The Influence of Alkyl Groups upon Reaction Velocities in Solution. Part V. The Dissociation Constants of Ketone Cyanohydrins in Aqueous Alcohol.*

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A study of the dissociation constants of the cyanohydrins of R·CO·R′ where R = C_6H_5, C_6H_{11}, or alkyl, and R′ varies through a series of alkyl groups for each R, indicates that the hyperconjugative electron release is an important factor in determining the stability of the ketone relative to the cyanohydrin. In *tert.*-butyl *iso*propyl ketone there is marked steric effect of the alkyl groups.

The hypothesis of hydrogen bonding in the transition complex during the acid-catalysed bromination of propiophenone was suggested in Part I (Evans, *J.*, 1936, 785) to explain the high activation energy of this reaction. Baker (*J.*, 1939, 1150) has interpreted the results of Part I on the basis of hyperconjugative electron release from methyl or methylene in alkyl phenyl ketones. It was stated in Part I (*loc. cit.*, p. 786) that, although yielding a possible interpretation of the changes in E_a, Baker and Nathan's (*J.*, 1935, 1844) postulates did not afford an explanation of the observed variations in the probability factor P of the kinetic equation $k = PZe^{-E_a/RT}$. Moreover, in the subsequent Parts of this series (*J.*, 1938, 1434; 1938, 1439; 1940, 339) evidence appeared in support of the hydrogen-bonding hypothesis. The many recent confirmations of the reality of hyperconjugation of alkyl groups, however, led us to attempt to decide which of the above explanations is the more correct. It was considered that the dissociation constants of ketone cyanohydrins might afford useful data towards this end and that, coupled with further work on the bromination of suitable dialkyl ketones (Part VI, following paper), a decision could be reached.

The work of Lapworth and Manske (*J.*, 1928, 2533; 1930, 1976) and of Baker and Hemming (*J.*, 1942, 191) had revealed that cyanohydrin equilibria are sensitive to structural and electronic influences, and moreover, this reaction may be used for unsymmetrical dialkyl ketones, which cannot be readily used in bromination experiments owing to the possibility of attack on either α-carbon atom (cf. Hey, Jones, *et al.*, *J.*, 1948, 272, 276).

The dissociation constants of a series of cyanohydrins (formed from the ketones R·CO·R′) determined by the method employed by Baker and Hemming (*loc. cit.*) in constant-boiling ethyl alcohol, triethylamine being used as catalyst at 35°, are given in Table 1. For convenience in discussing these results, series of compounds have been selected in each of which one group (R′) is constant while the other (R) varies from methyl through the alkyl series. The order of decreasing dissociation constants, *i.e.*, decreasing ketone stability, is the order of decreasing electron release towards the carbonyl group. Lapworth and Manske's results for the alkyl phenyl ketones are included for comparison; the values quoted have been calculated for 35° by multiplying their 20° values by 2·4. This factor was obtained by a subsidiary investigation of the temperature variation of the cyanohydrin dissociation constants of certain alkyl *cyclo*hexyl ketones and acetophenone which is reported in Table 1.

Table 1. *Cyanohydrin dissociation constants in constant-boiling ethyl alcohol at 20° and 35°.*

Ketone R·CO·R′					Ketone R·CO·R′				
R	R′	Temp.	100K	Error, %	R	R′	Temp.	100K	Error, %
Ph	Me	35°	333	3·0	*cyclo*Hexyl	Pr^{n}	20°	8·79	—
*cyclo*Hexyl	Me	20	3·51	1·7	*cyclo*Hexyl	Pr^{i}	20	8·69	—
*cyclo*Hexyl	Et	20	4·10	2·7					

Using Lapworth and Manske's results at 20° for acetophenone and the alkyl methyl ketones and the later results of this paper for the alkyl methyl and alkyl *cyclo*hexyl ketones

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* Part IV, *J.*, 1940, 339.

at 35°, we obtain the values for the ratio K_{35}/K_{20} which are reported in Table 2. The constancy of K_{35}/K_{20} indicates the reasonable constancy of ΔH for each reaction. All the reactions involve the same kinds of bond rupture and formation, and an exact constancy of ΔH is only prevented by minor variations of bond energies in the various structures and by small differences in the heats of solution. Hence the value 2·4, the mean of the Table 2 ratios, has been used for the conversion referred to above.

TABLE 2. *Values of* K_{35}/K_{20} *for cyanohydrins of ketones* R·CO·R′.

Group R	Group R′					
	Me	Et	Pr^{n}	Pr^{i}	Bu^{n}	Bu^{t}
Ph	2·6	—	—	—	—	—
Me	2·3	2·0	2·5	3·5	2·6	2·4
*cyclo*Hexyl	2·2	2·4	2·4	2·5	—	—

Alkyl phenyl ketones at 35°. Values for these dissociation constants are as follows :

R	n-C_6H_{13}	n-C_5H_{11}	Me	Bu^{n}	Pr^{n}	Et	Pr^{i}	Bu^{t}
100K	348	312	312	276	216	148	60	21

It is to be noted that there is inversion of the order of inductive electron release for the Me, Et, Pr^{i}, and Bu^{t} compounds, but the dissociation constants for the normal alkyl compounds increase steadily from ethyl to *n*-hexyl, and have regained the value for methyl phenyl ketone at the *n*-pentyl compound. The low value of K for the *tert.*-butyl compound indicates the absence of large steric effects of the type found by Hughes *et al.* (*J.*, 1946, 157, *et seq.*) in the *neo*pentyl halides, and since the values of $+I$ for the alkyl groups are not markedly different, it must follow that Baker's explanation that the variation of K is the result of hyperconjugation effects is correct. The conclusion that *marked* steric effects are absent does not preclude the possibility of proximity effects in this series of compounds.

In ascending the series of alkyl phenyl ketones from the ethyl ketone there is a progressive increase in the dissociation constant, which is maintained even up to the *n*-hexyl compound. We conclude that in this series there is a steric effect of the proximity type which increases with chain length and in which the long-chain structure is restricted in its movement by the larger volume occupied by the phenyl group. The results for the *cyclo*hexyl ketones, where a similar structural influence appears, support this view.

Alkyl methyl ketones at 35°. The following Table gives the values of these constants :

R	Pr^{n}	n-C_6H_{13}	n-C_5H_{11}	Bu^{n}	Bu^{t}	Me	Pr^{i}	Et
100K	9·11	8·95	8·50	8·27	7·61	7·03	5·42	5·33

In this series partial inversion occurs in the order of electron release from the last four groups, but the values of K for *n*-propyl and higher ketones are almost constant. As for the *n*-alkyl phenyl ketones, there is a minimum value of K at the ethyl member, but there is no *marked* fall in the dissociation constant in passing from acetone to ethyl methyl ketone. The approximate constancy of K for the *n*-propyl and higher members indicates the absence of proximity steric effect as found in the previous series.

Alkyl ethyl ketones at 35°. The relevant data are :

R	Bu^{t}	Bu^{n}	Pr^{n}	Pr^{i}	Me	Et
100K	17·5	10·3	9·96	6·19	5·33	4·94

The only inversions evident in this series are Me > Et and Pr^{n} > Pr^{i}. The picture is thus similar to that in the methyl series, except that *iso*propyl shows definitely greater electron release than ethyl.

Alkyl n-*propyl ketones at* 35°. The following values show that the four groups Bu^{t}, Pr^{i}, Et, and Me have attained the normal order of inductive electron release, the dissociation constant of di-*n*-propyl is still measurably greater than that of *n*-propyl *iso*propyl ketone, and there is no minimum value of K at the ethyl member.

R	Bu^{t}	Pr^{n}	Pr^{i}	Et	Me
100K	26·9	13·4	10·9	9·96	9·11

Alkyl iso*propyl ketones at* 35°. Here again the normal order of inductive release is found. However, the extremely high value of K for *tert.*-butyl *iso*propyl ketone indicates the appearance of a new steric factor in the reaction, the influence of which is also indicated in di*iso*propyl ketone by the appreciable difference between the *iso*- and the *n*-compound.

R	$\mathrm{Bu^t}$	$\mathrm{Pr^i}$	$\mathrm{Pr^n}$	Et	Me
$100K$	808	19·3	10·9	6·19	5·42

Alkyl cyclo*hexyl ketones at* 35°. In this series there are no inversions of position, and *n*- and *iso*-propyl are in better accord with the expected order of inductive electron release from these groups. As expected, this series is comparable with the alkyl *iso*propyl ketones and there is no minimum at the ethyl member.

R	$\mathrm{Pr^n}$	$\mathrm{Pr^i}$	Et	Me
$100K$	21·6	20·7	9·82	7·78

Alkyl tert.*-butyl ketones at* 35°. In this series there is a qualitative repetition of the situation found in the *iso*propyl ketones. However, the appreciable increase in K for the ethyl over that for the methyl compound appears to indicate that some steric effect is present in the former, a conclusion which is supported by the further appreciable rise in K for the *n*-propyl and the very large increase observed for the *iso*propyl ketone.

R	$\mathrm{Pr^i}$	$\mathrm{Pr^n}$	Et	Me
$100K$	808	26·9	17·5	7·61

Hyperconjugation Effects of Alkyl Groups in Ketones.—It is evident that in moving from the first to last of the above series of ketones, there is a change from a fully inverted sequence of the groups Me, Et, $\mathrm{Pr^i}$, and $\mathrm{Bu^t}$ in the alkyl phenyl ketones to the normal sequence of inductive release when *iso*propyl, *cyclo*hexyl, or *tert.*-butyl is the constant group. The differences between the K values of the methyl and ethyl members of the various ketone series also show an interesting gradation :

Common group R...	Ph	Me	Et	$\mathrm{Pr^n}$	$\mathrm{Pr^i}$	*cyclo*Hexyl	$\mathrm{Bu^t}$
$\Delta 100K_{(\mathrm{Me-Et})}$	164	1·7	0·39	−0·85	−0·77	−2·04	−9·89

$\Delta K_{(\mathrm{Me-Et})}$ is a measure of the difference between the sum of the effects of inductive and hyperconjugative electron release in the methyl and in the ethyl compounds, steric effects being absent, and the figures point to a marked influence of the phenyl nucleus on the hyperconjugative electron release from methyl in methyl phenyl ketone (cf. Baker *J.*, 1939, 1150). This influence of the other group attached to carbonyl is very small or absent in the dialkyl ketones.

Again the values of $\Delta K_{(\mathrm{Pr^n-Pr^i})}$ for the different series bring out a further interesting observation :

Common group R...	Ph	Me	Et	$\mathrm{Pr^n}$	*cyclo*Hexyl	$\mathrm{Pr^i}$	$\mathrm{Bu^t}$
$\Delta 100K_{(\mathrm{Pr^n-Pr^i})}$	156	3·69	3·77	2·5	−0·9	−8·4	−780

The marked enhancement of hyperconjugation in the alkyl phenyl ketones is again shown here, but in addition there is indicated a very large effect in the opposite direction in the *tert.*-butyl ketones owing to a steric influence the exact nature of which is postulated below.

Steric Effects in Ketone Cyanohydrin Equilibria.—It is suggested that the steric impedance present in a given ketone is determined approximately by the extent and efficiency with which the approaches to carbonyl-carbon are screened, the side remote from the oxygen atom being particularly important. The absence of steric effects in methyl ketones establishes an arbitrary zero structure. Construction of molecular models and simple diagrams shows that in all ketones based on the groups Et, $\mathrm{Pr^i}$, and $\mathrm{Bu^t}$ some restriction of alkyl-group rotation must occur and in the most highly branched ketone studied (*tert.*-butyl *iso*propyl ketone) rotation of either group is only possible if its motion is synchronised with that of the other. We thus attribute the large steric effect observed in the latter ketone to a steric meshing of the rotating groups.

The steric effect evident in the other structures (*e.g.*, phenyl and *cyclo*hexyl ketones with normal alkyl groups having three or more carbon atoms in the chain) is regarded as being more random than the above and arises as the volume of rotation of the ring is increasingly entered by the irregular volume of the alkyl chain.

EXPERIMENTAL

Preparation of Ketones.—All ketones used, except a few purchased, were made by standard methods outlined below.

Alkyl methyl ketones were prepared by alkylation of acetoacetic ester with the appropriate alkyl halide or dialkyl sulphate. Acetone was used as a solvent, and a small amount of potassium iodide with twice the equivalent amount of potassium carbonate (based on the alkylating agent) were included in the reaction mixture which was stirred at reflux temperature until only traces of potassium carbonate remained. Finally, the reaction mixture was filtered, the solvent removed, and the derivative hydrolysed with excess of 2N-aqueous sodium hydroxide. Ethyl alcohol–ketone binary or ethyl alcohol–ketone–water ternary mixtures were obtained on distillation, and these were separated by repeated extraction with brine and distillation. Final yields were 40—50%.

Other alkyl ketones were made by reaction of aliphatic aldehydes with a suitable Grignard reagent; the alcohols were isolated and oxidised to the ketones by sulphuric acid–chromic acid in cold acetone (Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39). The alkyl-*tert.*-butylcarbinols were made by a modification of Whitmore and Houk's general procedure (*J. Amer. Chem. Soc.*, 1932, **54**, 3714). The yields of carbinol were generally 60—70% except in the *cyclo*hexyl series for members above methyl, for which 40—50% yields were obtained, and for the *tert.*-butylcarbinols prepared from *tert.*-butyl chloride, for which approximately 20% yields were recorded. The oxidation of the alcohols was uncomplicated and the yields were usually 45—65%.

The final ketones showed physical constants (b. p.s and refractive indices) agreeing reasonably with those of Timmermans ("Physicochemical Constants of Pure Organic Compounds," Elsevier, 1950) or of Beilstein. Samples for equilibrium and kinetic study (see following paper) were obtained from the bulk yields above by stringent fractional distillation in which a small middle fraction, of boiling range $\not>$0·3°, was taken.

Equilibrium-constant Determination.—All measurements were made by a slight modification of Baker and Hemming's method (*J.*, 1942, 191). The solvent, constant-boiling ethyl alcohol, and the anhydrous hydrogen cyanide were similarly prepared; but all measurements at both 20° and 35° were made in sealed tubes and triethylamine instead of tri-*n*-propylamine was used as a catalyst. The ketones (*ca.* 0·3 mmole) were directly weighed into the drawn-out and calibrated tubes, which were stoppered during the operation. The walls were washed down with solvent, and 2 ml. of 1M-hydrocyanic acid in the solvent were added, followed by 1 ml. of 2% triethylamine solution also in the solvent. The volume was made up to approximately 9·8 ml. and finally adjusted to 10 ml. when the tube had been brought to the experimental temperature. The tube was then sealed.

All samples were kept for 24 hr. at 35° ± 0·05° or for 72 hr. at 20° ± 0·05° before analysis. The equilibrium concentration of hydrocyanic acid was determined by breaking the cleaned tubes by shaking in a wide-necked glass-stoppered bottle containing standard silver nitrate solution in slight excess over the expected hydrocyanic acid, in 75 ml. of 0·5% nitric acid. The contents were filtered and washed, the filtrate being made up to 150 ml. before titration with N/20-ammonium thiocyanate solution. In all experiments several blank determinations were performed, the titres so obtained serving as a measure of the amount of hydrocyanic acid added to the tests.

Specimen results for ethyl *cyclo*hexyl ketone are given below, the concentrations being expressed as equivalent ml. of N/10 per 10 ml. of solution. The general accuracy achieved was approximately ±3·0% which is comparable with that of Lapworth and Manske (*J.*, 1928, 2533). The unusually high dissociation of *tert.*-butyl *iso*propyl ketone led to very small consumption of

Cyanohydrin dissociation of ethyl cyclo*hexyl ketone at* 20°.

Time,	Initial volumes				Equilibrium volumes			
hr.	Ag^+	CNS^-	HCN	Ketone	HCN	Cyanohydrin	Ketone	100K
72	9·95	3·32	19·64	20·82	6·63	13·01	7·81	3·98
72	9·95	3·82	19·64	22·75	6·13	13·51	9·24	4·20
72	9·95	3·55	21·09	24·05	6·40	14·69	9·36	4·07
72	9·95	3·86	21·09	25·23	6·09	15·00	10·23	4·17

Mean value: $K \times 10^2 = 4·10 \pm 0·11$.

hydrocyanic acid, with the result that the accuracy here is considerably lower but the value is still sufficiently sound for the purposes of the discussion.

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