180. *The Influence of Alkyl Groups upon Reaction Velocities in Solution. Part I. The Acid-catalysed Prototropy of Phenyl Alkyl Ketones.*

By David P. Evans.

The acid-catalysed prototropy of a series of nuclear-substituted acetophenones, $CH_3{\cdot}CO{\cdot}C_6H_4X$, has recently been discussed by Evans, Morgan, and Watson (J., 1935, 1167) in the light of the mechanism put forward by Watson, Nathan, and Laurie (*J. Chem. Physics*, 1933, **3**, 170). On their view, a fruitful collision between ketone and catalyst leads to the formation of a bond at the carbonyl oxygen with resultant electronic activation expressed as $>C{=}\overset{\frown}{O} \longrightarrow >\overset{+}{C}{-}\bar{O}$. This energised form may then revert to the original ketone, or may be transformed into enol. The velocity of prototropic change therefore depends upon (*a*) the rate of reaction between ketone and catalyst and (*b*) the proportion of semipolar form which changes into enol.

The present communication deals with the acid-catalysed prototropy (measured by Lapworth's bromination method) of a series of phenyl *n*-alkyl ketones, $CH_2R{\cdot}CO{\cdot}C_6H_5$, extending from acetophenone to *n*-hexophenone, and also of *iso*butyrophenone. On Watson, Nathan, and Laurie's scheme, the mechanism of the change is represented by

$$CH_2R{-}\underset{\text{Ph}}{C}{=}\overset{\frown}{O} + H^+ \longrightarrow CH_2R{-}\underset{\text{Ph}}{\overset{+}{C}}{-}\bar{O}(H^+) \begin{cases} \xrightarrow{(1)} CH_2R{-}\underset{\text{Ph}}{C}{=}O + H^+ \\ \xrightarrow{(2)} H^+ + CHR{=}\underset{\text{Ph}}{C}{-}\bar{O}(H^+) \end{cases}$$

the later stages (1) and (2) being alternative (compare Evans, Morgan, and Watson, *loc. cit.*, p. 1170).

Alkyl groups are weakly electron-repulsive, and to much the same extent (as shown, *e.g.*, by the small differences in the strengths of the homologues of acetic acid). The introduction of the alkyl group R should therefore give rise to (*a*) a decrease in the work necessary for the approach of oxonium ion, manifested in a smaller energy of activation, and (*b*) a facilitation of the electronic change in (2) relatively to that in (1), together with a decreased tendency for ionisation of the α-hydrogen atom. If the velocity constant is expressed as $k = PZe^{-E/RT}$, therefore, the $+I$ effect of the alkyl group would be expected to lead to a small decrease in E and but little change in P, different alkyl groups having similar effects. These predictions are not, however, borne out by experiment. Table I records the values of the velocity coefficients (expressed as fall in $N/50$-thiosulphate titre

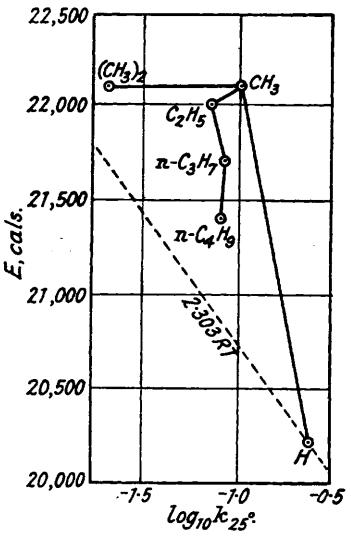
per minute for 20 c.c. of 0·1*M*-ketone solutions in 75% acetic acid containing 0·5*M*-hydrochloric acid), the energies of activation calculated in the usual manner, and the values of *P* calculated on the assumption that [H·] = [HCl].

TABLE I.

Bromination of Phenyl Alkyl Ketones, $CH_2R{\cdot}COPh$.

R.	$k_{25°}$.	$k_{35°}$.	$k_{45°}$.	*E* (cals.).	*P*.
H	0·241	0·739	2·14	20,200	0·15
CH_3	0·104	0·352	1·12	22,100	1·53
C_2H_5	0·0721	0·244	0·774	22,000	0·85
n-C_3H_7	0·0851	0·284	0·875	21,700	0·59
n-C_4H_9	0·0817	0·267	0·824	21,400	0·32
(CH_2R = $CHMe_2$)	0·0213	0·0728	0·231	22,100	0·30

There is a marked fall in velocity with increasing length of the straight alkyl chain up to *n*-butyrophenone; α-methyl, indeed, has a greater effect than *p*-nitro (Evans, Morgan, and Watson, *loc. cit.*). As the alkyl series is ascended, however, the velocity coefficients tend to a limiting constant value, but *iso*butyrophenone reacts more slowly than any of the other ketones; these results resemble those of Bennett and Reynolds (J., 1935, 131) for the reaction of hydrogen bromide with aliphatic alcohols. In passing from acetophenone (R = H) to propiophenone (R = CH_3) there is a marked increase in energy of activation, accompanied by a considerable rise in *P* (roughly 10-fold). Further lengthening of the straight alkyl chain causes a small, yet continuous decrease in *E* with simultaneous decrease in *P*. These changes are illustrated diagrammatically in the figure; the graphical method of Hinshelwood and his collaborators (J., 1935, 587, 1111, 1147, 1588), here employed, is based on the equation $E = c - 2{\cdot}303RT \,.\, \log k$, which holds when *P* is constant.

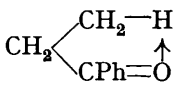


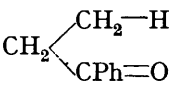
Changes in Energy of Activation.—The large increase in *E* in passing from acetophenone to propiophenone is unexpected both in magnitude and in direction, and it indicates the operation, in the latter compound, of a factor (or factors) of considerable magnitude in addition to the inductive effect. An apparent explanation of this increased energy of activation for propiophenone (and the higher phenyl *n*-alkyl ketones) is obtained from the recent postulates of Baker and Nathan (J., 1935, 1844) regarding the capacity for electron-release by alkyl groups attached to conjugate systems, —C—C=O. On their view, the introduction of an alkyl group at the α-carbon of acetophenone would cause a decrease in this electron-release with a resultant rise of *E*. The approximate constancy of the (higher) energy of activation for propio-, *n*-butyro- and *n*-valero-phenones (one α-hydrogen atom replaced) is in harmony with this view. On the other hand, the observation that the energies of activation for propiophenone and *iso*butyrophenone (two α-hydrogen atoms replaced) are almost identical is not expected on Baker and Nathan's postulates, which, moreover, do not provide an interpretation of the considerable increase in the *P* factor in passing from aceto- to propio-phenone.

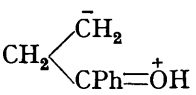
The similarity in the values of *E* for propio-, *n*- and *iso*-butyro-phenones shows that the larger activation energy (greater than that for acetophenone by approximately 2000 cals.) results from the introduction of the first methyl at the α-carbon atom. It is suggested, therefore, that in these (and higher) ketones a β-hydrogen atom co-ordinates with the unshared electrons of carbonyl oxygen, giving (I), with a resultant increase in

the work necessary for the approach of oxonium ion to form the activated complex.* Such interaction between a methyl group and the unshared electrons of a nitrogen atom is indicated by the smaller co-ordinating power of α-picoline and dimethyl-*o*-toluidine than of pyridine and dimethylaniline respectively (Klaus and Baudisch, *Ber.*, 1918, **51**, 1036; 1921, **54**, 413; who speak of a "neutralisation" between tertiary nitrogen and methyl), and by the different dipole moments of quinoline and 2 : 6-dimethylquinoline (Le Fèvre and Le Fèvre, J., 1935, 1471). Earp and Glasstone (J., 1935, 1709) have recently formulated the compounds of chloroform with acetone and quinoline in a similar way.

The above suggestion postulates the two-covalency of hydrogen, which is now regarded as a resonance phenomenon (Sidgwick, *Ann. Reports*, 1934, **31**, 43); in the present case the "unperturbed forms" would be (II) and (III). By using the interatomic distances


(I.)


(II.)


(III.)

C—C (aliphatic) 1·53, and C=O 1·25 A. (Robertson, *Chem. Reviews*, 1935, **16**, 434) and assuming the valency angle between the carbonyl bond and an alkyl chain to be 125° and that between the valencies of the chain as 109°, calculation gives the following approximate values for the minimum distances (*d*) between the centres of the oxygen and the terminal carbon atoms of the alkyl chain in the phenyl *n*-alkyl ketones :

Alkyl group, R	(H)	CH_3	C_2H_5	C_3H_7	C_4H_9
d, A.	2·5	2·8	2·1	0·7	1·1

The distances of the α- and the β-carbon atoms from the oxygen are very similar to those between the two oxygens linked through co-ordinate hydrogen in sodium bicarbonate (2·55 A., Zachariasen, *J. Chem. Physics*, 1933, **1**, 634), and between the two fluorine atoms in the anion of the "acid" fluorides (2·36 A., *idem*, *ibid.*). This fact favours the possibility of resonance in the ketones. The absence of such resonance in acetophenone, indicated by the lower energy of activation, is probably due to the instability of a four-membered chelate ring; for this reason also it must be supposed that the β- and not the α-hydrogen atom in propiophenone (and the other ketones) is concerned. The "activation" of the hydrogen necessary to make resonance possible may be ascribed to the inductive effect ($-I$) of carbonyl (cf. the high dipole moments of ketones), which will probably be transmitted to the β-carbon atom to a sufficient extent. Steric considerations also show that this atom is likely to be concerned in all the ketones, for only here is there a linear disposition of the carbon, hydrogen, and oxygen atoms (which is necessary for the two-covalency of hydrogen, Sidgwick, *Ann. Reports*, 1933, **30**, 113). Further, the radii 0·75 A. and 0·5 A. being assumed for carbon and oxygen respectively, there is insufficient space between γ-carbon and carbonyl oxygen for an intervening hydrogen atom of radius 0·6 A. If this resonance phenomenon involves the β-carbon atom in every case, the approximate constancy of the activation energy for propiophenone and the higher ketones receives a simple explanation.†

The view here presented is also in harmony with the results of Hinshelwood and Legard (J., 1935, 587, 1588) for the acid-catalysed esterification of trimethylbenzoic and trimethylacetic acids, where the methyl groups again lead to a large increase in E. The dissociation constant of the latter acid, however ($K \times 10^5 = 0{\cdot}978$, Billitzer, *Monatsh.*, 1899, **20**, 670; cf. $K \times 10^5 = 1{\cdot}8$ for acetic acid), is interpretable solely on the basis of

* A "direct" effect opposite in sign to the inductive effect has been ascribed to methyl by Lapworth and Manske (J., 1928, 2539) and by Bennett and Mosses (J., 1930, 2366; compare Kenner and Morton, J., 1934, 679).

† There is actually a very small but continuous *decrease* in E for the ketones above propiophenone. This may be due to the slowly increasing inductive effect of the alkyl group, as found from studies of unsymmetrical mercury and lead alkyls (Kharasch and Flenner, *J. Amer. Chem. Soc.*, 1932, **54**, 686; Jones, Evans, Gulwell, and Griffiths, J., 1935, 43).

the inductive effect of methyl. The operation of the factor discussed above is no doubt prevented here by the resonance of the carboxyl group, which removes ketonic properties. The addition of an acid catalyst will, however, eliminate the resonance normally associated with carboxyl, and hence acid-catalysed esterification is comparable with the prototropy of ketones. Lowry (J., 1925, **127**, 1381) has, indeed, suggested that the organic acid shows a " development of its ketonic functions " in catalysed esterification reactions.

Changes in the Probability Factor.—A ten-fold increase of the *P* factor in passing from acetophenone to propiophenone appears sufficiently large to warrant theoretical deductions. It has already been pointed out that the introduction of α-methyl will result in a definite increase in the proportion of the energised form which changes to enol (see p. 785). Further, the inductive effect of the alkyl group R will be reinforced by the distortion of the electronic system of carbonyl oxygen due to the co-ordination of β-hydrogen. The total electron-repulsion may therefore be of sufficient magnitude to account for the large change in *P* (compare the important effects of methyl groups upon the velocity and the mechanism of hydrolysis of alkyl halides; Hughes and Ingold, J., 1935, 244). Higher *n*-alkyl groups will have a similar effect.

The relatively small but continuous decrease in *P* when the chain is further lengthened may be ascribed to steric hindrance of the true geometric type, which causes (*inter alia*) a decrease in the probability of obtaining the correct orientation of the ketone molecule at the moment of impact with oxonium ion.

Further studies are being carried out on the bromination of alkyl substituted acetophenones.

Experimental.

(All temperatures are corrected.)

Preparation of Materials.—Phenyl alkyl ketones. Acetophenone was distilled twice under reduced pressure and was further purified by freezing. The specimen used had m. p. 19·6°, $n_D^{20°}$ 1·5328, $d_4^{20°}$ 1·0289. *n*-Propiophenone was twice recrystallised from light petroleum, and the last traces of solvent were removed by vacuum distillation; m. p. 18·6°, $n_D^{20°}$ 1·5269, $d_4^{20°}$ 1·0105 (Wagner, *J. Russ. Phys. Chem. Soc.*, 1884, **16**, 325, gives m. p. 18·5°). *n*-Butyrophenone was prepared by the Friedel–Crafts reaction from *n*-butyryl chloride and purified by several distillations in a vacuum; m. p. 12·2°, $n_D^{20°}$ 1·5196 (Elson, Gibson, and Johnson, J., 1930, 1129, give m. p. 13°); semicarbazone, m. p. 191·5° (Stadnikow, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 462, gives m. p. 188—189°); 2 : 4-*dinitrophenylhydrazone*, orange-red plates from aqueous acetic acid, m. p. 190° (Found : C, 58·7; H, 5·0. $C_{16}H_{16}O_4N_4$ requires C, 58·5; H, 4·9%). *iso*Butyrophenone, prepared in similar manner from *iso*butyryl chloride, had b. p. 97·5°/10 mm., $n_D^{20°}$ 1·5190; semicarbazone, m. p. 181·5° (Lapworth and Steele, J., 1911, **99**, 1885, give m. p. 181°); 2 : 4-*dinitrophenylhydrazone*, orange-yellow plates from aqueous acetic acid, m. p. 163° (Found : C, 58·2; H, 4·6%).

n-Valerophenone was obtained in good yield by refluxing benzonitrile with a slight excess of *n*-butylmagnesium bromide in ether, decomposing the mixture with dilute sulphuric acid, and steam-distilling the product; b. p. 130°/16 mm., $n_D^{20°}$ 1·5150; semicarbazone, needles from aqueous alcohol, m. p. 166° (Layroud, *Bull. Soc. chim.*, 1906, **35**, 224, gives m. p. 166°); 2 : 4-*dinitrophenylhydrazone*, bright red needles from glacial acetic acid, m. p. 166° (Found : C, 59·5; H, 5·4. $C_{17}H_{18}O_4N_4$ requires C, 59·65; H, 5·3%). *n*-Hexophenone, prepared by the Friedel–Crafts method, was steam-distilled from an equal volume of 10% sodium hydroxide solution and recrystallised from alcohol, m. p. 27° (Sabatier and Mailhe, *Compt. rend.*, 1914, **158**, 834, give m. p. 27°); semicarbazone, m. p. 133° (Schroeter, *Ber.*, 1907, **40**, 1603, gives m. p. 132°); 2 : 4-*dinitrophenylhydrazone*, thick, red needles from glacial acetic acid, m. p. 168° (Found : C, 60·6; H, 5·8. $C_{18}H_{20}O_4N_4$ requires C, 60·7; H, 5·6%).

Velocity Determinations.—The reaction medium (75% acetic acid containing 0·5*M*-hydrochloric acid) was prepared at 25°, 35°, and 45° by adding the necessary volume of constant-boiling hydrochloric acid to 750 c.c. (at the temperature of the bath) of acetic acid purified by the method of Orton and Bradfield (J., 1927, 983), and diluting to 1 litre at the temperature of the bath with conductivity water. The medium did not react measurably with bromine during 2—3 days. Solutions containing 0·1*M*-ketone and about 0·005*M*-bromine were made up in the medium at each temperature in 100 c.c. (or 50 c.c.) flasks, and the reactions were followed by withdrawing 20 c.c. (10 c.c.) at intervals and adding it to 80 c.c. (40 c.c.) of aqueous

potassium iodide containing a 50% excess over the anticipated titre. The liberated iodine was titrated against $N/50$-thiosulphate. In the case of the four higher phenyl alkyl ketones, after addition of starch, the end-point was observed by adding 5 c.c. of carbon tetrachloride to the liquid, closing the mouth of the flask tightly with a rubber stopper, and shaking well after each addition of thiosulphate. The tetrachloride dissolves the bromo-ketone, which otherwise clouds the liquid in the titration flask in addition to adsorbing small quantities of iodine.

The author records his indebtedness to Dr. H. B. Watson for his invaluable criticism and encouragement, and to Imperial Chemical Industries, Ltd., for grants.

TECHNICAL COLLEGE, CARDIFF. [*Received, February 27th,* 1936.]