Base-Catalysed Bromination of Phenyl Alkyl Ketones, R.CH$_2$.COPh.

R	k_{45°	k_{55°	k_{65°	E (cals.)
H	.0520	.131	.330	19,400
CH_3	.00799	.0219	.0567	19,900
C_2H_5	.00624	.0172	.0435	20,200
n-C_3H_7	.00704	.0188	.0479	20,100
iso-C_3H_7	.00305	.00849	.0224	20,500
R.CH_2 = $(CH_3)_2CH$	.00155	.00444	.0119	20,900

In order to facilitate discussion, the results recorded by Evans (loc.cit.) for the acid-catalysed change of the same ketones are given in Table II, which includes the new measurements on isovalerophenone.

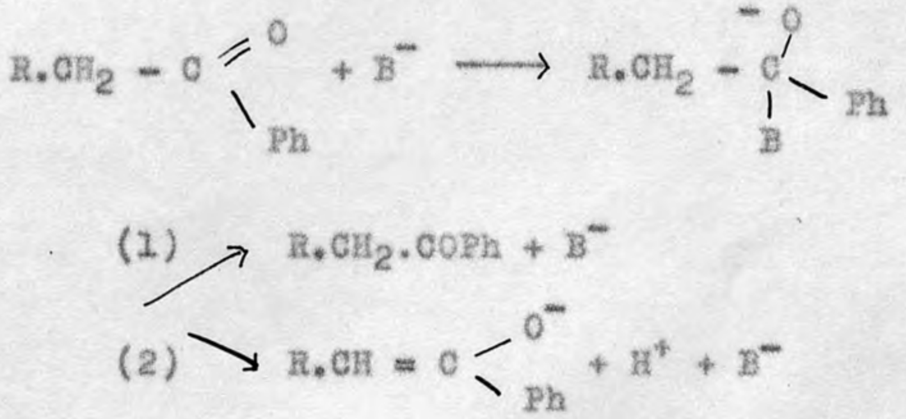
TABLE II.

The Acid-Catalysed Bromination of Phenyl Alkyl Ketones, $R.CH_2.COPh$.

R	k_{25}	k_{35}	k_{45}	E (cals.)	P
H	.241	.739	2.14	20,200	.15
CH_3	.104	.352	1.12	22,100	1.53
C_2H_5	.0721	.244	.774	22,000	.85
n-C_3H_7	.0851	.284	.875	21,700	.59
$CH_2R = CH(CH_3)_2$	.0213	.0728	.231	22,100	.30
iso-C_3H_7	.0335	.112	.347	21,700	.23

In marked contrast to the acid-catalysed change, there is no *sudden* change in activation energy when the protropy of these ketones is studied in basic medium. There is instead a small increment of some 300 to 500 calories in passing from acetophenone to propiophenone and from the latter to n-butyrophenone, but no further change in n-valerophenone. The values of E for n- and isovalerophenone differ by a similar amount, but there is a larger difference (1000 calories) between propiophenone and isobutyrophenone. A further unexpected observation is that the change in E on replacing hydrogen of acetophenone by an alkyl group is in the *same direction* as for the acid-catalysed reaction, although the changes are of distinctly different polar type (Class B and Class A reactions respectively).

In accordance with the views of Watson, Nathan and Laurie (loc.cit.), the mechanism of the reaction is represented:



$$R.CH_2-C(=O)Ph + B^- \longrightarrow R.CH_2-C(O^-)(Ph)B$$

$$(1) \nearrow R.CH_2.COPh + B^-$$

$$(2) \searrow R.CH=C(O^-)Ph + H^+ + B^-$$

the later stages, (1) and (2), being alternative.

Further, it is assumed that the measured energy of activation is that concerned in the addition of catalyst to ketone, whilst changes in the probability factor are due mainly to the variation in the proportion of activated complex (i.e. the semipolar form) which is transferred into enol or enolic ion (cf. Evans, Morgan and Watson, loc.cit., also Section II, p. 57).

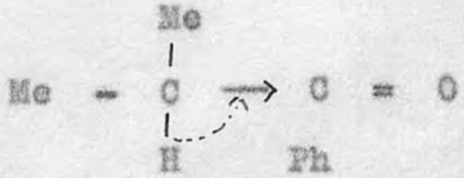
The hydrogen bond postulated by Evans (loc.cit.) provided a satisfactory interpretation of the variations in the energy of activation of the acid-catalysed prototropy of the phenyl alkyl ketones but, as was pointed out in the discussion of the alkaline hydrolysis of o-benzoic esters (Section II, p. 59), the effect of this linkage upon the activation energy of the base-catalysed change will be small. Therefore it is concluded that the gradual rise in activation energy during the base-catalysed prototropy of the phenyl alkyl ketones is to be ascribed to the increasing inductive effect of the alkyl group R,

$$Me < Et < n-Pr \sim n-Bu, \text{ etc.}$$

and the larger increment observed in isovalerophenone and isobutyrophenone is in harmony with this view.

In this connection it is of interest to note that in the acid-catalysed reaction there is equality of the activation energies for propiophenone ($Me.CH_2.COPh$) and isobutyrophenone ($Me_2CHCOPh$). It seems reasonable to suppose that in the latter ketone, although the presence of two β-methyl groups probably increases the tendency for the formation of the hydrogen bond, only one β-carbon can be involved at the same instant, and therefore the influence of this bond upon E will be the same in both ketones. However, it would be expected that the inductive effect of the second β-methyl in isobutyrophenone would lead to a decreased activation energy, and therefore the results lead to the conclusion that there is present some factor which opposes this inductive influence of the second methyl. This factor may be the smaller electron-release from isopropyl than from ethyl, postulated by Baker and Nathan (loc.cit.), since the system appears to be one which might well allow the electromeric changes, represented by broken arrows, to operate in addition to the normal inductive effect.

$\mathrm{Me - \underset{H}{\overset{H}{C}} \rightarrow \underset{Ph}{C} = O}$



$\mathrm{Me - \underset{H}{\overset{Me}{C}} \rightarrow \underset{Ph}{C} = O}$

A similar balancing of inductive and new type of electron-release must account for the equality of the activation energies of n- and isovalerophenone.

An effect in the opposite direction to that of methyl, diminishing in the order

$$Me_3C > Me_2CH > Et,$$

as postulated by Dippy (J.C.S., 1937, 1777), will also account for the equality of the energies under discussion. In the base-catalysed prototropy the reaction is of Class B, in which the new type of electron release functions less powerfully, and hence the inductive effect of the alkyl substituent is the only important factor which causes variation in E. The gradual increase in activation energy as the alkyl chain is lengthened or branched is therefore readily understood on the basis of the inductive effects.

The diagram (Fig. 11), where the values of E are plotted against those of log k_{65}, indicates that the value of the P-factor for the base-catalysed prototropy of all the ketones above acetophenone is almost the same. It is, however, rather less than that found for acetophenone. This contrasts with the variation of P observed in the acid-catalysed prototropy of the same ketones (see Fig. 10) where P increases by a power of ten in passing from acetophenone to propiophenone and then

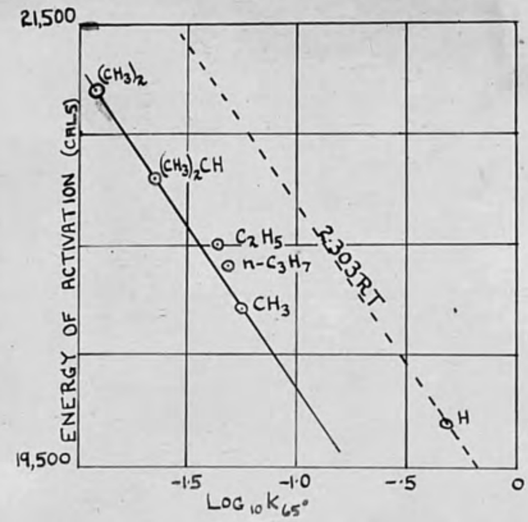
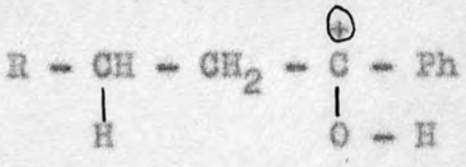

21,500
19,500
ENERGY OF ACTIVATION (CALS)
$(CH_3)_2$
$(CH_3)_2CH$
C_2H_5
$n-C_3H_7$
CH_3
H
2.303RT
-1.5
-1.0
-.5
0
$\log_{10} K_{65°}$

FIG. 11.

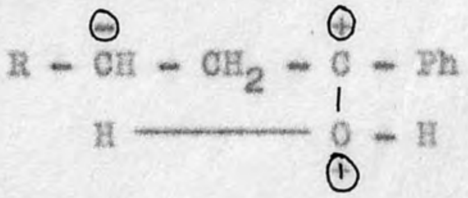
decreases gradually for the higher n-alkyl derivatives but more markedly for the branched chain compounds. These results show that the variation in velocity cannot be ascribed to a bulk effect of the alkyl chain in the first stage of reaction (addition of catalyst) since this would be expected to decrease P in both the acid and the base catalysed process. Further, in the latter case the change in P from acetophenone to propiophenone with the trivial or zero effect in passing to the higher ketones indicates that hydrogen bond formation is again the cause of the variation. It is therefore concluded that the explanation based on geometrical steric hindrance, given by Evans (loc.cit.), for the small continuous fall in P in the acid-catalysed prototropy of higher ketones, is incorrect and should be replaced by the following.

During the catalysed prototropy of the ketones the hydrogen bond is formed simultaneously with the approach of catalyst and reduces the electron availability of the carbonyl oxygen. This causes a high energy of activation for the acid-catalysed prototropy of propiophenone and higher phenyl alkyl ketones, whereas, as pointed out previously, the effect of hydrogen-bond upon E for the base-catalysed change is unimportant. The ketone-catalyst complexes once formed will therefore be resonance hybrids, which include the structures I and II for acid-catalysis and III and IV for base-catalysis.



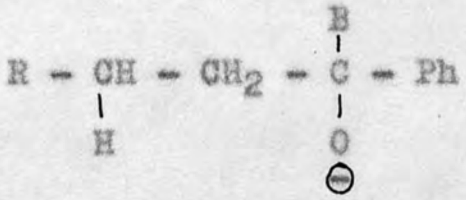
$R-\underset{H}{\underset{|}{CH}}-CH_2-\overset{\oplus}{\underset{O-H}{\underset{|}{C}}}-Ph$

I.



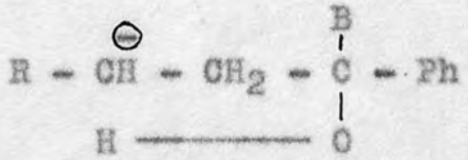
$R-\overset{\ominus}{\underset{H}{CH}}-CH_2-\overset{\oplus}{\underset{\underset{\oplus}{O}-H}{\underset{|}{C}}}-Ph$

II.



$R-\underset{H}{\underset{|}{CH}}-CH_2-\overset{B}{\overset{|}{\underset{\underset{\ominus}{O}}{\underset{|}{C}}}}-Ph$

III.



$R-\overset{\ominus}{\underset{H}{CH}}-CH_2-\overset{B}{\overset{|}{\underset{O}{\underset{|}{C}}}}-Ph$

IV.

In the case of the acid-catalysed change, the complex (Structures I and II) possesses a carbon atom with a deficiency of electrons, and it is reasonable to suppose that the driving force in the transformation of the complex (to enol <u>or</u> the original ketone) is the tendency of this atom to complete its octet. However, the participation of the structure II will militate against the electromeric change

$$C - \overset{+}{C} \overset{\curvearrowleft}{-} O \longrightarrow C - C = O$$

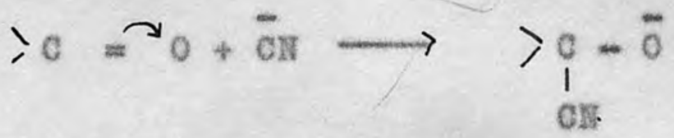
which leads to the ketone. Hence the proportion of complex which is converted into enol is greater in those ketones which allow of a hydrogen bond between β-carbon and carbonyl oxygen; i.e., propiophenone and the higher phenyl alkyl ketones. In addition to this, however, variation in the group R (in $R.CH_2COPh$) will influence the ease with which the α-proton ionises (a necessary step in the formation of enol, but not of ketone), and this accounts for the small but measureable decrease in P in the ketones above propiophenone, and more especially in iso-butyrophenone, which has a second methyl group directly linked to the α-carbon atom. The same explanation holds for the decrease in P in passing from n-valero to isovalerophenone.

The ketone-base complex (Structures III and IV) is of a different character, however. Here the carbonyl carbon is saturated and a tendency towards octet completion does not exist. In fact the electromeric changes leading to enolic or ketonic forms can only occur subsequently to, or simultaneously with, removal of catalyst, and it necessarily follows that any factor tending to facilitate or oppose such removal will affect the formations of both tautomerides to an equal extent. On the other hand removal of α-hydrogen is required only for the production of enolic ion, and therefore the ease of ionisation of the α-proton now becomes the principal factor governing the proportion of enol formed from the complex. In structure IV we have a negative charge on C_β which will definitely oppose ionisation of α-hydrogen and cause a decrease in the P factor. The fall in P in passing from acetophenone to propiophenone is thus explained. Further, the influence of the negative charge on C_β is not neutralised by any neighbouring positive charge (as in II) and is therefore so strong as to make any variation in the inductive effect of further alkyl substituents negligible. This accounts for the constancy of P in the ketones above acetophenone.

The observations of both acid and base-catalysed prototropy of phenyl alkyl ketones thus receive a reasonable interpretation on the basis of the inductive effects of alkyl groups (coupled with that postulated by Baker and Nathan), the interaction of β-hydrogen with carbonyl oxygen to form a hydrogen bond in the ketone-catalyst transition complex, and the mechanism of the change put forward by Watson, Nathan and Laurie.

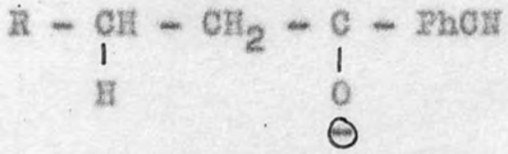
These views, when applied to the relative stabilities of the cyanohydrins of phenyl alkyl ketones, afford an interpretation of the results obtained by Lapworth and Manske (loc.cit.). Hitherto, no explanation of the peculiar variations in stabilities of these compounds has been given. There is a marked increase in stability from acetophenone to propiophenone, followed by a gradual but consistent decrease as the n-alkyl series is ascended (cf. variations in E for the acid-catalysed prototropy of the same ketones).

It has been shown (see p. 79) that in cyanohydrin formation the primary step consists of addition of cyanide ion to the carbonyl carbons,



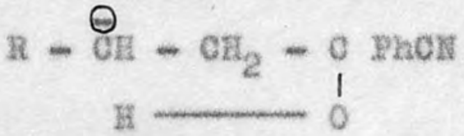
$$>C \overset{\curvearrowright}{=} O + \bar{CN} \longrightarrow >\underset{\displaystyle CN}{\underset{|}{C}} - \bar{O}$$

to form the cyanohydrin ion and, according to the theory outlined above, it is assumed that the ions derived from propiophenone and the higher n-alkyl ketones will be in resonance between the structures V and VI.



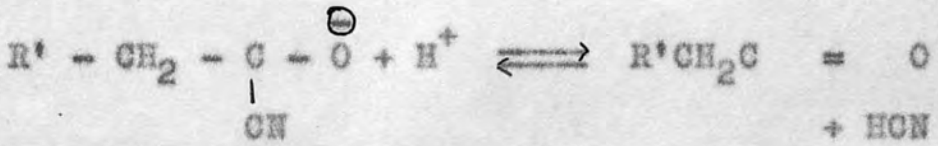
$$R-\underset{\displaystyle H}{\underset{|}{C}}H-CH_2-\underset{\displaystyle O^{\ominus}}{\underset{|}{C}}-PhCN$$

V.



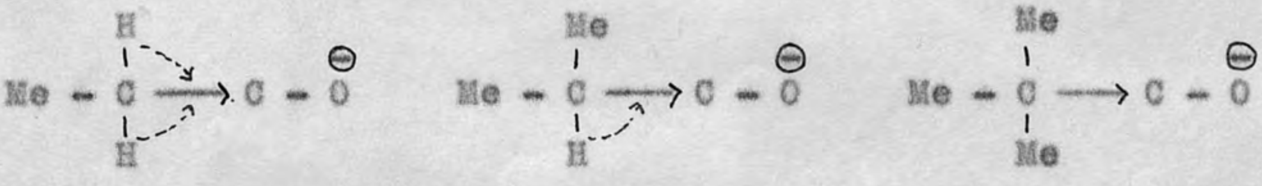
VI.

The participation of VI will then operate against the electromeric change $\curvearrowleft CN - C \curvearrowleft - O^{\ominus}$ necessary for dissociation of the cyanohydrin by the process



$$R'-CH_2-\underset{\displaystyle CN}{\underset{|}{C}}-\overset{\ominus}{O}+H^+ \rightleftharpoons R'CH_2C = O + HCN$$

which accounts for the greater stability of the propiophenone over the acetophenone derivative. The further decrease in stability after propiophenone is due, in all probability, to the increasing inductive effect of R' which facilitates the above electromeric change. On the other hand the marked <u>rise</u> in stability of the cyanohydrins of the series $Me.CH_2.COPh$, $Me_2CH.COPh$, $Me_3C.COPh$ may be attributed to the operation of the Baker-Nathan effect.



In connection with the stabilities of the cyanohydrins it is noteworthy that a similar order of stabilities is not obtained in the dialkyl ketones (Lapworth and Manske, loc. cit.), nor is there a sudden change in the rate of acid-catalysed prototropy of aliphatic ketones (Dawson and Wheatley, J.C.S., 1910, 97, 2048). This points to the conclusion that some factor necessary for hydrogen bond formation is absent in these cases, and the work described below on the alkaline hydrolysis of esters offers a clue to the explanation.

Having thus obtained further knowledge regarding the influence of alkyl groups R upon the base-catalysed prototropy of a series of ketones, $R.CH_2.COPh$, an investigation of the alkaline hydrolysis of the ethyl esters of a number of saturated aliphatic acids was undertaken. The hydrolyses were carried out in 85% aqueous alcohol in exactly the same manner as the work on the substituted ethyl benzoates described in Section II, and analysis of the results by use of the modified Arrhenius equation, $k = PZe^{-E/RT}$, was resorted to, in order to gather the maximum possible information.

The results are tabulated below and include the velocity coefficients (in l./g.-mol.-sec.) at three temperatures for twelve esters, together with the energies of activation obtained from the Arrhenius line, which was accurately followed in each case.

Ethyl ester	$k_{25}\times10^{3}$	$k_{35}\times10^{3}$	$k_{50}\times10^{3}$	E cals.
Acetic	6.21	13.6	38.7	14,200
Propionic	3.63	8.31	24.7	14,500
n-Butyric	1.72	3.94	12.2	15,000
Isobutyric	.801	1.84	5.72	14,500
n-Valeric	1.92	4.42	13.3	14,700
Isovaleric	.427	1.02	3.34	15,700
Methylethylacetic	.308	.735	2.36	15,400
Trimethylacetic	.0254	.0635	.241	16,500
n-Hexoic	2.08	4.81	14.5	14,800
Diethylacetic	.0157	.0409	.154	17,400
n-Heptoic	1.79	4.06	12.7	15,000
n-Octoic	1.84	4.30	13.3	15,000

At a given temperature the velocity coefficients for the alkaline hydrolysis of the ethyl esters of the straight chain fatty acids in 85% alcohol decrease regularly from acetic to n-butyric esters and then remain almost constant to n-octoic ester. Isobutyric ester hydrolyses about four times more slowly than propionic; isovaleric and α-methylbutyric esters are still slower, whilst trimethylacetic and di-ethylacetic esters are markedly slow. Similar results at one temperature have been recorded by Reicher (Annalen, 1885, <u>228</u>, 257 et seq.) and by Kindler (ibid, 1927, <u>452</u>, 90; Ber., 1937, <u>69</u>, 2792).

The plot of E against log k_{25} is shown in Fig. 12, which

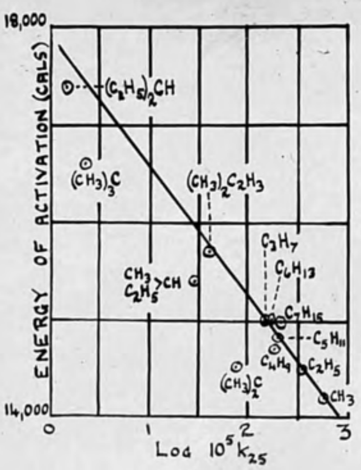

18,000
14,000
ENERGY OF ACTIVATION (CALS)
0
1
2
3
Log $10^5 k_{25}$
$(C_2H_5)_2CH$
$(CH_3)_3C$
$(CH_3)_2C_2H_3$
$CH_3 > CH$ C_2H_5
C_3H_7
C_6H_{13}
C_7H_{15}
C_5H_{11}
C_4H_9
$(CH_3)_2C$
C_2H_5
CH_3

FIG.12.

clearly indicates that on the whole the changes in velocity are due mainly to changes in activation energy. In all esters which are branched at C_{α}, however, there appears to be a definite fall in P. In actual dimension this fall is not considerable (P increases about six-fold in passing from <u>iso</u>-butyric to propionic ester), but in view of the reproducibility of the results (the estimated experimental error in k is ±1.5%) and the remarkable constancy of P for the normal esters, it is held that this decrease must be considered in any interpretation of the results.

The mechanism of the reaction under study has been discussed in Section II, p.57) and for the saturated aliphatic esters is represented as

$$R-C\genfrac{}{}{0pt}{}{/\!\!/ O}{\diagdown OEt} + OH^- \rightleftharpoons R-C\genfrac{}{}{0pt}{}{/ O^-}{\diagdown OEt}-OH \longrightarrow R-CO\bar{O} + Et\,OH$$

The measured energy of activation is again assumed to be that associated with the production of the transition complex, $R-C\genfrac{}{}{0pt}{}{/ O}{\diagdown OEt}-OH$, whilst changes in the non-exponential factor, P, of the kinetic equation are determined very largely by variation of the proportion of this complex which actually yields the reaction products.

On this view, an increase in the electron-repulsion of the alkyl group, R, should cause a rise in the energy of activation for the base-catalysed hydrolysis owing to the tendency to increase the electron density around carboxyl carbon. The gradual rise in E, to a maximum at about n-butyric as the normal series is ascended, is in accord with the increasing inductive influence in the series

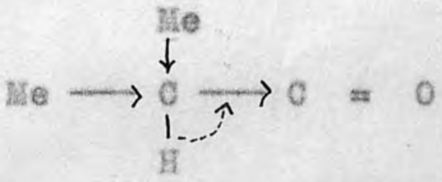
$$\mathrm{Me} < \mathrm{Et} < n\text{-}\mathrm{Pr} < n\text{-}\mathrm{Bu};$$

any further variation in the +I effect in the higher n-esters being too small to be detected. Iso-valeric ester has a value of E greater than that for the normal ester by about 1,000 cals., a result which should be compared with the high energy of activation for the base-catalysed prototropy of iso-valerophenone (compared with that of n-valerophenone), both of which may be accounted for by the higher inductive effect of the isobutyl group in the branched chain than that of the n-butyl group in the straight chain compound.

A noteworthy observation, however, is the equality of the energies of activation for isobutyric and propionic esters. This is especially significant in view of the variations noted above and indicates the total electron-repulsion of the isopropyl group in the former, and the ethyl group in the latter, must be equal in the system under consideration. The equality (a) of the values of E for the acid-catalysed prototropy of isobutyrophenone and propiophenone (Evans, loc.cit.) and (b) the dissociation constants of isobutyric and propionic acids (Dippy, in the press) are results which are completely in harmony with the above observation. The energies of activation found in the present work for the alkaline hydrolysis of the esters R.COOEt, where R is varied, stand in the order

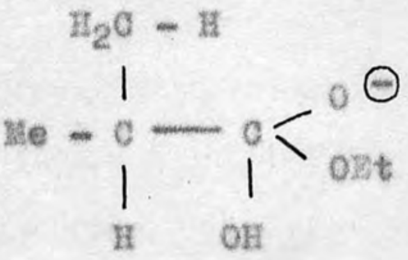
$$CH_3 < MeCH_2 \sim Me_2CH \ll Me_3C;$$

this is in harmony with the order of the dissociation constants of the corresponding acids. It appears reasonable to assume that the same influences are operating in both cases, and for the acids it has already been pointed out by Dippy (loc. cit.) that the results can be explained on the basis of the normal inductive effect together with the new type of electron-release of alkyl groups postulated by Baker and Nathan (loc.cit.). In the esters the increase in the +I effect, when ethyl is changed to isopropyl, is balanced by the decrease in the new type of electron release, so that the total electron repulsion is the same in both groups:-

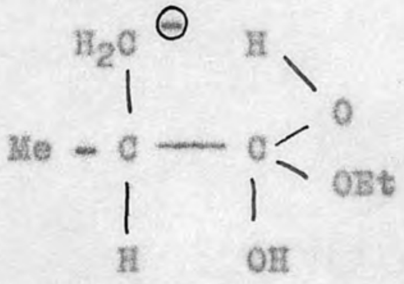


The value of E for ethyl methylethylacetate is not unusually large, but that for ethyl diethylacetate, which is higher than the activation energy for ethyl trimethylacetate by nearly 1,000 cals., is surprisingly high. There appears to be no obvious reason why the inductive effect of Et_2CH- should be higher than that of Me_3C--(it is to be expected that tertiary groups in general have higher inductive effects than secondary groups [cf. Hughes and Ingold, loc.cit., and Hughes, J.A.C.S., 1935, 57, 708]), and there appears to be here some abnormal influence due to the presence of the two ethyl radicles in ethyl diethylacetate. The result is reminiscent of the unusually high strength of diethylaniline (pK_H = 7.09 compared with that of ethyl methyl aniline, 5.98, and of dimethylaniline, 5.06; Hall and Sprinkle, J.A.C.S., 1932, 54, 3469) and also of the low reactivity of diethylaniline with alkyl bromide (Thomas, J.C.S., 1913, 103, 594). Owing to lack of data, however, any attempt at explanation of this peculiarity is not justified at present.

With regard to the variations in the non-exponential factor, P, found in the present work, it has been noted that iso-butyric and trimethylacetic esters have a value of P lower by about one-sixth that of the normal esters. This decrease in the probability factor for the hydrolysis of ethyl isobutyrate, compared with that for ethyl acetate, has previously been indicated by the results of Newling and Hinshelwood (J.C.S., 1936, 1357) for both acid and base-catalysed hydrolysis, and it is now suggested that the smaller P is due to hydrogen bond formation between the β-carbon and carboxyl oxygen, a process which, as shown previously (Section II, p. 59, also this Section, p. 77) may be supposed to take place simultaneously with approach of catalyst to the ester molecule. The transition complex is then a resonance hybrid which includes the forms VII and VIII.



VII.



VIII.

Introduction of the second β-methyl group thus causes a decrease in the tendency for anionisation of ethoxyl (a necessary condition for alkaline hydrolysis, see Section II, p.58), owing to the reduced facility for the electromeric shifts, $\overset{\ominus\searrow}{O} - C \overset{\curvearrowright}{-} OEt$. In the aliphatic esters it appears that branching at the α-carbon is essential for formation of the hydrogen bond in the transition complex, a condition which suggests the necessity for restricting the movement of the carbon atom concerned in the bond. In the phenyl alkyl ketones and the ortho-substituted benzoic esters (Section II) this restriction is obtained by the presence of the benzene nucleus. In the former, the phenyl occupies one position on the carbonyl carbon, thus restraining the movement of the alkyl chain, whilst in the benzoic esters the ortho group is similarly restricted in its movement in space by the nuclear linkage with carbethoxyl. Given the necessary damping of the oscillation of the alkyl chain, the lower potential energy of the resonance structure (compared with that of the normal form as in formulae I, III, V and VII) will cause the complex to take up the ring structure, which will be retained until further transformation to products or reactants occurs.

As a result of the participation of VIII in the resonance hybrid, the negative charge (partial) on the β-carbon will outweigh any effect due to the small variations in the inductive influence of the group R (i.e. R.COOEt). Hence the P factor for isobutyric is the same as that for trimethylacetic ester (the points for these two compounds in Fig. 12 lie on a line which runs parallel to the line through the point for ethylacetate with slope -2.303RT). In methylethylacetic and diethylacetic esters, however, there is a distinct tendency for P to increase from the lower to the value associated with the n-aliphatic esters. The explanation for this is not certain, but it may be due to a smaller tendency <u>in this system</u> for hydrogen bond formation in β-methylene [as in $(CH_3CH_2)_2CH.COOEt$] than in β-methyl [as in $(CH_3)_2CH.COOEt$].

The formation of a hydrogen bond appears to be necessary for a complete explanation of the results recorded above. The effect referred to by Baker and Nathan (loc.cit.), although capable of interpreting the changes in energies of activation, is not sufficient to account for the peculiar variations in the non-exponential factor, P, of the kinetic equation. The presence of a hydrogen bond in the ketone-catalyst or ester-catalyst complex may be regarded as probable for the following reasons:-

(i) The position of the β-hydrogen with respect to carboxyl oxygen appears to be such as to make interaction easy.

(ii) The sudden rise in E from acetophenone to propiophenone in the acid-catalysed prototropy is unparalleled throughout the investigation and requires some powerful influence to explain its occurrence.

(iii) The hydrogen bond would be expected to influence the E in the acid-catalysed change but not in the base-catalysed reactions - an expectation which is quite in harmony with the observations that the activation energies in the latter process fall in the anticipated order of electron repulsion.

(iv) The hydrogen bond offers a reasonable explanation of the rise in P from acetophenone to propiophenone in the acid-catalysed prototropy, as opposed to the fall in the base-catalysed change.

In all the transition complexes described in this section, the postulated hydrogen bond leads to the formation of a five-membered "chelate ring", whereas in the transition complex in the alkaline hydrolysis of ethyl o-toluate, the ring formed has six members. However, in the case of the complexes formed by the catalyst with a phenyl alkyl ketone or a saturated aliphatic ester, the rings contain single bonds only, whilst in the o-toluic ester complex the "chelate ring" possesses either one or <u>two</u> bonds which approximate in nature to double bonds. This difference will be reflected in the natural valency angles (of which, unfortunately, we have no precise knowledge in the cases cited), and the electron-donating oxygen will react with the hydrogen atom which is most favourably placed.

EXPERIMENTAL

PREPARATION OF MATERIALS

Esters.

Ethyl benzoate, m-aminobenzoate, acetate, propionate, isobutyrate, n-butyrate, caproate, isovalerate, heptoate and octoate were all purchased (ethyl benzoate from Messrs. Hopkin & Williams, ethyl acetate from Messrs. Boots and the others from Messrs. British Drug Houses), and purified by repeated distillation. The boiling points of the purified esters are recorded below:

Ethyl benzoate, 103°/20 mm. (Perkin, J.C.S., 1896, 69, 1174, gives 211.7°-211.9°/760).

" m-aminobenzoate, 144°/5 mm. (Müller, Ber., 1886, 19, 1494, gives 294°/760).

" acetate, 77°/760 mm. (Young and Fortey, J.C.S., 1903, 83, 47, give 77.2°).

" propionate, 98°/760 mm. (Linemann, Annalen, 1871, 160, 219, gives 98.8°).

" n-butyrate, 120°/760 mm. (Schiff, Annalen, 1883, 220, 111, gives 120°).

" isobutyrate, 110°/760 mm. (Schiff, ibid, b.p. 110°).

" isovalerate, 134.1°/760 mm. (Schumann, Ann. der Phys., 1881, NF12, 42, gives b.p. 134.3°).

" caproate, 165°/760 mm. (Lieben, Rossi, Annalen, 1873, 165, 122, give 166°).

" heptoate, 114°/80 mm. (Henry, Rec.Trav.Chim., 1905, 24, 362, gives 187°-188°/760).

Ethyl octoate, 104°/80 mm. (van Renesse, Annalen, 1874, 171, 382, gives 207°-208°/753).

Ethyl o- and m-chlorobenzoate, o- and m-methylbenzoate, o-aminobenzoate, n-valerate and diethyl-acetate were all prepared by esterification of the corresponding acid by the Fischer-Speier method. In the case of the o- and m-chloro- and o- and m-methyl-benzoic acids, 50 gms. of the acid were dissolved in 100 g. of absolute alcohol and 12.5 c.c. of strong sulphuric acid added. The mixture was refluxed on a water-bath for a certain time, the times required for esterification in the individual cases being as follows:-

m-chloro- and m-methylbenzoic acids, 6 hours,

o-chloro- and o-methylbenzoic acids, 9 hours.

In the case of the o-aminobenzoic, n-valeric and diethylacetic acids, which are more difficult to esterify, 50 g. of the acid were dissolved in 200 g. absolute alcohol and refluxed with 25 c.c. of concentrated sulphuric acid. The times required were:- o-aminobenzoic acid, 50 hours; n-valeric acid, 30 hours; diethylacetic acid, 24 hours.

After refluxing, the solution in each case was cooled and poured into four times its volume of water, neutralised with washing soda and finally extracted with ether. The ethereal solution of ester was dried over anhydrous sodium sulphate and the ether removed. Finally, the ester was purified by fractionation at reduced pressure at least three times. The yield in each case was 90% of the theoretical, calculated on the amount of organic acid employed; in the case of the amino-ester, however, the yield was only 50%. The boiling points of the pure esters are given in the following table:-

Ethyl *o*-chlorobenzoate, 130°/20 mm. (Glutz, Annalen, 1867, *143*, 196, gives 243°/760).

" *o*-methylbenzoate, 110°/17 mm. (Perkin, J.C.S., 1896, *69*, 1177, gives 227°/760.

" *m*-chlorobenzoate, 121°/20 mm. (Limpricht, v.Ulsar, Annalen, 1857, *102*, 262, gives 245°/760).

" *m*-methylbenzoate, 110°/20 mm. (Perkin sen., J.C.S., 1907, *91*, 845, gives 231°/750).

" *n*-valerate, 145°/760 mm. (Lieben, Rossi, Annalen, 1873, *165*, 117, give 145°/760).

" diethylacetate, 151°/760 mm. (Saizew, Annalen, 1878, *193*, 352, gives 151°).

" o-aminobenzoate, 105°/5 mm. (O.Schmidt, Ber., 1903, *36*, 2476, gives 137.5°-138°/13mm.).

Ethyl *o*-, *m*- and *p*-nitrobenzoates were purchased from Messrs. British Drug Houses and purified by a series of recrystallisations from 70% alcohol. In the case of the low-melting *o*-nitro ester, solution was made in alcohol at 30° and then cooled in a freezing mixture. In each case the crystals, after filtering off, were dried by standing over calcium chloride in a vacuum desiccator for a few days. The following were the melting points obtained:

o-Nitrobenzoate - snow-white needles - had m.p. 30.5°.
(Beilstein, Kuhlberg, Annalen, 1872, 163, 137, give 30°).

m-Nitrobenzoate - pale yellow transparent plates - had m.p. 42°.
(Tafel, Enoch, Ber., 1890, 23, 1551, m.p. 43°).

p-Nitrobenzoate - pale yellow flakes - had m.p. 57°.
(Wilbrand, Beilstein, Annalen, 1863, 128, 262, give 57°).

Ethyl-o-fluorobenzoate.

The o-fluorobenzoic acid was first prepared from anthranilic acid, according to the Baltz-Schiemann method previously employed by Dippy and Williams (J.C.S., 1934, 1466). 250 C.c. of 10% hydrochloric acid were added to 60 g. of anthranilic acid in 200 c.c. of water. The mixture was kept below 0°, whilst an aqueous solution containing 30 g. of sodium nitrite was added gradually with vigorous stirring. After complete addition of nitrite the solution was kept cool for about half an hour and was then poured gradually, with constant stirring, into 96 g. of 40% hydrofluoboric acid solution. The precipitate of diazonium borofluoride, which formed on standing, was filtered off, collected and dried for three weeks in a vacuum desiccator over calcium chloride. About 500 g. of anthranilic acid was treated in this way in batches of 60 g. each. The borofluoride was decomposed as follows:- a 2-litre r.b. flask fitted with a long vertical condenser was placed in an oil-bath maintained at 125°C. and the borofluoride added in small amounts at a time. On completion of the decomposition, the tarry residue in the flask was extracted by boiling with aqueous sodium carbonate solution and filtering. The filtrate was acidified with hydrochloric acid and on cooling crystals of o-fluorobenzoic acid were deposited. The crude acid was boiled with water containing animal charcoal and on filtering and cooling white crystals of pure o-fluorobenzoic acid were obtained having m.p. 126° (Dippy and Williams (loc.cit.) gave 126.5°). The acid was then esterified by the method of Fischer and Speier under the same conditions as those described for the o-chloro-acid. Yield, 15%, calculated on the amount of anthranilic acid used. The ester, after being purified by fractionation, had b.p. 105°/10 mm.

Ethyl p-fluorobenzoate was prepared according to the method of Schiemann and Winkelmüller (Organic Syntheses, Vol. XIII, p. 52). 60 G. of ethyl p-aminobenzoate were dissolved in a solution of 110 c.c. of concentrated hydrochloric acid in 260 c.c. of water, and 30 g. of sodium nitrite in aqueous solution gradually added to the cooled liquid. After complete addition, the diazotised solution was added to 75 g. of 40% hydrofluoroboric acid solution, as in the previous case, and the precipitate collected and dried rigorously. This was then decomposed in the manner described in the preparation of o-fluobenzoic acid. The product was steam distilled and the p-fluoro-ester isolated from the distillate by extraction with ether. On distillation under reduced pressure a colourless oil was obtained, boiling at 105°/30 mm., which formed transparent plates melting at 26° (Dippy and Williams, loc.cit., give m.p. 26°). Yield, 25% theoretical, calculated on the amount of ethyl p-aminobenzoate.

Ethyl trimethylacetate.

Trimethylacetic acid was first obtained by the method of Puntambeker and Zoëllner (Organic Syntheses, Coll. vol., p.510). The Grignard reagent formed from 116 g. of tertiary butyl chloride and 31 g. of magnesium in 650 c.c. anhydrous ether was treated with carbon dioxide under pressure until saturated, and the resulting solution was decomposed with 25% aqueous sulphuric acid. The main bulk of organic acid was frozen out of solution and filtered off, and the remaining liquor was distilled until no more oily liquid came over. The distillate was salted out and the organic acid extracted with ether. The main bulk of the acid was added to the ethereal solution which was dried by standing in contact with calcium chloride. On removal of the solvent the crude acid remained, which on distillation gave 53 gm. of trimethylacetic acid, boiling at 162°-165° (Puntambeker and Zoëllner, loc.cit., give b.p. 162°-165°). Yield of pure acid, 52%, calculated on the amount of tertiary-butyl chloride. A 40 g. sample of the acid was then esterified, using the same conditions as for o-aminobenzoic acid. The ester was purified by redistillation at ordinary pressure, which gave a colourless liquid of boiling point 119°/760 mm. (Butlerow, Annalen, 1874, 173, 379, gives b.p. 118.5°/760 mm.). Yield of pure ester, calculated on the amount of trimethylacetic acid, 60%.

Methylethylacetic acid was prepared from diethyl methylethylmalonate (cf. Conrad, Bischoff, Annalen, 1880, 202, 151). The malonic ester was hydrolysed with 56% potassium hydroxide solution containing twice the required quantity of KOH. The resulting solution was neutralised and the acid isolated as its calcium salt. The calcium salt was then decomposed with strong hydrochloric acid and the acid extracted with ether. The ethereal solution was dried, the solvent distilled off and the dicarboxylic acid was then heated to 130° to drive off carbon dioxide. The remaining mono-carboxylic acid was distilled over and the fraction, of b.p. 173°, was collected. This was esterified in the same way as described for trimethylacetic acid. Yield of ester from 23 g. of acid, 70%. The pure ester had b.p. $132^{\circ}/760$ mm. (Pagenstechen, Annalen, 1879, 195, 120, gives b.p. $133.5^{\circ}/760$).

Ketones.

Acetophenone was purchased and was purified by freezing out several times, and finally distilling under reduced pressure. The pure substance formed transparent plates, m.p. 19.6 (Evans, Morgan and Watson, J.C.S., 1935, 1172, give m.p. 19.6).

Propiophenone.

For a sample of this compound the author is indebted to

Dr. D. P. Evans. On being recrystallised from petrol ether and distilled at 30 mm. it gave a colourless oil freezing to transparent plates, m.p. 18.5° (Evans, J.C.S., 1936, 788, m.p. 18.6°).

n-Butyrophenone.

This was prepared by the Friedel-Crafts process from n-butyryl chloride. The acid chloride was first prepared by adding 38 g. of the acid very gradually to 47 g. of thionyl chloride, placed in a distilling flask fitted with a reflux condenser. On complete addition the mixture was refluxed for about half an hour and then distilled twice, the fraction having b.p. 100°-102° being collected.

25 G. of the acid chloride were then added gradually to a mixture of 30 g. of dry powdered aluminium chloride, 34.5 g. of dry benzene and 125 g. of freshly-distilled carbon disulphide, in an apparatus protected from moisture. On complete addition, the reaction mixture was heated to drive off all hydrogen chloride fumes, and the carbon disulphide was then distilled off. The residue was cooled and thrown into a mixture of 200 c.c. of concentrated hydrochloric acid and crushed ice. After vigorous stirring, the oily layer was separated, the aqueous layer extracted with ether, and the ethereal extract added to the oil. The ethereal solution was washed with water twice, with 10% caustic soda three times and finally with water three times. It was then dried over

calcium chloride. On removing the ether and distilling several times under reduced pressure, the ketone was obtained as a colourless oil which, when frozen out, gave white plates, having m.p. 12.0° (Evans, loc.cit., gives m.p. 12.2°). Yield, 65% of theoretical, calculated on the amount of acid chloride.

Isobutyrophenone.

This was prepared from isopropyl bromide and benzonitrile. The Grignard reagent formed from 10 g. of magnesium and 47 c.c. isopropyl bromide in 250 c.c. of anhydrous ether was treated with 22 c.c. of benzonitrile dissolved in 50 c.c. of anhydrous ether, and the mixture was refluxed for six hours. The compound was then hydrolysed by the addition of 25% sulphuric acid and the ether layer run off. The crude ketone was isolated by distillation, and any possible traces of benzonitrile present in the ketone were removed by first fractionating at low pressure and then refluxing the distillate for about two hours in 33% sulphuric acid. The ketone was isolated by making the solution alkaline with caustic soda and steam-distilling. Finally, purification of the isobutyrophenone was effected by several distillations in vacuo, which yielded a colourless oil, b.p. 120°/32 mm. (Evans, loc.cit., gives b.p. 97.5°/10 mm.). Yield, 40% theoretical, calculated on the amount of alkyl chloride.

<u>Isovalerophenone</u> was prepared from isobutyl bromide and benzonitrile in the same manner as isobutyrophenone. Purification by repeated distillation in vacuo gave a colourless oil, b.p. 126°/20 mm. Yield, 40%.

<u>n-Valerophenone</u> was similarly prepared in 45% yield from n-butyl chloride and benzonitrile. The pure substance was a colourless oil, b.p. 120°/9 mm. (Evans, loc.cit., 130°/16 mm.).

<u>Reaction Medium for Hydrolyses.</u>

The medium used throughout for the alkaline hydrolysis of esters consisted of 85% aqueous ethyl alcohol by weight, and was made up as follows:- Rectified spirit was first shaken vigorously with freshly-precipitated silver oxide, the mixture was filtered and the filtrate was allowed to stand over freshly-baked lime for a few weeks. The alcohol was then distilled off in an apparatus guarded from moisture by tubes filled with calcium chloride. The silver oxides removes impurities such as aldehydes, etc. by oxidising them to acids, and the lime removes acids and water. The exact composition of the alcohol was determined by a density measurement and the alcohol was then diluted to the required concentration by adding conductivity water, which was kindly provided by Mr. J. E. Page, B.Sc. The composition of the medium was finally checked by another density determination. Using this procedure it was possible to reproduce the medium with sufficient accuracy. The density values for the different batches of aqueous alcohol used in the velocity determinations being as follows:-

d_4^{20} = .83140 (84.8%)

d_4^{20} = .83130 (84.85%)

d_4^{20} = .83090 (85.02%)

d_4^{20} = .83050 (85.20%)

The medium was used at each temperature, the correction for expansion of solvent being neglected since it is comparatively small.

Hydrolysing solution.

The hydrolysing agent employed consisted of $\frac{N}{5}$ caustic soda, made up in the medium. "Analar" caustic soda was dissolved in the alcoholic medium in the required proportion and the solution filtered once through a sintered glass funnel to remove cloudiness. The alkali was accurately standardised at each temperature immediately before use.

$\frac{N}{15}$ hydrochloric acid solution was made up from constant boiling hydrochloric acid and standardised against $\frac{N}{20}$ caustic soda solution.

$\frac{N}{20}$ caustic soda solution.

This solution was made from "Analar" caustic soda pellets and stored in a 12-litre aspirator fitted with soda-lime tubes.

A burette having a two-way tap was employed in the titrations. The caustic soda solution was standardised against $\frac{N}{20}$ hydrochloric acid, which had been standardised gravimetrically by precipitation as silver chloride.

Determination of the velocities of alkaline hydrolysis of esters.

The three thermostats employed were set at 25°, 35° and 50° respectively and were kept to within ±05° of these temperatures by means of toluene-gas thermo-regulators. It was decided to study the reaction as a bimolecular one and not as pseudo-unimolecular, as was done by Ingold and Nathan (J.C.S., 1936, 222). In all measurements the concentrations of the two reactants were made exactly equivalent, so that the value of k_2 is given by

$$k_2 = \frac{1}{t} \cdot \frac{x}{a(a - x)}$$

Procedure.

The required weight of ester (calculated from the strength of the $\frac{N}{5}$ caustic soda solution) was weighed into a 100 c.c. standard stoppered flask and placed in the thermostat. The ester was made up to 75 c.c. with the reaction medium. After standing for a short time, until thermal equilibrium was attained, 25 c.c. of $\frac{N}{5}$ caustic soda (made up in the medium at the temperature of the bath) were added and the solution shaken vigorously. Zero time was taken at half delivery of the caustic soda solution. At measured intervals 10 c.c. samples of the reaction mixture were removed with a pipette and run into 10 c.c. of $\frac{N}{15}$ hydrochloric acid to arrest the reaction. The excess acid was then titrated with $\frac{N}{20}$ caustic soda solution, using bromothymol blue as indicator. Each end point in a run was matched against a colour standard consisting of 15 c.c. of a freshly prepared sodium benzoate solution in 15 c.c. of 50% aqueous alcohol containing the same amount of indicator as used in the titration. The accuracy of the velocity coefficients is estimated as ±1.5%, except in the case of the rapid reactions of the nitro-benzoic esters. In every case the Arrhenius straight line was followed closely. Owing to the rapidity with which the m- and p-nitrobenzoic esters are hydrolysed, measurements at 50° were impracticable. The velocity coefficients are expressed as l/g.-mol.-sec.

Indicator.

The selection of a suitable indicator for the titration of the weak organic acids in alcoholic solution presented some difficulty. A weak organic acid requires an indicator changing at a pH value of about 7-8. At the same time it is essential that the indicator should be unaffected as far as possible by atmospheric or other carbon dioxide. Another factor which had to be considered was the effect of the presence of alcohol on the end-point. The following is a list of indicators which were considered:-

	Indicator	p-H range
1.	Lacmoid	4-6
2.	Bromocresol green	3.2 - 5.2
3.	Methyl red	5-7
4.	Cresol red	7-9
5.	Phenol red	6-8
6.	Phenolphthalein	5.5 - 7.5
7.	Bromothymol blue	6-8

Of the above 1, 2 and 3 were rejected as being useless in titrating weak acids. A practical comparison was made of the last four, as follows:- 10 c.c. samples of $\frac{N}{30}$ aqueous benzoic acid solution were titrated with $\frac{N}{20}$ aqueous alkali in the presence of each indicator. The operation was repeated in the presence of 33% alcohol, and the two sets of results were compared. Phenolphthalein was found to give slightly high results in the presence of alcohol; cresol red showed a tendency to be affected by carbon dioxide on standing, thus making it rather difficult to match end-points. Both bromothymol blue and phenol red, however, were found to give accurate results in both water and alcoholic solution. Bromothymol blue was finally chosen because the intermediate shades of green at the end-point are more easy to detect than the reddish-violet of phenol red.

Determination of the velocities of base-catalysed prototropy of ketones.

Medium.

The medium used for these measurements consisted of 75% (by volume) of aqueous acetic acid, containing 20 g. of sodium acetate per litre as basic catalyst, and was made up separately at each temperature. Acetic acid was first purified by the method of Orton and Bradfield (J.C.S., 1927, 983), by standing for twelve hours over chromic oxide in the presence of a little acetic anhydride (to remove moisture); after heating the mixture gently for an hour, the acid was distilled through a column. 750 C.c. of pure acetic acid (at the bath temperature) were poured into a litre graduated flask containing 20 g. of sodium acetate dissolved in some conductivity water. The flask was then immersed in the thermostat and filled up to the mark with conductivity water. The medium was stored in Winchester bottles immersed in the thermostats.

Bromine.

A B.D.H. specimen of A.R. quality was shaken three times with distilled water and allowed to stand for several hours under pure concentrated sulphuric acid; after separation it was distilled in an all-glass apparatus, neglecting head and tail fractions (cf. Watson, J.C.S., 1925, 2067).

Measurements.

The technique used was the same as that described by

Morgan and Watson (J.C.S., 1935, 1174). The ketone (.1M) was weighed into a clean, dry 100 c.c. flask and the solution made up to approximately 90 c.c. with medium at the required temperature. The flask was then filled up to the mark with a solution of bromine in the medium at the bath temperature, of concentration approximately .05M (to become .005M in reaction mixture). The solution was shaken vigorously and allowed to stand in the thermostat. The reaction was followed by removing 20 c.c. samples of the liquid at measured intervals and running into excess aqueous potassium iodide solution, containing about 50% excess potassium iodide over that required for complete removal of the free bromine, and 20 c.c. of $\frac{N}{4}$ hydrochloric acid. The latter was added to neutralise the sodium acetate present in solution. The liberated iodine was finally titrated with $\frac{N}{50}$ thiosulphate solution, using starch solution as indicator. In those cases where the bromoketone is not very soluble, as in the higher ketones, it was found necessary when approaching the end-point to add 5 c.c. of carbon tetrachloride and shake vigorously, in order to liberate particles of iodine which had become adsorbed by the globules of bromo-ketone. The velocity coefficients of the bromination experiments are expressed as fall of $\frac{N}{50}$ thiosulphate titre per minute for 20 c.c. of .1M-ketone solution.

RESULTS.

VELOCITY DATA FOR ALKALINE HYDROLYSIS OF ESTERS

Ethyl Benzoate

(HCl = .0711N; NaOH = .0506N)

	Time secs.	Titre	k_2x10^3	Time secs.	Titre	k_2x10^3	Time secs.	Titre	k_2x10^3
50°	(a = .04910)			(a = .0482)			(a = .0482)		
	1,065	6.80	6.30	1,770	7.87	6.38	1,200	7.05	6.26
	2,205	8.21	6.06	2,410	8.60	6.46	2,460	8.60	6.31
	2,820	8.86	6.30	3,270	9.26	6.30	3,060	9.11	6.31
	3,610	9.44	6.27	3,900	9.68	6.30	3,780	9.51	6.29
	4,570	10.00	6.23	4,500	9.99	6.24	4,560	10.05	6.29
	5,850	10.58	6.30	6,500	10.82	6.21	5,640	10.40	6.06
35°				(a = .04837)					
	3,600	6.66	1.69	6,960	7.96	1.69	3,600	6.68	1.71
	5,520	7.46	1.70	10,800	8.50	1.73	7,200	8.01	1.68
	7,380	8.05	1.67	12,480	9.32	1.68	9,000	8.50	1.66
	9,660	8.60	1.62	14,700	9.65	1.64	11,040	9.00	1.68
	13,620	9.43	1.63	15,900	9.81	1.63	12,960	9.37	1.68
	15,480	9.72	1.66	19,020	10.21	1.61	15,720	9.80	1.65
25°				(a = .04854)					
	10,800	6.85	.635	10,800	(20) * 20.85	.622			
	14,100	7.32	.624	14,280	7.33	.619			
	16,200	7.59	.618	21,720	8.18	.609			
	18,240	7.90	.634	23,280	(20) 22.52	.640			
	21,600	8.23	.620	25,800	(20) 22.72	.625			
	24,660	8.53	.618	29,880	9.00	.622			

k_2 (50) = 6.28×10^{-3}
k_2 (35) = 1.68×10^{-3}
k_2 (25) = $.621 \times 10^{-3}$

* The (20) means that 20ml. of acid were used to arrest reaction instead of 10ml., as usual.

Ethyl o-chlorobenzoate

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
50°		(a =	.04818)					(a =	.04967)
		NaOH =	.0506N;	HCl	= .0711			HCl =	.0686N
	912	7.65	11.3	910	7.60	10.9	897	7.08	11.6
	1,517	8.88 (20)	11.5	1,297	8.41	11.0	1,967	8.88	11.2
	1,962	23.54	11.6	2,047	9.50 (20)	11.1	2,287	9.18	10.9
	2,472	9.91 (20)	11.0	2,317	24.83	11.0	2,612	9.49	10.9
	3,042	24.39 (20)	10.7	2,777	10.18	10.9	2,897	9.79	11.2
	4,212	25.10	10.9	3,217	10.50	10.8	3,212	9.98	10.9
35°	(a	=	.5000)			(a =	.04993)		
	HCl	=	.0688N			HCl =	.0686N)		
	2,340	6.50	3.36	3,605	7.44	3.41	2,762	6.95	3.50
	3,610	7.52	3.47	4,560	8.03	3.45	4,657	7.99	3.32
	4,920	8.15	3.31	5,460	8.42	3.43	5,297	8.39	3.35
	5,710	8.51	3.31	6,150	8.76	3.34	6,360	8.83	3.43
	7,500	9.11	3.26	7,290	9.09	3.28	7,650	9.29	3.44
	10,220	9.96	3.38	8,820	9.53	3.30	9,550	9.70	3.28
25°	(a	=	.0502)	HCl	=	.0688			
	6,120	6.65	1.40	5,700	6.50	1.39			
	7,800	7.29	1.47	7,200	7.00	1.40			
	9,480	7.61	1.38	9,130	7.53	1.39			
	11,950	8.15	1.37	10,800	7.93 (20)	1.39			
	14,430	8.60 (20)	1.36	13,620	22.10	1.40			
	16,920	22.55	1.35	16,200	8.88	1.39			

k_2 (50) = 11.0×10^{-3}

k_2 (35) = 3.38×10^{-3}

k_2 (25) = 1.39×10^{-3}

Ethyl o-methyl-benzoate

HCl = .0686N; NaOH = .0506N

	Time secs.	Titre	k_2x10^3	Time secs.	Titre	k_2x10^3	Time secs.	Titre	k_2x10^3
50°	(a = .0497)			(a = .0487)					
	9,900	6.84	.819	4,460	5.40	.825			
	13,140	7.51	.827	11,100	7.02	.815			
	14,640	7.72	.812	15,120	7.52	.801			
	18,000	8.21	.803	20,670	8.15	.800			
	19,380	8.42	.808	28,410	9.00	.806			
	20,610	8.50	.785	86,295	11.18	.731			
35°	(a = .0499)						(a = .0494)		
	49,740	7.02	.205	19,740	5.32	.206	34,500	6.55	.231
	54,900	7.29	.198	24,780	5.67	.208	86,460	8.39	.209
	61,740	7.50	.205	31,110	6.10	.208	103,020	8.82	.209
	69,840	7.81	.206	86,760	8.22	.196	109,110	9.00	.212
	74,940	7.96	.204	103,380	8.70	.200	119,130	9.10	.203
	80,400	8.18	.208	111,060	8.85	.198	212,430	10.35	.195
25°	(a = .0502)			(a = .0496)					
	68,280	5.76	.0793	96,060	6.41	.0781			
	100,680	6.45	.0783	144,780	7.24	.0769			
	155,820	7.44	.0796	247,380	8.44	.0749			
	192,600	7.92	.0787	495,900	10.15	.0765			
	241,200	8.40	.0764	577,740	10.48	.0764			
	591,240	10.50	.0759	596,760	10.60	.0786			

k_2 (50) = .809 x 10^{-3}
k_2 (35) = .207 x 10^{-3}
k_2 (25) = .0776 x 10^{-3}

Ethyl o-nitrobenzoate

	Time secs.	Titre	$k_2 \times 10^3$	Time secs.	Titre	$k_2 \times 10^3$
50°	HCl = .0686N;			NaOH = .0506N		
	(a = .04870)					
	292	7.33	38.4	132	5.72	35.5
	452	8.38	39.2	257	7.15	40.2
	592	9.05	39.5	612	9.13	39.7
	732	9.53	38.9	792	9.68	38.5
	852	9.83	38.2	972	10.12	38.1
	1,032	10.21	38.3	1,212	10.53	37.9
35°	(a = .0494)					
	610	6.52	12.9	702	6.85	13.2
	910	7.35	12.8	1,002	7.65	12.9
	1,215	8.00	12.6	1,322	8.20	12.6
	1,510	8.50	12.2	1,692	8.79	12.6
	1,810	8.96	12.6	2,112	(20) 22.82	12.3
	2,290	9.42	12.1	2,712	9.80	12.0
25°	(a = .0496)					
	HCl = .0686N			HCl = .0668N		
	580	5.20	6.03	560	4.70	5.49
	1,390	6.48	5.47	1,210	5.81	5.43
	2,230	7.42	5.42	2,110	6.91	5.33
	2,760	7.88	5.32	2,675	7.42	5.24
	3,550	8.45	5.23	3,300	7.95	5.30
	5,410	9.39	5.05	5,440	8.98	4.92

$k_2\ (50) = 38.8 \times 10^{-3}$

$k_2\ (35) = 12.75 \times 10^{-3}$

$k_2\ (25 \doteq 5.41 \times 10^{-3}$

Ethyl m-nitrobenzoate

$HCl = .0667N$; $NaOH = .0506N$

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
35°			(a = .0490)			
	133	7.24	96.4	130	7.31	101
	193	8.20	99.6	253	8.91	102
	258	8.83	96.9	368	9.95	111
	528	10.44	97.8	493	10.39	102
	608	10.72	98.5	608	10.82	104
25°			(a = .0492)			
	188	6.26	43.7	128	5.55	43.5
	373	7.76	43.2	253	6.86	43.2
	548	8.74	44.2	368	7.68	42.4
	733	9.38	43.2	553	8.70	43.0
	908	9.80	42.0	728	9.36	43.1
	1,093	10.20	42.2	913	9.80	41.7
	1,268	(20) 23.68	42.2	1,213	10.40	42.0

k_2 (35) = 100×10^{-3}

k_2 (25) = 42.9×10^{-3}

Ethyl p-nitrobenzoate

HCl = .0667N; NaOH = .0506N

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
35°			(a =	.04921)		
	68	6.91	164	70	6.80	161
	133	8.42	159	133	8.44	160
	188	9.40	170	188	9.40	170
	253	10.00	165	253	10.02	166
	375	10.70	158	373	10.80	166
25°			(a =	.0483)		
	113	6.28	70.3	128	6.55	71.1
	253	8.10	71.9	253	8.10	71.9
	368	9.05	73.7	368	8.98	71.6
	733	10.45	73.8	493	(20) 22.85	72.3
	908	10.80	68.6	628	10.11	68.7

k_2 (35) = 162×10^{-3}

k_2 (25) = 72.0×10^{-3}

Ethyl o-fluorobenzoate

HCl = .0667N; NaOH = .0506N

	Time secs.	Titre	k_2x10^3	Time secs.	Titre	k_2x10^3
50°	(a = .0476)					
	312	6.02	21.4	240	5.70	22.6
	680	7.56	21.1	570	7.20	21.2
	890	8.24	21.3	840	8.06	20.6
	1,460	9.36	20.8	1,150	8.80	20.8
	1,900	9.85	20.6	1,425	9.30	21.1
	2,415	10.15	19.0	1,690	9.64	21.1
35°	(a = .0479)					
	940	5.81	6.28	990	5.87	6.20
	1,830	7.13	6.42	2,800	7.86	5.77
	2,940	7.97	5.86	3,960	8.69	5.82
	3,660	8.53	5.88	4,830	9.18	5.90
	4,750	9.08	5.76	5,700	(20) 22.70	5.79
	5,580	9.46	5.77	6,460	9.78	5.74
25°	(a = .0479)					
	2,280	6.02	2.72	2,630	6.01	2.34
	4,480	6.88	2.34	3,760	6.87	2.79
	7,020	7.86	2.29	6,950	7.82	2.29
	8,940	8.51	2.33	8,970	8.48	2.34
	14,000	9.44	2.28	14,400	9.50	2.28
	18,000	10.99	2.30	18,000	10.13	2.33

k_2 (50) = 21.0×10^{-3}

k_2 (35) = 5.81×10^{-3}

k_2 (25) = 2.32×10^{-3}

Ethyl m-methylbenzoate

HCl = .0762N; NaOH = .0506N

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
50°			(a =	.0444)		
	1,350	6.34	4.72	1,295	6.15	4.33
	3,780	8.20	4.54	5,325	8.95	4.54
	5,460	9.02	4.57	7,240	9.65	4.62
	7,320	9.63	4.51	9,040	10.10	4.59
	9,150	10.12	4.59	11,200	10.41	4.36
	12,510	10.81	4.75	13,000	10.78	4.61
35°			(a =	.0452)		
	2,885	5.40	1.19	6,350	6.49	1.20
	4,050	5.77	1.17	9,810	7.24	1.17
	6,780	6.54	1.16	13,300	7.94	1.20
	13,240	7.89	1.18	24,330	9.22	1.17
	17,080	8.42	1.16	31,410	9.80	1.19
	36,060	10.10	1.20	36,120	10.10	1.20
25°			(a =	.0455)		
	57,540	8.90	.431	15,600	6.22	.428
	66,120	9.17	.424	85,080	9.75	.430
	75,840	9.51	.432	93,600	9.92	.424
	89,400	9.87	.434	100,800	10.11	.404
	147,400	10.84	.439	116,400	10.37	.435
	159,240	11.01	.451	174,420	11.12	.440

k_2 (50) = 4.57×10^{-3}

k_2 (35) = 1.18×10^{-3}

k_2 (25) = $.433 \times 10^{-3}$

Ethyl m-chlorobenzoate

$HCl = .0762N; \ NaOH = .0506N$

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
50°	(a = .0444)					
	140	6.40	38.9	202	6.44	36.7
	540	8.42	36.1	360	7.58	37.7
	740	9.27	38.7	750	9.32	40.8
	960	9.81	37.8	935	9.76	39.2
	1,330	10.52	40.2	1,160	10.20	39.2
	1,500	10.73	40.1	1,360	10.50	39.2
35°	(a = .04517)					
	540	6.23	12.1	465	6.06	12.6
	1,110	7.45	11.4	880	7.05	11.7
	2,445	9.22	11.7	1,490	8.20	12.1
	2,700	9.49	11.8	2,956	9.73	12.1
	3,020	9.71	11.8	3,730	10.18	12.1
	4,020	10.30	11.8	4,570	10.58	11.7
	5,090	10.68	11.6	5,455	10.90	11.7
25°	(a = .04549)					
	1,395	6.25	4.85	1,500	6.33	4.73
	2,470	7.28	4.79	2,580	7.35	4.75
	5,010	8.81	4.76	5,175	8.89	4.77
		(20)				
	7,335	22.70	4.60	6,360	9.40	4.89
	10,550	10.36	4.70	10,560	10.38	4.74
	13,760	10.85	4.74	13,815	10.82	4.63

$k_2 (50) = 39.6 \times 10^{-3}$

$k_2 (35) = 11.8 \times 10^{-3}$

$k_2 (25) = 4.77 \times 10^{-3}$

Ethyl p-fluorobenzoate

HCl = .0762N; NaOH = .0506N

	Time secs.	Titre	$k_2 x10^3$	Time secs.	Titre	$k_2 x10^3$
50°			(a = .0487)			
	600	5.85	11.0	600	5.88	11.2
	1,500	7.98	11.9	1,260	7.80	11.9
	1,860	8.50	11.9	2,280	8.80	12.0
	2,340	(20) 22.21	12.2	2,910	9.58	11.9
	3,040	9.60	11.4	3,870	10.20	12.2
	3,930	10.20	12.0	4,680	10.50	11.7
35°			(a = .0491)			
	2,470	6.03	3.03	2,405	6.14	3.29
	4,650	7.49	3.16	4,590	7.50	3.22
	6,930	8.53	3.26	9,690	9.23	3.14
	11,550	9.67	3.19	11,460	9.68	3.23
	13,500	10.00	3.18	15,300	10.30	3.24
	15,800	10.20	3.00	19,320	10.73	3.22
25°			(a = .0493)			
	7,860	6.56	1.25	3,870	5.23	1.23
	11,490	7.42	1.25	7,800	6.57	1.27
	15,800	8.18	1.25	11,410	7.41	1.25
	19,750	8.61	1.19	15,750	8.18	1.25
	25,450	9.40	1.29	19,680	8.76	1.27
	30,450	9.76	1.26	30,450	9.75	1.26

k_2 (50) = 12.0×10^{-3}

k_2 (35) = 3.22×10^{-3}

k_2 (25) = 1.26×10^{-3}

Ethyl m-aminobenzoate

HCl = .0658N; NaOH = .0502N

	Time secs.	Titre	k_2x10^3	Time secs.	Titre	k_2x10^3
50°	(a = .0483)					
	2,420	6.31	3.57	2,515	6.35	3.51
	4,680	7.53	3.22	4,920	7.65	3.22
	6,520	8.35	3.26	6,640	8.40	3.26
	9,250	9.15	3.21	9,250	9.17	3.24
	11,610	9.64	3.18	11,730	9.67	3.17
	15,070	10.15	3.18	15,120	10.20	3.17
35°	(a = .0487)					
	9,410	6.32	.937	9,140	6.15	.887
	19,130	7.66	.843	18,350	7.02	.842
	24,780	(20) 21.40	.842	18,840	7.61	.841
	28,920	8.60	.823	24,590	8.22	.824
	32,820	8.90	.819	28,580	8.56	.815
				32,670	8.80	.816
25°	(a = .0498)					
	63,840	8.13	.313	64,080	8.11	.310
	70,080	8.32	.308	75,660	8.50	.307
	75,420	8.53	.312	84,480	8.77	.307
	84,360	8.75	.305	90,240	8.90	.303
	90,240	8.90	.304	151,400	10.04	.297
	151,200	9.98	.289			

$k_2\ (50) = 3.21 \times 10^{-3}$

$k_2\ (35) = .830 \times 10^{-3}$

$k_2\ (25) = .308 \times 10^{-3}$

Ethyl o-aminobenzoate

HCl = .06580N; NaOH = .0502N

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
50°	(a = .0492)					
	14,100	6.50	.683	22,630	7.54	.684
	46,800	9.20	.660	46,900	9.20	.657
	53,940	9.54	.657	54,040	9.48	.643
	63,240	9.90	.662	63,250	9.81	.635
	70,680	10.10	.651	70,720	(20) 23.08	.615
	77,700	10.30	.653	77,740	10.27	.643
35°	(a = .0496)					
	25,680	4.79	.148	25,680	4.79	.149
	83,760	6.94	.145	90,240	7.13	.146
	96,360	(20) 20.40	.147	96,720	7.27	.145
	105,800	(20) 21.63	.140	106,740	7.46	.142
	169,700	8.68	.147	170,460	8.70	.148
	199,900	9.15	.151	200,700	9.08	.146
25°	(a = .0495)					
	352,800	7.89	.0513	352,800	(20) 20.83	.0478
	432,000	8.24	.0483	432,000	8.20	.0473
	518,400	8.70	.0481	518,400	8.66	.0475
	604,800	9.08	.0481	604,800	9.00	.0469
	864,000	9.84	.0473	864,000	9.84	.0473

$$k_2\ (50) = .647 \times 10^{-3}$$

$$k_2\ (35) = .146 \times 10^{-3}$$

$$k_2\ (25) = .0476 \times 10^{-3}$$

Ethyl Acetate

HCl = .0658N; NaOH = .0502N

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
50°	a = .0492					
	176	5.73	38.1	342	7.22	39.7
	321	7.05	39.2	517	8.23	39.8
	442	8.30	38.0	717	9.00	39.4
	897	9.47	38.5	1,090	9.93	38.7
	1,157	10.00	37.9	1,302	10.28	38.6
	1,320	10.25	37.7	1,717	10.77	37.9
35°	a = .0495					
	517	5.87	14.2	852	6.90	14.0
	1,495	8.15	13.4	1,460	8.13	13.8
	1,890	8.78	13.7	1,740	8.57	13.6
	2,350	9.30	13.7	2,166	9.05	13.3
	3,145	9.89	13.3	2,675	9.57	13.6
	3,765	10.23	13.0	3,025	9.76	13.0
25°	a = .0498					
	1,215	6.07	6.82	1,372	6.25	6.58
	2,915	7.88	6.23	2,895	7.90	6.32
	3,525	8.36	6.25	3,740	8.54	6.32
	4,320	8.81	6.14	4,530	8.95	6.19
	5,060	9.18	6.10	5,300	9.30	6.14
	7,570	10.70	6.64	7,610	10.09	6.07

$$k_2\ (50) = 38.7 \times 10^{-3}$$

$$k_2\ (35) = 13.6 \times 10^{-3}$$

$$k_2\ (25) = 6.21 \times 10^{-3}$$

Ethyl Propionate

HCl = .0653N; NaOH = .0502N

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
50° a = .0492	640	7.50	24.8	300	5.84	25.0
	895	8.31	24.7	600	7.34	24.8
	1,220	9.02	24.3	900	8.32	24.7
	1,620	9.72	24.4	1,225	9.11	25.2
	2,010	10.16	24.2	2,065	10.24	25.1
	2,435	10.52	24.0	2,970	10.91	25.2
35°			a =	.0495		
	1,220	6.50	8.55	1,405	6.79	8.45
	1,685	7.21	8.41	2,010	7.63	8.40
	2,320	7.94	8.26	2,620	8.23	8.22
	2,825	8.43	8.27	3,240	8.89	8.70
	4,205	9.38	8.28	3,700	9.08	8.27
	5,265	9.91	8.41	4,950	9.70	8.12
25°			(a =	.0498)		
	1,360	5.16	3.92	3,535	6.99	3.69
	3,380	6.84	3.71	5,250	7.88	3.61
		(20)				
	4,935	20.80	3.71	6,485	8.41	3.60
	6,275	8.33	3.59	7,890	8.90	3.61
	9,395	9.30	3.59	9,540	9.33	3.58
	11,340	9.78	3.57	11,400	9.73	3.56

$k_2\ (50) = 24.7 \times 10^{-3}$

$k_2\ (35) = 8.31 \times 10^{-3}$

$k_2\ (25) = 3.63 \times 10^{-3}$

Ethyl Isobutyrate

HCl = .0655N; NaOH = .0487N

	Time secs.	Titre	k_2x10^3	Time secs.	Titre	k_2x10^3
50°			a = .0487			
	1,770	7.00	6.39	1,720	7.07	6.78
	2,555	7.70	5.94	3,453	8.46	5.98
	3,110	8.16	5.75	4,140	8.85	5.82
	3,810	8.60	5.73	5,260	9.40	5.73
	4,530	8.99	5.64	6,170	9.74	5.65
	5,662	9.49	5.54	6,910	10.02	5.69
35°			a = .0484			
	3,340	6.05	2.13	3,480	6.11	2.11
	5,460	6.95	2.01	8,890	7.97	1.87
	9,940	8.21	1.87	11,220	8.56	1.90
	12,070	8.65	1.84	13,320	8.90	1.84
	14,400	(20) 22.54	1.84	16,110	9.33	1.82
	17,700	9.53	1.80	18,960	9.70	1.80
25°			(a = .0488)			
	8,440	6.17	.916	8,550	6.18	.909
	15,600	(20) 20.70	.811	14,780	7.18	.830
	19,620	7.81	.813	19,680	7.82	.813
	22,620	8.15	.808	22,680	8.13	.800
	26,440	8.50	.795	26,840	8.54	.796
	29,710	8.76	.785	29,950	8.80	.781

k_2 (50) = 5.72×10^{-3}

k_2 (35) = 1.84×10^{-3}

k_2 (25) = $.801 \times 10^{-3}$

Ethyl trimethylacetate

HCl = .0653N; NaOH = .0487N

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
50°			(a = .0472)			
	64,740	7.88	.241	64,980	7.90	.242
	76,980	8.30	.241	77,160	8.32	.242
	86,220	8.61	.244	86,280	8.60	.243
	97,560	8.90	.244	97,620	8.86	.239
	162,840	9.94	.227	163,020	10.02	.234
	177,840	10.20	.236	178,020	10.23	.236
35°			(a = .0542)			
	237,900	7.44	.0658	68,700	4.58	.0685
	320,760	8.27	.0657	154,800	6.32	.0637
	403,200	8.81	.0635	241,200	7.41	.0641
	489,300	9.30	.0628	500,400	9.41	.0641
	573,900	9.70	.0639	586,200	9.92	.0643
	843,900	10.61	.0628	672,600	10.19	.0653
25°			(a = .0546)			
	486,600	6.77	.0255	486,600	6.85	.0262
	659,400	7.55	.0250	659,400	7.65	.0258
	916,800	8.41	.0248	916,800	8.51	.0253
	1,003,200	8.70	.0248	1,003,200	8.81	.0262
	1,089,600	8.93	.0241	1,089,600	9.00	.0247
	1,257,000	9.40	.0255	1,257,000	9.53	.0268

k_2 (50) = .241, x 10^{-3}

k_2 (35) = .0635 x 10^{-3}

k_2 (25) = .0254 x 10^{-3}

Ethyl n-butyrate

$HCl = .0689$; $NaOH = .0484$

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
50°			(a = .0518)			
	573	6.40	12.4	635	6.56	12.0
	990	7.63	12.1	990	7.62	12.1
	1,380	8.48	12.1	1,410	8.60	12.3
	1,785	9.22	12.3	1,800	(20) 23.40	12.0
	2,290	9.85	12.2	2,295	9.82	12.0
	2,735	10.28	12.4	2,780	10.36	12.3
35°			(a = .0523)			
	1,575	6.10	4.00	1,845	6.28	3.73
	2,565	7.14	3.91	2,640	7.25	3.98
	3,620	8.03	3.93	3,483	8.06	3.93
	4,800	8.80	3.95	6,155	9.45	3.92
	6,030	9.41	3.94	7,590	10.02	3.94
	8,360	10.18	3.81	10,280	10.68	3.80
25°			(a = .0528)			
	3,480	6.03	1.80	3,600	6.10	1.80
	7,320	7.75	1.77	6,780	7.45	1.70
	10,500	8.64	1.72	9,660	8.42	1.76
	13,380	9.27	1.70	12,570	9.10	1.70
	15,780	9.77	1.74	14,940	9.67	1.72
	18,000	10.10	1.73	22,560	10.60	1.68

$$k_{2\ (50)} = 12.2 \times 10^{-3}$$

$$k_{2\ (35)} = 3.94 \times 10^{-3}$$

$$k_{2\ (25)} = 1.72 \times 10^{-3}$$

Ethyl n-valerate

HCl = .0659N; NaOH = .0484N

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
50°	a = .0563			a = .0485		
	980	6.81	13.0			
	1,265	(20) 20.88	14.7	435	5.87	13.3
	1,600	8.18	13.2	695	6.67	13.1
	1,985	8.70	13.4	1,070	7.60	13.3
	2,270	9.10	13.3	1,710	8.68	13.3
	3,365	10.11	13.9	2,160	9.22	13.1
				2,620	9.69	13.7
35°	(a = .0488)					
	1,560	6.14	4.45	1,650	6.23	4.43
	2,750	7.17	4.28	2,790	7.28	4.43
	3,850	7.96	4.35	3,910	8.02	4.40
	4,715	8.45	4.40	4,775	8.50	4.43
	5,820	8.94	4.41	5,840	8.95	4.41
	7,775	7.62	4.48	7,800	9.70	4.43
25°	(a = .0491)					
	4,380	6.48	1.94	2,630	5.58	1.91
	6,010	7.12	1.94	4,700	6.60	1.92
	7,940	7.70	1.90	6,300	7.20	1.91
	9,690	8.20	1.93	8,240	7.80	1.91
	11,660	8.62	1.93	11,980	8.66	1.90
	13,660	9.03	1.96	13,980	9.08	1.79

k_2 (50) = 13.3×10^{-3}

k_2 (35) = 4.42×10^{-3}

k_2 (25) = 1.92×10^{-3}

Ethyl Caproate

HCl = .0693N; NaOH = .0516N

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
50°	a = .0478					
	300	5.82	14.4	300	5.83	14.5
	600	6.95	14.5	600	6.92	14.2
	900	7.81	14.6	880	7.75	14.5
	1,500	8.95	14.5	1,200	8.42	14.4
	1,800	9.40	14.7	1,500	8.96	14.5
	2,340	9.99	14.7	1,760	9.43	15.1
35°	a = .0488					
	600	5.32	5.35	1,800	6.88	4.89
	2,520	7.49	4.68	2,700	7.68	4.75
	3,070	7.98	4.78	3,750	8.44	4.76
	3,850	8.50	4.75	4,510	8.92	4.85
	4,620	8.93	4.75	5,460	9.36	4.83
	5,760	9.47	4.80	6,350	9.72	4.87
25°	a = .0492					
	4,380	6.92	2.08	2,820	6.16	2.15
	7,200	8.01	2.08	5,160	7.28	2.10
	9,270	8.60	2.07	9,320	8.59	2.06
	11,340	9.08	2.07	11,190	9.02	2.06
	14,530	9.66	2.08	12,490	9.26	2.04
	15,960	9.90	2.10	13,980	9.60	2.10

$$k_{2(50)} = 14.5 \times 10^{-3}$$

$$k_{2(35)} = 4.81 \times 10^{-3}$$

$$k_{2(25)} = 2.08 \times 10^{-3}$$

Ethyl Isovalerate

$HCl = .0516N$; $NaOH = .0696N$

	Time secs.	Titre	k_2x10^3	Time secs.	Titre	k_2x10^3
50°	a = .0500					
	2,465	6.69	3.44	2,040	6.32	3.44
	3,660	7.50	3.37	3,300	7.31	3.43
	4,980	8.24	3.39	4,990	8.20	3.32
	7,260	9.07	3.28	5,970	8.66	3.36
	8,940	9.59	3.31	7,380	9.13	3.31
	10,830	10.02	3.30	9,210	9.68	3.36
35°	a = .0532			a = .0541		
	3,000	4.68	1.07	7,420	6.10	1.04
	10,950	7.09	1.04	10,970	7.03	1.04
	14,460	7.75	1.03	15,070	7.81	1.03
	17,340	8.18	1.02	22,080	8.72	1.01
	21,300	8.68	1.01	28,800	9.35	1.01
	24,480	9.04	1.01			
25°	a = .0544					
	49,500	8.59	.426	49,380	8.58	.426
	55,080	8.91	.433	54,900	8.90	.433
	62,640	9.21	.428	62,980	9.23	.432
	70,980	9.51	.426	70,980	9.50	.424
	78,720	9.74	.423	78,660	9.72	.416
	85,200	9.91	.420	85,560	9.90	.416

$$k_{2(50)} = 3.34 \times 10^{-3}$$

$$k_{2(35)} = 1.02 \times 10^{-3}$$

$$k_{2(25)} = .427 \times 10^{-3}$$

Ethyl Heptoate

HCl = .0718N; NaOH = .0515N

	Time secs.	Titre	k_2x10^3	Time secs.	Titre	k_2x10^3
50°			a = .0489			
	420	6.40	12.9	420	6.42	12.8
	720	7.40	12.9	720	7.39	12.8
	1,080	8.25	12.7	1,090	8.29	12.9
	1,355	8.82	12.9	1,340	8.78	12.8
	1,680	9.26	12.6	1,680	9.30	12.8
	2,550	10.22	12.5	2,100	9.80	12.6
35°			a = .0492			
	1,440	6.54	4.11	1,520	6.65	4.15
	2,540	7.58	4.03	2,640	7.68	4.05
	3,480	8.30	4.06	3,580	8.38	4.08
	4,210	8.71	4.00	4,320	8.81	4.07
	5,380	9.30	4.01	5,440	9.35	4.05
	6,990	9.93	4.02	6,720	9.88	4.10
25°			a = .0500			
	3,200	6.40	1.80	3,360	6.48	1.80
	4,830	7.16	1.80	4,900	7.20	1.80
	6,690	7.85	1.78	6,780	7.87	1.77
	8,580	8.43	1.78	8,670	8.50	1.81
	10,830	8.96	1.76	11,130	9.02	1.75
	15,230	9.70	1.70	15,310	9.80	1.76

$$k_{2(50)} = 12.7 \times 10^{-3}$$

$$k_{2(35)} = 4.06 \times 10^{-3}$$

$$k_{2(25)} = 1.79 \times 10^{-3}$$

Ethyl Octoate

HCl = .0705N; NaOH = .0515N

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
50°	a = .0490					
	300	5.76	13.6	900	7.65	13.0
	600	6.86	13.3	1,200	8.33	13.1
	900	7.70	13.3	1,500	8.88	13.3
	1,200	8.40	13.3	1,800	9.30	13.2
	1,500	8.93	13.6	2,100	9.70	13.2
	1,800	9.37	13.6	2,400	9.98	13.3
35°	a = .0492					
	770	5.56	4.63	835	5.67	4.67
	2,370	7.30	4.25	1,505	6.50	4.34
	3,210	8.00	4.27	2,425	7.35	4.25
	3,870	8.43	4.29	3,245	8.05	4.34
	4,860	8.98	4.30	4,925	9.03	4.33
	6,470	9.67	3.80	6,155	9.57	4.35
25° a = .0491	3,360	6.33	1.79	3,600	6.46	1.85
	7,560	7.98	1.80	7,720	8.10	1.86
	9,480	8.55	1.84	9,640	8.60	1.84
	11,220	8.95	1.83	11,380	9.00	1.85
	13,380	9.40	1.86	13,480	9.44	1.88
	16,260	9.86	1.83	16,540	9.85	1.83

$$k_{2(50)} = 13.3 \times 10^{-3}$$

$$k_{2(35)} = 4.30 \times 10^{-3}$$

$$k_{2(25)} = 1.84 \times 10^{-3}$$

Ethyl diethylacetate

HCl = .0718N; NaOH = .0515N

	Time secs.	Titre	$k_2 x 10^3$	Time secs.	Titre	$k_2 x 10^3$
50°			a = .0521			
	60,840	7.16	.156	60,780	7.11	.153
	69,060	7.46	.157	69,060	7.38	.151
	77,700	7.80	.160	77,700	7.68	.153
	86,880	8.01	.156	86,820	7.89	.150
	145,080	9.30	.157	145,020	9.10	.145
	163,860	9.65	.159	173,700	9.58	.146
35°			a = .0526			
	81,000	5.30	.0430	81,000	5.31	.0433
	159,480	6.29	.0401	159,480	6.31	.0405
	245,880	7.21	.0402	245,800	7.32	.0421
	490,680	8.87	.0394	490,680	8.97	.0410
	611,280	9.54	.0401	611,280	9.56	.0416
	679,680	9.70	.0416	679,680	9.90	.0428
25°			a = .0531			
	17,000	5.05	.0177	339,360	6.00	.0168
	513,000	6.68	.0155	584,160	6.99	.0156
	667,800	7.32	.0158	738,960	7.56	.0157
	822,600	7.80	.0156	893,760	8.03	.0157
	1,087,000	8.48	.0154	1,158,000	8.70	.0158
	1,260,000	8.83	.0153	1,331,000	9.65	.0158

$k_{2(50)} = .154 \times 10^{-3}$

$k_{2(35)} = .0409 \times 10^{-3}$

$k_{2(25)} = .0157 \times 10^{-3}$

Ethyl methylethylacetate

HCl = .0705N; NaOH = .0515N

	Time secs.	Titre	$k_2 \times 10^3$	Time secs.	Titre	$k_2 \times 10^3$
50°			a = .0485			
	5,040	7.87	2.39	3,600	7.50	2.68
	6,720	8.35	2.34	5,760	8.20	2.38
	8,220	8.85	2.32	6,600	8.50	2.37
	12,000	9.78	2.36	9,120	9.24	2.39
	16,020	10.00	2.00	10,800	9.50	2.28
				13,080	9.94	2.30
35°			a = .0494			
	8,040	6.88	1.02	8,160	6.96	.960
	15,660	7.60	.730	16,140	7.67	.743
	18,540	8.00	.729	18,960	8.03	.740
	21,600	8.35	.745	22,440	8.50	.733
	28,080	8.93	.731	28,800	9.00	.732
	35,100	9.26	.887	32,160	9.29	.961
25°			a = .0491			
	51,180	8.30	.306	13,200	6.23	.431
	56,160	8.53	.308	26,320	6.92	.316
	63,660	8.86	.300	28,200	7.31	.316
	69,960	9.00	.301	35,580	7.70	.338
	134,760	10.29	.282	100,800	9.41	.305
				117,900	9.53	.261

$k_{2(50)} = 2.36 \times 10^{-3}$

$k_{2(35)} = .735 \times 10^{-3}$

$k_{2(25)} = .308 \times 10^{-3}$

Experimental data for base catalysed prototropy of ketones

Acetophenone

Time mins.	Titre	Fall	k	Time mins.	Titre	Fall	k
65° (Thiosulphate = 1.05 $\frac{N}{50}$)				65° (Thiosulphate = .930 $\frac{N}{50}$)			
0	9.24	-	-	0	11.90	-	-
7'	7.08	2.16	.323	6'	9.78	2.12	.328
12'	5.46	3.78	.329	12'	7.66	4.26	.330
17'	3.70	5.54	.340	18'	5.56	6.34	.325
55° (Thiosulphate = .930 $\frac{N}{50}$)							
0	9.46	-	-	0	10.40	-	-
18'	6.98	2.48	.128	16'	8.24	2.16	.126
30'	5.24	4.22	.131	30'	6.20	4.20	.130
45'	3.00	6.46	.134	47'	3.60	6.80	.134
45° (Thiosulphate = 1.05 $\frac{N}{50}$)							
0	10.20	-	-	0	10.34	-	-
30'	8.82	1.38	.0480	32'40"	8.74	1.60	.0510
60'	7.26	2.94	.0511	81'30"	6.18	4.16	.0531
90'	5.66	4.54	.0525	147'30"	4.68	5.66	.0544
				0	7.40	-	-
				30'	5.96	1.44	.0500
				62.5'	4.28	3.12	.0524
				90'	2.86	4.54	.0530

$k_{(65)} = .330$

$k_{(55)} = .131$

$k_{(45)} = .0520$

Propiophenone

Time mins.	Titre	Fall	k	Time mins.	Titre	Fall	k
65° (Thiosulphate = .930 $\frac{N}{50}$)							
0	9.84	-	-	0	12.96	-	-
25'	8.30	1.54	.0572	30'	11.16	1.80	.0557
50'	6.80	3.04	.0565	65'	9.08	3.88	.0555
85'	4.68	5.16	.0564	108'	6.54	6.42	.0553
55° (Thiosulphate = .930 $\frac{N}{50}$)							
0	10.96	-	-	0	9.98	-	-
86'	8.96	2.00	.0226	94'	8.04	1.94	.0216
181'	6.76	4.20	.0225	162'	6.56	3.42	.0220
261'	5.00	5.96	.0226	241'	4.96	5.02	.0219
				55° (Thio. = 1.20 $\frac{N}{50}$)			
				0	9.60	-	-
				94'	7.72	1.88	.0210
				165'	6.12	3.48	.0222
				241'	4.60	5.00	.02:9
45° (Thiosulphate = .930 $\frac{N}{50}$)							
0	10.60	-	-	0	10.68	-	-
180'	9.04	1.56	.00805	180'	9.14	1.54	.00794
360'	7.52	3.08	.00795	360'	7.54	3.14	.00810
480'	6.48	4.12	.00798	480'	6.58	4.10	.00793

$k_{(65)}$ = .0567

$k_{(55)}$ = .0219

$k_{(45)}$ = .00799

Isobutyrophenone

(Thiosulphate = .930 $\frac{N}{50}$)

Time mins.	Titre	Fall	k	Time mins.	Titre	Fall	k
65°							
0	10.40	-	-	0	10.18	-	-
150'	8.46	1.94	.0118	150'	8.24	1.94	.0118
300'	7.56	3.94	.0122	300'	6.32	3.86	.0120
450'	4.64	5.76	.0199	450'	5.50	5.68	.0117
55°							
0	9.08	-	-	0	9.64	-	-
240'	7.92	1.16	.00449	240'	8.52	1.12	.00434
360'	7.36	1.72	.00445	360'	7.92	1.72	.00444
480'	6.76	2.32	.00454	480'	7.36	2.28	.00442
45°							
0	14.00	-	-	0	14.32	-	-
840'	12.60	1.40	.00154	840'	12.90	1.42	.00157
1,380'	11.64	2.36	.00152	1,380'	11.88	2.44	.00163
2,280'	10.20	3.80	.00156	2,280'	10.46	3.86	.00157

$k_{(65)}$ = .0119

$k_{(55)}$ = .00444

$k_{(45)}$ = .00155

Isovalerophenone

(Thiosulphate = .930 $\frac{N}{50}$)

Time mins.	Titre	Fall	k	Time mins.	Titre	Fall	k
			65°				
0	8.90	-	-	0	9.08	-	-
70'	7.14	1.76	.0233	65'	7.44	1.64	.0232
153'	5.20	3.70	.0225	151'	5.40	3.68	.0227
249'	2.96	5.94	.0221	244'	3.22	5.86	.0223
			55°				
0	11.16	-	-	0	11.00	-	-
180'	9.50	1.66	.00857	180'	9.32	1.68	.00868
330'	8.16	3.00	.00845	330'	8.00	2.98	.00840
480'	6.84	4.32	.00837	480'	6.62	4.38	.00848
			45°				
0	12.76	-	-	0	12.88	-	-
300'	11.72	1.04	.00322	300'	11.82	1.06	.00328
480'	11.20	1.56	.00302	480'	11.30	1.58	.00306
600'	10.76	2.00	.00310	600'	11.90	1.98	.00303

$k_{(65)}$ = .0224

$k_{(55)}$ = .00849

$k_{(45)}$ = .00305

n-Butyrophenone

(Thiosulphate = .933 $\frac{N}{50}$)

Time mins.	Titre	Fall	k	Time mins.	Titre	Fall	k
			65°				
0	9.62	-	-	0	9.92	-	-
52'	7.18	2.44	.0438	51'	7.50	2.42	.0434
84'	5.70	3.92	.0436	83'	5.96	3.96	.0437
127'	3.78	5.84	.0429	126'	4.04	5.88	.0442
			55°				
0	10.20	-	-	0	10.02	-	-
120'	8.04	2.16	.0168	120'	7.66	2.36	.0184
187'	6.82	3.38	.0169	187'	6.54	3.48	.0174
248'	5.62	4.58	.0173	248'	5.42	4.60	.0173
			45°				
0	11.44	-	-	0	11.40	-	-
180'	10.22	1.22	.00632	180'	10.20	1.20	.00622
300'	9.44	2.00	.00622	300'	9.38	2.02	.00628
420'	8.66	2.78	.00618	420'	8.62	2.78	.00618

$k_{(65)}$ = .0435

$k_{(55)}$ = .0172

$k_{(45)}$ = .00624

n-Valerophenone

(Thiosulphate = .922 $\frac{N}{50}$)

Time mins.	Titre	Fall	k	Time mins.	Titre	Fall	k
65°							
0	9.46	-	-	0	9.80	-	-
40'	7.14	2.32	.0512	40'	7.72	2.08	.0479
70'	5.84	3.62	.0476	70'	6.12	3.68	.0471
100'	4.20	5.26	.0485	100'	4.54	5.26	.0485
55°							
0	11.52	-	-	0	16.86	-	-
118'	9.12	2.40	.0188	118'	14.32	2.54	.0198
224'	7.02	4.50	.0185	224'	12.30	4.56	.0188
284'	5.74	5.78	.0188	284'	10.00	6.86	.0190
45°							
0	10.28	-	-	0	11.24	-	-
239'	8.46	1.82	.00702	237'	9.42	1.82	.00702
386'	7.36	2.92	.00698	386'	8.28	2.96	.00707
480'	6.56	3.72	.00714	480'	7.60	3.64	.00700

$k_{(65)}$ = .0479

$k_{(55)}$ = .0188

$k_{(45)}$ = .00704