CCLVI.—*The Conditions determining the Thermodynamic Stability of Cyanohydrins of Carbonyl Compounds. Part II. Dissociation Constants of some Cyanohydrins derived from Methyl Alkyl and Phenyl Alkyl Ketones.*

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In Part I (J., 1928, 2533) the dissociation constants of a number of cyanohydrins derived from (i) substituted benzaldehydes and (ii) closed-chain ketones were given. In the present communication these are supplemented by dissociation constants of a number of cyanohydrins derived from ketones belonging to two main types, namely, Alk·CO·CH_3 and Alk·CO·C_6H_5.

As before, the number of compounds examined makes it impracticable to do much more than indicate the source of each and the mode adopted for purification preparatory to the quantitative measurements. Most of the ketones examined were liquids and were therefore at the final stages subjected to repeated fractionation as recommended by Richards (*J. Amer. Chem. Soc.*, 1912, **34**, 978).

The majority of the purely aliphatic ketones, higher than methyl ethyl ketone, were purchased and carefully fractionated several times. Methyl *tert.*-butyl ketone (pinacolin) was made from pure pinacone hydrate by Hill's process (*ibid.*, 1923, **45**, 1559).

Most of the phenyl alkyl ketones, Alk·CO·C_6H_5, were prepared by the action of benzene and aluminium chloride on the acid chlorides. Propionyl, *n*-butyryl, and *iso*butyryl chlorides were purchased from British Drug Houses, Limited, and fractionated. Other chlorides were prepared by the action of thionyl chloride on the corresponding acids. Of the latter, *iso*valeric acid was purchased from Kahlbaum, and *n*-hexoic (caproic) acid from British Drug Houses, Limited; *n*-valeric acid was synthesised from *n*-butyl bromide by acting on the Grignard derivative with carbon dioxide (Gilman and Parker, *ibid.*, 1924, **46**, 2816); *iso*butyl- and *iso*amylacetic acids were synthesised by the malonic ester process. The boiling point ranges of the fractionated phenyl alkyl ketones in no case exceeded 1°.

Phenyl iso*hexyl ketone,* $C_6H_5{\cdot}CO{\cdot}[CH_2]_3{\cdot}CH(CH_3)_2$, does not appear to have been prepared before. It had b. p. 273—274°/740 mm. (Found: C, 81·8; H, 9·5. $C_{13}H_{18}O$ requires C, 82·1; H, 9·4%). *cyclo*Hexyl phenyl ketone was made by heating *cyclo*hexyl magnesium bromide in ether with benzonitrile for 3 hours, evaporating the solvent, decomposing the pasty residue with ice and ammonium chloride, and then distilling it in steam. The later portions of the volatilised oil solidified; these were collected, dried, and recrystallised from light petroleum. From 82 g. of *cyclo*hexyl bromide, 30 g. of ketone (m. p. 57°) were obtained. The compound had previously been made by other methods (*Compt. rend.*, 1904, **139**, 345; *Ber.*, 1897, **30**, 1942; 1915, **48**, 1698).

Phenyl *tert.*-butyl ketone was made from pure phenyl *iso*propyl ketone by the action of methyl iodide and potassium hydroxide in a closed tube (Nef, *Annalen*, 1900, **310**, 318). The process was repeated, and the final product fractionated three times through a short column; it had b. p. 219—219·5°/740 mm.

The next three ketones included do not belong to either of the two preceding categories; the dissociation constants of their cyanohydrins illustrate the result of replacement of α- and β-hydrogen respectively in an aliphatic ketone by a phenyl group.

Phenylacetone (methyl benzyl ketone) was made by Young's process (J., 1891, **59**, 623). Benzylacetone (methyl β-phenylethyl ketone) was prepared from ethyl benzylacetoacetate by alkaline hydrolysis (Guareschi and Conti, *Chem. Zentr.*, 1901, i, 581), separated from traces of indifferent oil by dissolving it in aqueous sodium bisulphite, and subsequently recovered from the solution. β-Phenylethylacetone (methyl γ-phenylpropyl ketone), $C_6H_5\cdot[CH_2]_3\cdot CO\cdot CH_3$, was prepared from ethyl β-phenylethylacetoacetate (b. p. 160—163°/10 mm.) by allowing the ester (34 g.) to remain with a cold solution of potassium hydroxide (15 g.) in dilute alcohol (70 c.c.) for two days, then heating them under reflux. The portion of the neutral product which boiled at 240—260° was converted into solid bisulphite compound, from which the ketone was recovered and twice fractionated. The ketone had b. p. 242·5°/740 mm. (Found: C, 81·1; H, 8·6. Calc. for $C_{11}H_{14}O$: C, 81·5; H, 8·6%).

The dissociation constants of the cyanohydrins were determined in 96% alcohol at 20° ± 0·5°, the procedure being precisely as described in Part I (*loc. cit.*, p. 2542).

The consistency of separate measurements for the same ketone in experiments carried on side by side was satisfactory throughout; the "probable errors" were less than 5% in all cases, but are omitted from the following tables since they tend to suggest a standard of accuracy for the absolute values of the constants which is in many cases much in excess of what the authors can claim. When the values of K are greater than about 0·02, not only the absolute but also the relative importance of experimental error increases rapidly. For this reason the numbers in the last column (free energy changes), which are rounded to the nearest unit or half-unit, according to the magnitude of K, are the least likely to be misleading.

TABLE I.

Dissociation constants of cyanohydrins of some methyl alkyl ketones.

Ketone.	No. of detns.	$K \times 10^2$.	$\Delta F \times 10^{-2}$.
Acetone	5	3·05	−20
Methyl ethyl ketone	5	2·65	−21
,, *n*-propyl ketone	4	3·55	−19
,, *n*-butyl ketone	4	3·2	−20
,, *iso*propyl ketone	4	1·55	−24
,, *tert.*-butyl ketone	4	3·1	−20

The following provide an interesting comparison :

Ketone.	No. of detns.	$K \times 10^2$.	$\Delta F \times 10^{-2}$.
Methyl benzyl ketone	4	2·15	−22
,, β-phenylethyl ketone	4	3·5	−20
,, γ-phenylpropyl ketone	3	3·6	−19

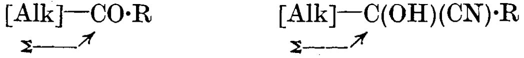
TABLE II.

Dissociation constants of cyanohydrins of some ketones containing both aliphatic and aryl residues.

Ketone.	No. of detns.	$K \times 10^2$.	$\Delta F \times 10^{-2}$.
Phenyl methyl ketone	6	130	2
,, ethyl ketone	5	60	−3
,, *n*-propyl ketone	5	90	−0·5
,, *n*-butyl ketone	4	115	1
,, *n*-amyl ketone	4	130	2
,, *n*-hexyl ketone	4	145	2
,, *iso*propyl ketone	4	25	−8
,, *iso*butyl ketone	3	155	3
,, *iso*amyl ketone	4	155	3
,, *iso*hexyl ketone	3	125	1
,, *tert.*-butyl ketone	4	9	−14
,, *cyclo*hexyl ketone	4	40	− 6
(Benzaldehyde		0·47	−31)

Discussion of Results.

Replacement of [H] in [H]·CO·CH_3 or in [H]·CO·C_6H_5 by an alkyl group leads in all cases to a large decrease in the stability of the corresponding cyanohydrin. The dissociation constant of the cyanohydrin is about 11 times as large in the case of acetone as in that of acetaldehyde (Jones, J., 1914, **105**, 1560), while, in passing from benzaldehyde to acetophenone there is a 280-fold increase. The authors take the view that the " primary " effect of the substituent on the carbon to which it is directly attached is here the main factor concerned (Part I, *loc. cit.*, p. 2536) :



$$\underset{\Sigma\longrightarrow\nearrow}{[\mathrm{Alk}]\text{—}\mathrm{CO{\cdot}R}} \qquad \underset{\Sigma\longrightarrow\nearrow}{[\mathrm{Alk}]\text{—}\mathrm{C(OH)(CN){\cdot}R}}$$

though direct effects of the substituent on the other atoms in the carbonyl group, on the one hand, and in the OH and CN groups, on the other, are by no means negligible.

The effect of phenyl as substituent in direct attachment to the carbonyl carbon is in the same sense as that of alkyl, but is much more striking, the cyanohydrin dissociation constant increasing in 42-fold ratio on passing from acetone to acetophenone. It seems probable that the influence of conjugation between the carbonyl and phenyl groups contributes largely to this result (J., 1928, 2536) by raising the stability of the carbonyl structure.

The effects observed on varying the size or structure of the alkyl groups enclosed in square brackets in the preceding formulæ do not admit of any simple interpretation. Any such change of structure must modify not only the primary effect of the alkyl group on the attached carbon atom, but also the direct effects (electropolar and "steric") of the alkyl group on other parts of the carbonyl and cyanohydrin systems. The data obtained by the authors indicate that the sum total of these direct effects may sometimes be in one sense and sometimes in the other, but in its influence on cyanohydrin equilibrium it remains subsidiary in importance to the primary effect.

The effect of replacement of hydrogen in the α-position in the ketone by alkyl or phenyl is, at the first and second steps at least, to increase the stability of the cyanohydrin, and in addition to examples occurring in Tables I and II, the similar case of 2-methyl*cyclo*hexanone may be cited (Part I, *loc. cit.*, p. 2548). Phenyl, as substituent in the α-position, is apparently more effective than methyl, ethyl, or *n*-propyl. These effects of α-substitution bear a close resemblance to those of ortho-substitution on the dissociation constants of cyanohydrins of aromatic aldehydes (Part I., *loc. cit.*, p. 2547), where a uniformly stabilising influence of the substituent was found.* In the study of ionisation constants of aliphatic carboxylic acids, effects which correspond closely with "ortho-effects" have also been observed, but more clearly in the β- than in the α-position (compare Flürscheim, J., 1909, **95**, 727), but it must be pointed out that in the ionisation of such acids the substituent is operating, directly or indirectly, on atoms of the carboxyl group only, while in the cyanohydrin equilibrium it may be operating effectively on the CN group of the cyanohydrin, and obviously α-methyl in the ketone must be reckoned as β-methyl in the corresponding cyanohydrin.

Perhaps the most disconcerting feature of the data relating to cyanohydrin stability is the fact that the substitution of methyl for hydrogen in the β-position in the aliphatic radical attached to the

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* There is a possible connexion between such stabilising effects at close quarters and the function, a, in van der Waals's equation,

$$RT = (p + a/v^2)(v - b).$$

carbonyl compounds shows nothing of the stabilising effect associated with ortho-substitution (the nearest analogue of β-substitution) in the aromatic series.

On comparing the constants for *iso*butyl with *n*-propyl and *iso*amyl with *n*-butyl in the series of phenyl alkyl ketones it would seem that, except in the α-position, methyl exercises a small destabilising effect on the cyanohydrin of an aliphatic ketone, which is consistent with the recognised electron-repulsive electropolar properties of alkyl groups. Nevertheless, as also may be gathered from consideration of the ionisation constants of the lower fatty acids, it seems evident that, in the near neighbourhood of the carbonyl or carboxyl group, the conditions are highly complex, and attempts to assign to each factor its precise share in any comparatively small observed effect are probably foredoomed to failure.

How slightly replacement of methyl by phenyl, except in direct attachment to the carbonyl carbon atom, affects the results, in spite of the supposed opposite electropolar effects of the two substituents in question, may be gathered by comparing the values of $\Delta F \times 10^{-2}$ for the cyanohydrins derived from the three pairs

$CH_2Ph{\cdot}CO{\cdot}CH_3$ (− 22) and $CH_2Me{\cdot}CO{\cdot}CH_3$ (− 21),
$Ph{\cdot}[CH_2]_2{\cdot}CO{\cdot}CH_3$ (− 20) and $Me{\cdot}[CH_2]_2{\cdot}CO{\cdot}CH_3$ (− 19),
$Ph{\cdot}[CH_2]_3{\cdot}CO{\cdot}CH_3$(− 19) and $Me{\cdot}[CH_2]_3{\cdot}CO{\cdot}CH_3$ (− 20).

(Differences of one unit in 20 cannot be guaranteed as real here.)

A remarkable variation from the usual effect of substitution of hydrogen by methyl is observed in passing from the cyanohydrin of dimethylacetone (*iso*propylacetone) to that of ααα-trimethylacetone (*tert.*-butylacetone). Here an analogy with the changes observed in basic affinity constant in passing through the series, NH_3, $NH_2{\cdot}CH_3$, $NH(CH_3)_2$ and $N(CH_3)_3$, may be suspected. Flürscheim has already discussed the latter case (J., 1910, **97**, 88, 89), and the present authors, without wishing to signify agreement with all his deductions, accept his theoretical demonstration that when two factors, each consistent in sign, are acting in opposition to one another, their joint influence on chemical properties in a second or third substitution may not be in the same sense as that produced by the first. Regarded from this point of view, the absence of a similar reversal in the series of dissociation constants in Table II appears less remarkable. Irregularities which are conspicuous in small molecules may become submerged in larger ones, and generally the constants for the *n*-alkyl ketones in Table II lie more nearly on a smooth curve than do those in Table I.

Summary.

A number of ketones of the types Alk·CO·CH_3 and Alk·CO·C_6H_5 have been obtained in nearly pure condition, and the dissociation constants of their cyanohydrins have been measured at 20° ± 0·5°, the medium being 96% alcohol.

The effect of replacing a hydrogen atom in the α-position in the alkyl group is usually to increase the stability of the corresponding cyanohydrin, though a decrease is noticed on passing from methyl *iso*propyl ketone to methyl *tert.*-butyl ketone. Methyl, replacing H in the β-position, usually causes a slight fall in the stability of the cyanohydrin. These effects are thought to be, in the main, due to direct influence of the substituent on the CO or C(OH)·CN groups—a stabilising " steric effect " at very close quarters and a destabilising " electropolar " effect at points more remote. A connexion between " steric " effects of this kind and the function, *a*, in van der Waals's equation is suggested.

The authors desire gratefully to acknowledge that a considerable proportion of the cost of materials required for the investigation was defrayed from a grant made by Imperial Chemical Industries, Limited.

THE UNIVERSITY, MANCHESTER. [*Received, July* 11*th*, 1930.]