271. *The Influence of Alkyl Groups upon Reaction Velocities in Solution. Part II. The Base-catalysed Prototropy of Phenyl Alkyl Ketones.*

By DAVID P. EVANS and JAMES J. GORDON.

A kinetic study of the prototropy of a series of phenyl alkyl ketones, $CH_2R{\cdot}COPh$, under the influence of acetate ion as catalyst has shown that lengthening or branching of the alkyl chain leads to an increase in the energy of activation probably reaching a constant maximum for the normal series at butyrophenone, while the P factor of the equation $k = PZe^{-E/RT}$ falls somewhat from acetophenone to propiophenone and thereafter remains constant. The changes in E are ascribed to the rising inductive effects of the alkyl groups, and the fall in P at one point only is interpreted on the basis of hydrogen-bond formation in propiophenone and the higher ketones. This is in harmony with the interpretation of the acid-catalysed prototropy of the same ketones suggested in Part I of this series.

THE acid-catalysed prototropy of a number of phenyl alkyl ketones has already been studied by one of us (Part I; Evans, J., 1936, 785), and the investigation has now been extended to include the base-catalysed reaction. Lapworth's bromination method has again been employed, the basic catalyst being the acetate ion (compare Morgan and Watson, J., 1935, 1173). In addition, the acid-catalysed prototropy of *iso*valerophenone has been studied under conditions identical with those employed in Part I. The following table summarises the results. The velocity coefficients are recorded as fall of N/50-thiosulphate titre per minute for 20 ml. of 0·1M-ketone solutions in 75% acetic acid containing 20 g. of sodium acetate per litre (for basic catalysis) or 0·5M-hydrochloric acid (for acid catalysis). The energies of activation were determined from the slope of the log k–$1/T$ plot, which in every case gives a good straight line.

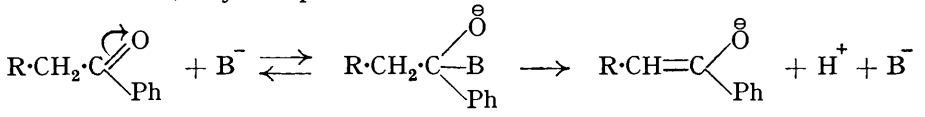
Base-catalysed Bromination of Phenyl Alkyl Ketones, $CH_2R{\cdot}COPh$.

R.	$k_{45°}$.	$k_{55°}$.	$k_{65°}$.	E, cals.
H	0·0520	0·1310	0·330	19,400
CH_3	0·00799	0·0219	0·0567	19,900
C_2H_5	0·00624	0·0172	0·0435	20,200
n-C_3H_7	0·00704	0·0188	0·0479	20,100
iso-C_3H_7	0·00305	0·00849	0·0224	20,500
($CH_2R = CHMe_2$)	0·00155	0·00444	0·0119	20,900

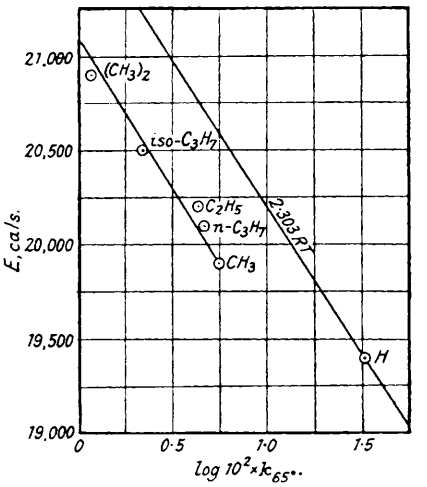
Acid-catalysed Bromination of iso*Valerophenone.*

R.	$k_{25°}$.	$k_{35°}$.	$k_{45°}$.	E.	P.
iso-C_3H_7	0·0335	0·112	0·347	21,700	0·23

The velocity of bromination of ketones in 75% acetic acid is almost immeasurably slow in the absence of a catalyst, and the addition of either hydrochloric acid or sodium acetate causes a very marked acceleration. There can be no doubt, therefore, that the results obtained in this work represent the speeds of prototropy by the " acid " and " basic " mechanisms respectively. For these changes we accept the schemes put forward by Watson, Nathan, and Laurie (*J. Chem. Physics*, 1935, **3**, 170; compare Part I for acid catalysis), according to which the measured energy of activation is that concerned in the initial collision of ketone and catalyst, while the P factor of the kinetic equation $k = PZe^{-E/RT}$ is determined, largely at least, by the proportion of the activated complex which is transformed into enol or enol ion. The mechanism of the base-catalysed change, which is here under consideration, may be represented as



The energy of activation for the *acid*-catalysed prototropy of propiophenone, as shown in Part I, has a value which is approximately 2000 cals. higher than the corresponding value for acetophenone. Further lengthening or branching of the alkyl chain (as, *e.g.*, in *n*- and *iso*-butyrophenones) has only a small effect upon E, however, and this has been confirmed by the new measurements on *iso*valerophenone. The *base*-catalysed prototropy of the same ketones offers a striking contrast in that there is no *sudden* change in E, but a relatively small increment (of some 300—500 cals.) in passing from acetophenone to propiophenone and from the latter to *n*-butyrophenone, at which point a maximum value appears to be reached since *n*-valerophenone shows no further increase. The values for *n*- and *iso*-valerophenones differ by 400 cals. only, but there is a difference of 1000 cals. between $CH_2Me{\cdot}COPh$ and $CHMe_2{\cdot}COPh$. Moreover, the change in E on replacing hydrogen of acetophenone by an alkyl group is in the *same direction* for the base-catalysed reaction as for the acid-catalysed change, in spite of their opposite polar types as indicated by the influence of substituents in the nucleus (Evans, Morgan, and Watson, J., 1935, 1167; Morgan and Watson, *loc. cit.*). These two significant observations are discussed in the sequel.



Base-catalysed prototropy of $CH_2R{\cdot}CO{\cdot}Ph$.

It is also interesting that the value of E for the base-catalysed reaction is lower than that for the acid-catalysed change of the same ketone, whereas the reverse is the case for acetone (Smith, J., 1934, 1744); this must be due to the presence of phenyl in the ketones dealt with here, and is reminiscent of the greater strength of benzoic than of acetic acid.

The diagram shows the plot of E against log $k_{65°}$ and the straight lines have the slope $-2{\cdot}303RT$; points falling on the same line represent ketones which give the same value for P. It is clear, therefore, that the value of P for the base-catalysed prototropy of all the ketones above acetophenone is almost the same; it is, however, rather less than that found in the case of acetophenone. This contrasts again with the phenomena observed in the acid-catalysed prototropy of the same ketones (Part I), where P increases by a power of ten from aceto- to propio-phenone and then decreases very gradually for the straight-chain derivatives but more markedly for the branched-chain compounds. This further contrast between acid- and base-catalysed prototropy is considered below.

The rise in both E and P from acetophenone to propiophenone in acid-catalysed prototropy is unparalleled throughout the whole investigation of the acetophenone system; for example, the introduction of a *p*-nitro-group raises E by less than 1000 cals., whereas the difference encountered here is 2000 cals. It is evident, therefore, that the substitution of methyl in the side chain of acetophenone must cause the operation of some additional and powerful factor. In Part I, a hydrogen bond linking the β-carbon with carbonyl oxygen was postulated, and we believe that the new observations are in complete harmony with this conception. It is necessary, however, to emphasise two extensions of this idea which were made by Dippy, Evans, Gordon, Lewis, and Watson (J., 1937, 1421). The suggestion of Sidgwick and Callow (J., 1924, **125**, 538) that the hydrogen of an alkyl group might, *in favourable circumstances*, become linked (by resonance) to an electron-donating atom (*e.g.*, in *o*-nitrotoluene) was adopted by these authors to interpret the relatively high dissociation constant of *o*-toluic acid; the hydrogen bond was regarded as being possible in the anion, the negative charge assisting its formation. This may perhaps be regarded as an attempt to give a more definite description of the interaction of a methyl group with carboxyl which was suggested originally by Bennett and Mosses (J., 1930, 2367). The presence of the bond in an ester such as ethyl *o*-toluate in its normal condition was not suggested, however, and the kinetics of the hydrolysis of this ester were explained by supposing that the " bond " is formed simultaneously with the approach of the attacking ion, and is therefore present *in the transition complex*. In the case of the phenyl alkyl ketones now under consideration, we adopt the same idea, *i.e.*, the ketones in their normal condition are not regarded as having a hydrogen bond. This is in harmony with the experiments of Gillette (*J. Amer. Chem. Soc.*, 1936, **58**, 1143; private communication) and of Hilpert, Wulf, Hendricks, and Liddel (*ibid.*, p. 548) on trimethylacetic acid and aldol respectively, which indicate the absence of a hydrogen bond in these compounds. During the catalysed prototropy of ketones, we consider that the formation of the hydrogen bond occurs simultaneously with the approach of the catalyst, *i.e.*, while the electromeric change $C\overset{\frown}{=}O$ is taking place. The bond reduces the electron-availability at carbonyl oxygen, and thereby makes the addition of the *acid* catalyst more difficult; the activation energy is therefore high.

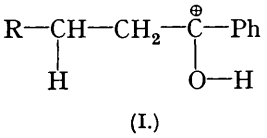
Dippy, Evans, Gordon, Lewis, and Watson (*loc. cit.*, p. 1425) also deduced that the effect of the hydrogen bond upon the energy of activation for alkaline hydrolysis will be small or negligible, since the attacking ion becomes linked at carbon and not at oxygen. We now suppose, therefore, that the hydrogen bond formed in the complex of a ketone and a *basic* catalyst will have no perceptible influence upon E, and there should therefore be no sudden rise in E in passing from acetophenone to propiophenone. The effect upon P is considered later.

Discussion of E *Values.*—The absence of a sudden rise in E at one point of the series of ketones under examination, predicted above, is completely borne out by experiment. There is no *sudden* increase at propiophenone, but a gradual rise as the chain lengthens, leading to a constant maximum value. We attribute this to the increasing inductive effect of the alkyl group (Me<Et<*n*-Pr, etc.), and the larger increment observed in the branched-chain ketones, $CHMe_2$·COPh and $CHMe_2$·CH_2·COPh is in harmony with this view. In the acid-catalysed change the relatively powerful effect of the hydrogen bond takes control, but there is even here a definite tendency for E to fall slowly (in accordance with an increasing + I effect of the alkyl group) as the series is ascended beyond propiophenone (see Part I).

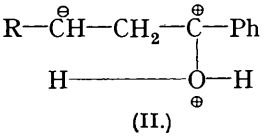
This small, but nevertheless detectable, fall in E for the acid-catalysed reaction as the alkyl chain lengthens would lead, however, to the expectation of an appreciably smaller E for *iso*butyrophenone, $CHMe_2$·COPh, than for propiophenone. This is not the case, for the two values are identical (Part I), and there must therefore be some compensating factor in the former. It seems reasonable to suppose that, although the presence of the two β-methyl groups in *iso*butyrophenone will increase the tendency for formation of the hydrogen bond, only *one* β-carbon can be involved at the same instant, and therefore the influence of the bond upon E will be the same in this ketone as in propiophenone. The

equality in the observed energies of activation may be due, however, to the ***smaller*** electron release from the secondary alkyl group than from the primary group by the mechanism postulated by Baker and Nathan (J., 1935, 1844)* which is referred to more fully in Part III (following paper); this effect is likely to be more pronounced in acid catalysis (which requires accession of electrons to the point of attack) than in basic catalysis, and in the latter case the inductive effect is therefore the only important factor governing the energy of activation.

Discussion of the P *Factor.*—We regard the *P* factor as governed mainly by the proportion of the transition complex which is transformed into enol or enol ion. On our view of a hydrogen bond linking carbonyl oxygen with β-carbon, the complex will be a resonance hybrid including structures such as (I) and (II) for acid catalysis and (III) and (IV) (where B = OAc, etc.) for base catalysis. The ketone–acid complex, (I) and (II),



(I.)



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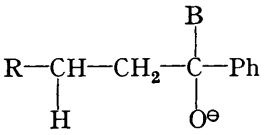
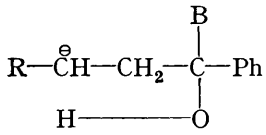
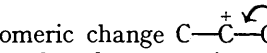


(III.)



(IV.)

contains a carbon atom having a deficiency of electrons, and it is reasonable to suppose that the driving force in the transformation of the complex (into the enol or the original ketonic form) is the tendency of this atom to complete its octet. Now, the participation of the structure (II) will operate against the electromeric change  which leads to the original ketone, with the consequence that the proportion of the complex transformed into enol is increased. Thus *P* is greater for propiophenone than for acetophenone. Variation in the group R will influence the ease with which α-proton can ionise (a necessary step in the production of enol, but not of ketone), and this accounts for the small but measurable fall in *P* in the ketones higher than propiophenone, and particularly in *iso*butyrophenone, where a second methyl group with its + *I* effect is linked directly to C_α (compare also the decrease in *P* on passing from *n*- to *iso*-valerophenone). In the light of our new results we consider this interpretation of the variation in *P* more probable than that put forward tentatively in Part I.

The complex including a basic catalyst, (III) and (IV), is of a different character, however. The carbonyl carbon has become saturated, and the tendency towards octet completion does not therefore exist; in fact, the electromeric change leading to the enolic or ketonic forms can occur only subsequently to or simultaneously with the withdrawal of the catalyst, and any factors tending to facilitate or oppose such withdrawal will influence equally the formation of both possible tautomerides. But the removal of α-hydrogen is required only for the production of enol. The ease with which this proton can ionise now becomes, therefore, the principal factor determining the proportion of enolic and ketonic forms into which the complex is transformed. The participation of structure (IV), with its negative charge at C_β, is definitely unfavourable to the removal of α-proton, and therefore the *fall* in *P* in passing from acetophenone to propiophenone is in accord with expectations. Moreover, the influence of the negative charge at C_β is not here neutralised by any neighbouring positive charge (as in II, for example), and is thus so powerful that the relatively small variation in the inductive effect of R has now no detectable influence.

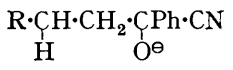
The postulate of a hydrogen bond in the transition complex thus provides a reasonable

* The necessary " compensating factor " might be an effect of opposite sign decreasing in the order secondary>primary, as postulated by Dippy (J., 1937, 1777), but the distinction between the acid- and base-catalysed reactions is not here so apparent.

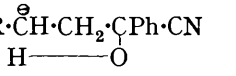
explanation of the *rise* in *P* from acetophenone to propiophenone in acid-catalysed prototropy, whereas there is a *fall* in the base-catalysed reaction.

Further Remarks concerning the Hydrogen Bond.—It has been shown above that the formation of a hydrogen bond linking carbonyl oxygen with β-carbon in the transition complex provides a satisfactory interpretation of the principal observations described here and in Part I; these are (*a*) the marked rise in *E* and *P* from acetophenone to propiophenone in acid-catalysed prototropy, (*b*) the absence of irregularities in the *E* values for base-catalysed prototropy, (*c*) the variations in *P* for the two changes. We know of no other interpretation which is applicable to all these facts, and we consider the presence of a hydrogen bond in the complex as very probable.

The relative stabilities of the cyanohydrins of phenyl alkyl ketones (Lapworth and Manske, J., 1930, 1976) are in harmony with the same conceptions. There is a marked increase in stability from acetophenone to propiophenone and then a gradual but consistent decrease as the *n*-series is ascended (cf. *E* for the acid-catalysed prototropy of the same ketones). On our view, the cyanohydrin ions derived from propiophenone and the higher *n*-alkyl ketones will be in resonance between structures such as (V) and (VI). There is



(V.)



(VI.)

here no question of the removal of an α-hydrogen or of a carbon atom with an incomplete octet; in the dissociation of the cyanohydrin the controlling process is  , and this is influenced unfavourably by the participation of the structure (VI), leading to the *increased* stability oberved in the cyanohydrin of propiophenone. The *decreasing* stability beyond this point is then due, in all probability, to the inductive effect of R, and the marked *rise* in stability of the cyanohydrins of the series $CH_2Me{\cdot}COPh$, $CHMe_2{\cdot}COPh$, $CMe_3{\cdot}COPh$ may be interpreted in the light of the Baker–Nathan effect.

One feature of Lapworth and Manske's results is of great significance. A similar order of stabilities is not found in dialkyl ketones, nor is there a sudden change in the rate of acid-catalysed prototropy of aliphatic ketones at any point in the series (Dawson and Wheatley, J., 1910, **97**, 2048). The velocities of formation of bisulphite compounds and oximes by aliphatic ketones, moreover, are in accordance with the inductive effects of the alkyl groups (Stewart, J., 1905, **87**, 185, 410). This suggests that it is necessary, for the formation of the hydrogen bond, that the movement of the carbon atom concerned should be restricted. In the phenyl alkyl ketones, one valency of the carbonyl carbon is occupied by phenyl, and this will provide adequate restriction of the movement of the alkyl chain to keep the β-carbon in the position necessary for hydrogen-bond formation, and in the *o*-substituted benzoic esters the *o*-group is similarly restricted in its movements by the nuclear linkage with carbethoxyl. Given the necessary damping of the movement in space for formation of the bond, the energy of the resonance structure will then probably keep the complex in this state until it is ruptured to yield products or reagents. In the aliphatic esters dealt with in Part III (following paper), branching at the α-carbon appears to provide the necessary conditions.

Experimental.

Materials.—Acetophenone, propiophenone, *n*-butyro- and *n*-valero-phenones were obtained and purified as described in Part I. *iso*Butyro- and *iso*valero-phenones were prepared by the Grignard synthesis previously employed for the *n*-valero-compound. The *iso*valerophenone had b. p. 126°/20 mm.; $n_D^{20°}$ 1·5127; semicarbazone, needles from aqueous alcohol, m. p. 209° (Auwers, *Ber.*, 1912, **45**, 2771, gives m. p. 208—209°); 2 : 4-dinitrophenylhydrazone, crimson plates from aqueous acetic acid, m. p. 131·5°.

Velocity Determinations.—The experimental procedure was similar to that employed in Part I. The medium consisted of 75% aqueous acetic acid (by vol.), made up at each temperature, and contained 20 g. of sodium acetate per litre (for basic catalysis) or 0·5M.-hydrochloric acid (for acid catalysis). The base-catalysed reactions were followed by running

20 ml. of reaction mixture at measured intervals into 80 ml. of a solution containing 50% excess of potassium iodide over the anticipated titre and 20 ml. of N/4-hydrochloric acid. The liberated iodine was titrated with N/50-thiosulphate, starch being the indicator. Carbon tetrachloride was added finally in those cases where the bromo-ketone separated during the titration. A typical set of results is included below.

Bromination of propiophenone at 55°.

Time (mins.)	0	94	162	241	
Titre, ml. of N/50-$Na_2S_2O_3$	10·40	8·36	6·82	5·16	
Fall in titre	—	2·04	3·58	5·24	
$k_{55°}$	—	0·0217	0·0221	0·0217	Mean 0·0218

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Note, added August 9th, 1938.—Since the preparation of this paper, the prototropy of phenyl alkyl ketones has been discussed by Ayling (this vol., p. 1014), who adopts the view of Bennett and Mosses in its original form; *i.e.*, he postulates an interaction of alkyl groups with carbonyl oxygen but regards this as a " field effect " and not as due to hydrogen-bond formation. The relatively high value of E found for the acid-catalysed prototropy of propiophenone is ascribed to the depressing effect of the α-methyl group upon the ease of ionisation of the proton; on the basis of the mechanism which we have accepted, this would decrease P and not influence E, whereas actually P increases by a power of 10 and E by 2000 cals. It is difficult to see how, on any mechanism, methyl can increase E for a reaction which is known to be of Type A, unless some factor quite distinct from its inductive effect is in operation Actually, Ayling's argument might lead to the expectation of a sudden rise in E at propiophenone in base-catalysed prototropy, and the work described above shows that this is not the case. Returning to the acid-catalysed reaction, the small and irregular changes in velocity for the ketones above propiophenone are due, of course, to the simultaneous gradual fall in E and P, and have, in themselves, no significance. It was further pointed out in Part I that the electron-attractive character of carbonyl is regarded as sufficient to make possible the formation of the bond by β-hydrogen; if, as we believe, the carbonyl carbon in the ketone–acid complex becomes far more positive than it is in the ketone itself (and even in the latter a dipole moment of about 2·7 D. is observed), there is still less difficulty in believing in the possibility of hydrogen-bond formation.