CCCXXXVI.—*The Conditions determining the Thermodynamic Stability of Cyanohydrins of Carbonyl Compounds. Part I. Some Effects of* (a) *Substitution in Aromatic Aldehydes and* (b) *Ring Formation.*

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Since the condition of equilibrium attained by a system undergoing a reversible thermal chemical change is subservient to the laws of thermodynamics and independent of considerations such as the relative velocities of the reactions by which the final state is attained, it follows that any factor connected with the constitution of one or more of the molecular species concerned, which is found to produce a definite alteration in the condition of equilibrium, is one which affects the " static " or average condition of the individual molecules. The adjective " static " is here used with full recognition of the principle that there is always a great variety of deviations from the average.

In recent discussions of the theory of mechanism of reaction of carbon compounds, there has been evident a tendency to regard some of the factors which control chemical change as operating primarily on reaction velocity and others on the conditions of equilibrium. Among the factors which have been most frequently considered are those to which Flürscheim originally applied the distinguishing terms " quantitative " and " electropolar " (compare J., 1909, **95**, 725). These two terms are retained throughout the present paper, being regarded as defined, not by any special hypothesis, but rather by the practical criteria originally laid down by Flürscheim.

The work of Victor Meyer and his pupils revealed the depressant effect of ortho-substituents on the rates of hydrolysis of benzoic esters. Flürscheim showed that all substituents when present in the ortho-position also have the effect of raising the ionisation constant of benzoic acids, no matter what the signs of the quantitative and electropolar factors. He attempted to account for this kind of effect by the introduction of a theory which had a kinetic basis (*loc. cit.*). His explanation still has a wide popularity, but is not accepted by the present authors, for it virtually postulates a mechanism by the automatic operation of which the second law of thermodynamics is rendered inoperative; the case is, in fact, one in which the principle restated in the foregoing paragraphs can be usefully applied. Since the ionisation constant of an acid at any given temperature and pressure and in any given solvent is simply a function of the increase in the free energy which is associated with the complete ionisation (including any simultaneous change of solvation) of 1 g.-mol. of the un-ionised acid as it exists in the solution, it is evident that the so-called " steric " factor does not, in this instance at least, operate primarily by modifying the speed at which a given change in entropy occurs, but actually alters the chemical potentials or entropies of the individual ions or molecules (or both) concerned.

Flürscheim also discovered and demonstrated in convincing manner that, not only the so-called " steric " factor, but also the quantitative and electropolar factors make themselves felt in the magnitudes of ionisation constants. It follows of necessity that all three factors affect the entropies of the separate molecules or ions or both. The data now given (see Experimental) seem to show beyond doubt that neutral molecules are influenced by all three factors, and it would be unreasonable to assume that the same is not also true of ions.

It should now be clear that, if the alternate effects associated with the factor which Flürscheim termed "quantitative" be admitted to have a polar origin, then it would not be logical to maintain that polar considerations primarily affect reaction velocity (compare E. H. Ingold, J., 1925, **127**, 470).

Evidence obtained during the course of measurements of cyanohydrin equilibria (on which subject the experimental section of the present paper forms the first communication) indicates the operation of other factors which are not conspicuous in the study of ionisation of carboxylic acids or of aromatic substitution. Whilst the substituents NMe_2, OH, OCH_3, Cl, and CH_3 produce on the stability of benzaldehydecyanohydrin effects which are not inconsistent with prevailing views on the modes of operation of their quantitative and electropolar factors, the nitro-group appears out of place (p. 2546). There is already evidence that the nitro-group is not singular among meta-directive substituents in simulating the properties of ortho-para-directive substituents when the practical issue is the reduction in the additive power of a carbonyl group. Thus Mr. Glyn Owen, in these laboratories, has found that the cyanohydrin of benzoylformic ester has a somewhat higher dissociation constant than benzaldehyde, and as it is well known that the carbonyl group of ethyl benzoate has but very feeble additive properties, it is clear that in respect to efficiency in producing such results CO_2Et also comes between H and OEt.

The tendency of two or more double bonds (this term being applied to systems present in ethylenes, in $\cdot NO_2$, $\cdot CO\cdot Alk$, and $\cdot CO_2Alk$) to arrange themselves alternately with single bonds indicates that such an arrangement is ordinarily associated with an element of stability (*i.e.*, of large entropy) which must therefore operate unfavourably on any chemical change in which that arrangement is destroyed. There is no reason to believe that this factor is *necessarily* associated with polarisation. It will hereafter be referred to as the "Thiele factor," in view of the circumstance that the term "conjugation" is now commonly applied in a much wider sense. This factor would operate so as to stabilise, though to a quite unknown extent, the carbonyl form in a ketone or aldehyde of the types $CR^1R^2{:}CR^3{\cdot}CR^4{:}O$, $O{:}CR^1{\cdot}CR^2{:}O$, and probably also $NO_2{\cdot}CR{:}O$. This may conceivably account for some apparent abnormalities in cyanohydrin formation, but there is yet another possibility which must not be overlooked.

The symbol $\overset{\cdot}{\bar{\mathrm{A}}}_0\underset{\curvearrowright}{\overline{\nearrow}}\mathrm{A}_1$, etc., was first used by one of us in an attempt to account for the alternate effects (associated with the quantitative factor) to which such substituents as NMe_2, OEt, CH_3, etc., in position A_0 give rise when they are attached directly to carbon in position A_1 in certain atomic assemblages. The symbol implied (1) an increase in the covalence between A_0 and A_1, and (2) a movement of Faraday tubes equivalent to a drift or displacement of electrons, relatively to nuclei, in the direction indicated by the arrow.

The view may now be expressed that what is here essential is (1) the direction of electron displacement, and (2) the resulting change in the properties of A_1 and the atoms to the right of A_1. If it be assumed, for simplicity in the first instance, that the molecule terminates at A_1, the operation suggested in the figure would clearly imply that the nucleus of A_1 is engaged with an increased share of electrons, and consequently the restraint which it can exercise over its proper valency electrons must diminish, much as if some of its central charge has been removed. The " fugacity " of the valency electrons of A_1 has increased.

It is not apparent that there is any mode of ascertaining how far an observed change in the restraint on the valency electrons of an atom caused by replacement of H by A_0 (when A_0 is, for example, CH_3) can be ascribed to change in the value of the covalency, how far to simple electron displacement relative to nuclei (electron drift), or how far to an external electrostatic field, such as one arising out of the formation of the arrangement A_0—A_1, etc., from H—A_1, etc. It is rather the *sum total* of these which we may hope to detect, and possibly to estimate roughly, by observing either the change in the properties of A_1 or the consequent effects of this change on the rest of the molecule. The latter method was in principle the practical basis of the criteria used by Flürscheim.

Henceforward, therefore, the modified form $\overset{\cdot}{\bar{\mathrm{A}}}\underset{\Sigma\text{—}\nearrow}{\text{—}}\mathrm{A}_1$, etc., will be used to denote an arrangement in which the replacement of H in H—A_1, etc., by A_0 produces, *by all effects from the left combined* (as indicated by Σ), an increase in the fugacity of the valency electrons of A_1, and this will be termed the " primary " interior effect of the substitution process. It is held that the classification of substituents based on Flürscheim's criterion for the quantitative factors gave the most satisfactory means hitherto discovered of ascertaining primary interior effects, *i.e.*, of ascertaining whether, and roughly to what relative extent, a given substituent normally increases or decreases the fugacity of the valency electrons of a tervalent carbon atom at which substitution occurs. Those substituents, like NMe_2, OEt, Cl, and alkyl, which produce the same type of quantitative effect as a negative charge would do, are supposed to be those which by such substitution raise, on the whole, the fugacity of the electrons of A_1, when A_1 is a tervalent * or bivalent carbon atom. Substituents such as NO_2, CO·R, and NMe_3^+ in place of A_0 are imagined to be those which in their totalised effect on A_1 (where A_1 is tervalent or bivalent carbon) reduce the fugacity of its valency electrons.

It should be noted that the hypothesis above defined has definite reference to effects on tervalent and bivalent carbon only. Evidence as to how such groups as NMe_2, OH, or OAlk affect the restraint on valency electrons of an attached saturated (quadrivalent) carbon atom is not conclusive, but the change is certainly small. It is the *difference* between the effects on quadrivalent and tervalent or between tervalent and bivalent carbon to which attention must be paid in considering the stability of covalence attachments.

In connexion with the stability of the cyanohydrins of aldehydes and ketones, Robinson and Rây have explained how a substituent which increases the fugacity of the electrons of the carbon atom of a carbonyl group virtually endows that atom with an increased negativity, which must tend to decrease its attraction for negative ions such as CN^- (J., 1925, **127**, 1610). The present authors concur in this idea in so far as the electrostatic attraction is concerned, but suggest that something even more far-reaching may be postulated.

It has been suggested above that introduction of a substituent such as NMe_2, OH, OCH_3, Cl, or CH_3 in place of H produces a *totalised* effect on unsaturated carbon which is equivalent to a decrease in the restraint exercised by the central positive charge on the octet. With such an alteration, the atom will tend to display properties approaching those of boron. It follows that those structures in which the atom displays tervalency will become more stable *relatively to those in which it displays quadrivalency.* Consistently with this, the capacity of carbonyl to form stable, neutral, addition

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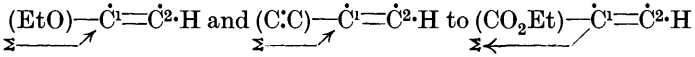
* " Tervalent " is applied in the present paper to an atom which is exercising the co-ordination number 3, in the sense originally intended by Werner. Thus, carbon in ethylene, carbonyl, and carboxyl is described as " tervalent," and carbon in carbon dioxide as " bivalent." This application of such terms is in no way novel (compare Smith's " Inorganic Chemistry," by J. Kendall, G. Bell and Sons, Ltd., 1927, pp. 158—161), and has now been adopted in view of recent tendencies to restrict the use of the term " co-ordination."

products with $H\cdot CN$, $H\cdot OH$, and $H\cdot NH_2$ decreases wherever the present theory, by utilising Flürscheim's criteria, predicts a large increase in the fugacity of the electrons of the carbonyl carbon atom, providing that the constitution of the substituent is not such as to form with the rest of the molecule a system with alternate single and double linkages and, therefore, is not such as to provide the carbonyl compound with an added non-polar element of stability (" Thiele factor," p. 2535). With singly bonded substituents, X in $X\cdot CO\cdot R$, it may with confidence be stated that the stability of the carbonyl addition products with neutral agents of the type above specified will be found to increase in the order : $X = NMe_2$, OAlk, Alk, (H). The truth of this is obvious enough in its application to the large contrast between OMe and CH_3 (in esters and ketones) and even to the comparatively small contrast between CH_3 and H, as consideration of the gradation in properties of $CH_3\cdot CO\cdot CH_3$, $H\cdot CO\cdot CH_3$, and $H\cdot CO\cdot H$ will show.

If the analogy of changing central restraint suggested above may legitimately be pursued further, it may be inferred that replacement of H in $H\cdot C^1R{:}X$ by a substituent of the meta-directive type, such as NO_2 or $CO\cdot R$, would have an effect on the carbon atom C^1 equivalent to an increase in the central charge on the latter. The atom C^1 might be said to show more " positiveness " in consequence of this; but it does not necessarily follow from this that the atom would more readily form a more stable covalency link by combination with a CN^- or OH^- ion. On passing from boron through carbon and nitrogen to oxygen, with increasing nuclear charge the capacity of the atom to exercise the co-ordination number 4 rises to a maximum and then decreases. Similarly, as A_0 in $A_0\cdot C^1R{:}X$ is replaced successively by NMe_2, OMe, CH_3, H, $CO\cdot R$, and NO_2, the compound becomes more cationoid, but the relative stability of the addition product in which C^1 is quadrivalent may attain a maximum (not *necessarily* at hydrogen), and then decline. In this connexion it is very significant that on passing from, say,



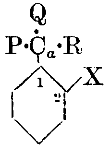
$$(\mathrm{EtO})\!-\!\dot{\mathrm{C}}^{1}{=}\dot{\mathrm{C}}^{2}\cdot\mathrm{H} \text{ and } (\mathrm{C{:}C})\!-\!\dot{\mathrm{C}}^{1}{=}\dot{\mathrm{C}}^{2}\cdot\mathrm{H} \text{ to } (\mathrm{CO_2Et})\!-\!\dot{\mathrm{C}}^{1}{=}\dot{\mathrm{C}}^{2}\cdot\mathrm{H}$$

there is a development of electron-accepting (cationoid) properties in the system $C^1{=}C^2$; but nevertheless it is still C^2 and not C^1 which retains the greater tendency to combine with the " active " (or carbon-covalence-seeking) part of the agent [CN in HCN; $CH(CO_2Et)_2$ in ethyl sodiomalonate; $Ar\cdot N_2$ in diazo-compounds; NO_2 in $HO\cdot NO_2$].

It is desirable that it should be realised from the outset that the primary interior effect of a given substituent on an atom varies, even in sign, with the nature of the atom at which substitution takes place. Thus, replacement of H in HCl^1 by Cl^2 does not increase the fugacity of the electrons of Cl^1; on the contrary, the product now shows nothing but strongly electron-seeking properties. Boron, on the other hand, resembles carbon, for while boron, in its hydrides, displays consistent quadrivalency, no neutral chloride is known in which boron displays a valency greater than three.

All ortho-substituents (other than OH) hitherto examined greatly increase the stability of the cyanohydrin group (see Table I), no matter what the quantitative or electropolar factors may be. This is quite irreconcilable with the idea that substituents so placed produce their effect in virtue of their occupation of space (compare also Kuhn and Wassermann, *Helv. Chim. Acta*, 1928, **11**, 3 *et seq.*).

In comparing the effects of ortho-substituents on the dissociation constants of cyanohydrins, on the one hand, and on the ionisation of carboxylic acids, on the other, it is natural to observe that both phenomena might at first sight be accounted for by assuming that a substituent X in position 2 in the annexed figure decreases the fugacity of electrons of C_a and, therefore (by consequent electron displacements), of the electrons of the atoms attached to C_a.



Having regard, however, to the possibility (for which reasons have been given above) that a large decrease in the fugacity of the electrons of C_a may not necessarily decrease the capacity of C_a to become quadrivalent, an alternative must not be overlooked. That alternative is a " direct " effect of X through space on the atoms or groups attached to C_a, rather than an effect on C_a itself, and it must in any case be an effect which both helps C_a to exercise its maximum co-ordination number and reduces the fugacity of the valency electrons of the atoms P, Q, and R attached to C_a; the latter requirement is shown by the decreased ability of the oxygen of ortho-substituted benzoic acids to retain a proton.

The most useful and significant measurements of thermodynamic changes associated with addition reactions of carbonyl compounds are certainly those of Adkins and Adams (*J. Amer. Chem. Soc.*, 1925, **47**, 1368), who studied the free energy of the formation of acetals from alcohols and carbonyl compounds, both aldehydes and ketones, by means of equilibrium measurements. This reaction, however, is highly complex, involving at equilibrium six molecules of four different chemical species :

$$2R'{\cdot}OH + R''{\cdot}CO{\cdot}R''' \longleftrightarrow R''{\cdot}C(OR')_2{\cdot}R''' + 2H_2O.$$

The ideal case for study is no doubt that in which only two molecules of two chemical species are concerned at equilibrium (exclusive of catalysts), $A \leftrightarrow A^1$, corresponding with the phenomenon of simple isodynamic change. Next to this in simplicity come two cases where three molecules are concerned:

$$(a) \quad A + A \leftrightarrow C \text{ (two species)}$$
$$\text{or} \quad (b) \quad A + B \leftrightarrow C \text{ (three species).}$$

Here, (*a*) would include all the simplest cases of polymerisation, and no simpler example of (*b*) could be taken than that of reversible cyanohydrin formation: $R_2CO + HCN \leftrightarrow R_2C(OH)\cdot CN$, which is probably a simpler case than that of oxime or hydrazone formation (Petrenko-Kritschenko, *Ber.*, 1901, **34**, 1702; *Annalen*, 1905, **341**, 150; *Ber.*, 1906, **39**, 1454; Fischer, *Annalen*, 1886, **236**, 146; Stewart, J., 1905, **87**, 185, 410) and corresponds more closely with the formation of bisulphite double compounds (Stewart, *loc. cit.*).

Ultée (*Rec. trav. chim.*, 1909, **28**, 248, 257) examined the stability of a number of cyanohydrins, mainly by admixture of an aldehyde or ketone with anhydrous hydrogen cyanide in equimolecular proportion and in absence of solvent. The results were not in a form suitable for quantitative comparison, and this was more especially the case with aliphatic aldehydes, the cyanohydrins of which are so stable that the concentrations of the free hydrogen cyanide and of the free aldehyde (which could only be estimated by difference) were very uncertain. The equilibrium constants calculated for Ultée's liquid systems are not directly comparable with those given in the present paper, which refer to a different medium.

W. J. Jones (J., 1914, **105**, 1560) compared the dissociation constants of one or two cyanohydrins in aqueous solution, and confirmed Ultée's conclusion that in general the formation of cyanohydrins is incomplete, even with aldehydes: he made a quantitative comparison between the values of the equilibrium constant $K = C_{R_2CO} \times C_{HCN}/C_{R_2C(OH)\cdot CN}$ in aqueous solution and found the constant for acetone to be about eleven times as large as that for acetaldehyde.

The present authors have extended this work and made observations with a large number of aldehydes and ketones; but, as water is not generally suitable as a solvent, 96% alcohol was used as the medium throughout. Chemically, the principle on which the measurements were based was the same as that applied by Ultée and by Jones; it has recently been discussed at sufficient length by Lapworth, E. B. Robinson, and Manske (J., 1927, 2052 *et seq.*), and it is only necessary here to give details of the modified procedure adopted during the present research.

EXPERIMENTAL.

Preparation and Purification of the Aldehydes and Ketones.—Exigencies of space make it impracticable to give details for so many different compounds. Where the aldehydes or ketones were solids with a fairly high melting point, the procedure, as a rule, was fairly straightforward, and frequent recrystallisation from suitable solvents was always resorted to in the final stages—as, for example, where a nearly pure sample had been made synthetically or purchased as " pure " from a firm of repute and had passed the necessary preliminary tests satisfactorily. Where the compounds were liquids or low-melting solids, the methods of preparation adopted often afforded the necessary preliminary guarantee of homogeneity, and the elimination of most of the remaining impurities was always attempted by applying Richards's method of repeated distillation, with rejection of large initial and final fractions (compare *J. Amer. Chem. Soc.*, 1912, **34**, 978) even when the boiling-point range of the original material was very narrow. In each fractionation, wherever practicable, only the middle two-thirds of the distillate were utilised, so that when several successive operations were carried out, the proportion ultimately retained was very small. Oxidisable or hygroscopic compounds were fractionated in an atmosphere of dry carbon dioxide and then used immediately with every necessary precaution to avoid access of air or moisture.

In all cases where the aldehyde or ketone gave a crystalline bisulphite compound this was made as a stage in the preparative process.

In the following cases the starting materials used, and subjected to further treatment on the lines above indicated, were the best products made by British Drug Houses, Ltd. : Fluorenone and *o*-chloro-, *o*-nitro-, *m*-hydroxy-, *p*-hydroxy-, and *p*-dimethylaminobenzaldehydes.

The original *p*-nitrobenzaldehyde was purchased from Kahlbaum. In the case of *o*-nitrobenzaldehyde, traces of *o*-nitrosobenzoic acid present were easily removed by two successive precipitations from benzene solution by addition of light petroleum. The crude methoxybenzaldehydes were made by methylating the purified hydroxy-aldehydes; *m*-nitrobenzaldehyde was made by the method described in Erdmann's " Anleitung der Organischen Preparate " (Stuttgart, 1894), and *p*-methoxy-*m*- and -*o*-methylbenzaldehydes were made by the application of Gattermann's process to pure *o*- and *m*-cresol respectively.

Crude *m*-chloro- and *m*- and *p*-methyl-benzaldehydes were obtained from the corresponding chloro- and methyl-benzonitriles by Stephen's process (J., 1925, **127**, 1874). It is worthy of remark that, owing to the retardation of reaction velocity (" steric hindrance "), this process did not prove satisfactory in the hands of the present authors for converting *o*-methylbenzonitrile into *o*-tolualdehyde, and it has not been possible to include any measurements on the cyanohydrin equilibrium in the case of the latter compound.

The original sample of *cyclo*pentanone was made from adipic acid by the method described in D.R.-P. 256,622; that of *cyclo*hexanone was purchased from Poulenc Frères. The methyl*cyclo*hexanones were made by catalytic reduction of pure cresols supplied by the Graesser Monsanto Co. The *cyclo*heptanone used was a specimen of this costly product kindly presented by Professor J. F. Thorpe; it was subsequently twice redistilled, small initial and final fractions being rejected as usual.

The following compounds were made in accordance with the authorities quoted: α-Ketotetrahydronaphthalene (Ingold and Piggot, J., 1923, **123**, 1483; compare also Kipping and Hill, J., 1899, **75**, 148), xanthrone (Perkin, *Ber.*, 1883, **16**, 339), and anthrone (Barnett and Cook, J., 1921, **119**, 904). In other cases the products were prepared by methods in general use.

Method of Determining the Equilibrium Constant.—The solvent used throughout was the binary constant-boiling 96% alcohol–water mixture, made from the strongest commercial spirit. This was purified by distillation first from 2% of its weight of oxalic acid, then from 5% of sodium hydroxide, and was finally carefully fractionated.

The anhydrous hydrogen cyanide was prepared from potassium ferrocyanide and dilute sulphuric acid, the vapours being conducted through a series of drying tubes containing calcium chloride, liquefied by cooling, and redistilled from phosphoric oxide.

Liquid aldehydes and ketones were weighed by difference from Lunge pipettes. This had numerous advantages, including ease in manipulation, increased accuracy by reduction of losses due to evaporation and oxidation, and prevention of access of moisture; moreover, by counting the drops, a rough control over the quantities used could be exercised.

A sufficient speed of reaction was ensured by the addition of a drop of *n*-tripropylamine, and it was ascertained that variations in the quantity of this base within limits many times wider than those which could accidentally be reached in practice had no measurable influence on the state of equilibrium. The equilibrium was finally " frozen," as in the experiments of Ultée and of Jones, by addition of excess of nitric acid.

In detail the operations were carried out as follows. A weighed amount of aldehyde or ketone was introduced into a 50 c.c. flask, followed in succession by 30 c.c. of the alcoholic medium and 10 c.c. of the alcoholic hydrogen cyanide.* A very small drop (approximately 0·02 c.c.) of *n*-tripropylamine was added, and the mixture diluted to 50 c.c. with the solvent, confined with a glass stopper, and sealed with paraffin wax. Blank experiments, in which the operations were conducted in exactly the same way but without addition of the aldehyde or ketone, were carried out in each case to determine the total amount of hydrogen cyanide in the system. All solutions were thoroughly mixed, allowed to remain at room temperature over-night, and then kept at 20·0° ± 0·5°, at which temperature any slight contraction, frequently observed after reaction, was corrected, the volumes being made up to the original 50 c.c. by addition of more solvent. Equilibrium in most cases was attained in ½ hour, but this was always checked by comparison with titrations made on the following day.

Among all the cases which the authors have now investigated, that of *o*-nitrobenzaldehyde was the only one in which there was considerable irregularity in the amount of uncombined hydrogen cyanide present after standing for several days, and this was probably due to the extraordinary readiness with which this particular cyanohydrin undergoes complex changes (*Ber.*, 1904, **37**, 948).

The amount of uncombined hydrogen cyanide at equilibrium was determined by withdrawing a measured volume (the amount suitable having been ascertained by a preliminary titration) and adding to it 10 c.c. of *N*/20-silver nitrate solution, acidified with 2 c.c. of concentrated nitric acid in 20 c.c. of water. The precipitated silver cyanide was filtered off, thoroughly washed with water, and the excess of silver in the filtrate and washings determined by titration with *N*/20-potassium thiocyanate, ferric ammonium sulphate being used as indicator in the light given by a Daylight Electric Bulb, with which readings concordant within 0·04 c.c. were easily obtained. Means of two or more results concordant within 0·06 c.c. were used. The blank experiments were completed in the same way.

In all cases the amount of hydrogen cyanide which had combined with the aldehyde or ketone was determined by difference, for although a direct determination of the combined hydrogen cyanide is possible, it involves serious practical difficulties. In the circumstances, the best evidence that no large error was made in the indirect determination is the consistency in the several values for

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* The alcoholic hydrogen cyanide was prepared by dissolving 10 c.c. of anhydrous hydrogen cyanide in 250 c.c. of the alcoholic medium; such as solution contained approximately 10 millimols. of HCN in 10 c.c., and remained unaltered in concentration for several weeks when kept in a stoppered glass flask sealed with paraffin wax.

the equilibrium constant calculated from the different determinations in which the relative quantities of reactants at equilibrium varied considerably.

It is evident that errors arising out of inaccurate measurements of the concentrations entering into the formula for the equilibrium constant are proportionately greatest when any of the three concentrations becomes very small, and this tends to be the case if the cyanohydrin has either a very low or a very high dissociation constant, the former being particularly unfavourable for accuracy. These considerations were always kept in mind while deciding the best ranges of concentration and proportions of constituents to be taken in the series of measurements made with each aldehyde and ketone examined.

Errors arising out of temperature variations may be regarded as relatively very small in the case of ketones; Ultée (*Rec. trav. chim.*, 1909, **28**, 281) showed that the increase in dissociation of the cyanohydrins which he used was less than 5% between 0° and 25°, so that even in some exceptional cases during the present series of measurements where the temperature employed was 18°, the difference was not detectable by the methods employed. With aldehyde-cyanohydrins the temperature coefficient is larger. In view of all the circumstances tending to detract from accuracy, the relative values of the functions in the last column in the tables are usually given to two significant figures only.

A serious source of possible error was impurity in the aldehydes and ketones studied, especially when these were liquids. This error as a rule would be largest when the impurity was chemically inert towards the hydrogen cyanide, for example, any residual alcohol used as solvent in the purification process. The presence of another nearly-related aldehyde or ketone (*e.g.*, an isomeride, in comparing constants for monosubstituted benzaldehydes) was less important, and obviously became less serious the more nearly the properties of the impurity approached those of the main constituent.

Example of Procedure and Calculation.—The case of *p*-chlorobenzaldehyde is selected to illustrate how the several independent values of the dissociation constant of each cyanohydrin were determined with various proportions of the interactants in neutral equilibrium. The total amount of the aldehyde or ketone originally taken was different in each determination, so that, although the total concentration of hydrogen cyanide (*i.e.*, free *plus* combined) was the same in each determination, yet the concentrations of both free aldehyde (or ketone) and hydrogen cyanide at equilibrium were different in each case.

In the example which follows, N_A, N_{HCN}, etc., are the numbers of millimols. of reactant per 50 c.c.; N_A refers to the aldehyde (or ketone) originally taken, and N_{HCN}, N_{R_2CO}, and $N_{R_2C(OH)\cdot CN}$ refer respectively to the *free* hydrogen cyanide, free carbonyl compound, and cyanohydrin found at equilibrium. The number of millimols. of *total* hydrogen cyanide, N_T, was taken as the mean of the two values given in the column N_{HCN} for the two blank experiments, *a* and *b*. Thus

$$N_{R_2C(OH)\cdot CN} = N_T - N_{HCN}, \text{ and } N_{R_2CO} = N_A - N_T + N_{HCN}.$$

The values of K given are the equilibrium constants expressed in the usual units, *viz.*, g.-mols. and litres, and are calculated from the arbitrary values, N_{HCN}, etc., by the relation

$$K = C_{HCN} \times C_{R_2CO}/C_{R_2C(OH)\cdot CN} = 2 \times 10^{-2} \times N_{HCN} \times N_{R_2CO}/N_{R_2C(OH)\cdot CN}.$$

The values of ΔF, in g.-calories, are obtained as usual from the relation $\Delta F = 1{\cdot}99 \times 293 \log_e K$ (for K at 293° abs.). Thus ΔF is zero when $K = 1$, *i.e.*, if cyanohydrin, hydrogen cyanide, and aldehyde or ketone are in equilibrium at normal (unit) concentrations; it is positive or negative accordingly as the dissociation constant of the cyanohydrin is greater or less than unity.

p-Chlorobenzaldehyde.

Expt.	N_A.	N_{HCN}.	N_{R_2CO}.	$N_{R_2C(OH)\cdot CN}$.	$K \times 10^3$.
a	0	8·88	0	0	—
b	0	8·87	0	0	—
1	9·02	1·33	1·47	7·55	5·18
2	9·35	1·18	1·65	7·70	5·06
3	10·40	0·83	2·35	8·05	4·84
4	10·68	0·75	2·55	8·13	4·78
5	11·21	0·66	2·99	8·22	4·80

Mean value of $K = (4{\cdot}94 \pm 0{\cdot}06) \times 10^{-3}$.

The " probable error " or " consistency measure," $\pm 0{\cdot}06 \times 10^{-3}$ (*i.e.*, 1·2% of the mean value), was calculated in the usual way.

Discussion of Results in Table I.

It will be convenient to consider in turn the effects of substituents in the para-, meta-, and ortho-positions.

(1) p-*Substitution.*—When the substituents are arranged in the order of their depressant effects on the affinity of the aldehyde for hydrogen cyanide, beginning with the most effective, the list runs :

Substituent	NMe_2	OH	OCH_3	NO_2	CH_3	Cl and H
$\Delta F \times 10^{-2}$	−5·5	−15·0	−20·0	−23·0	−27·0	−31·0

It will be observed that on this basis the three substituents, NMe_2, OH, and OCH_3, which are characterised by their very large

TABLE I.

Constants of Cyanohydrins of some Aromatic Aldehydes.

Benzaldehyde.	No. of determinations.	$K \times 10^2$.	% Error.	$\Delta F \times 10^{-2}$.
Unsubstituted	4	0·472	0·9	−31
o-Nitro- (m. p. 46°)	6	*ca.* 0·070	5·0	−42
m- ,, (m. p. 58°)	5	0·274	2·2	−34
p- ,, (m. p. 107°)	4	1·81	3·6	−23
o-Chloro-	5	0·0962	3·4	−40
m- ,, (m. p. 17°)	5	0·250	4·0	−35
p- ,, (m. p. 47°)	5	0·494	1·2	−31
o-Methoxy- (m. p. 35°)	6	0·259	3·9	−35
m- ,, ...	4	0·428	2·4	−32
p- ,, ...	4	3·12	0·6	−20
o-Hydroxy-	3	1·67	4·4	−24
m- ,, (m. p. 104°)	4	0·476	0·9	−31
p- ,, (m. p. 116°)	3	7·66	0·9	−15
m-Methyl-	5	0·604	2·3	−30
p- ,, ...	3	1·03	1·0	−27
2-Methyl-4-methoxy-	4	2·00	3·7	−23
3- ,, ,, ...	4	3·82	1·0	−19
p-Dimethylamino- (m. p. 73°)	4	39·0	1·1	− 5·5

"quantitative" effects, come first and in their usual order; Cl, however, with its large electropolar effect, takes a position indicating that the effects produced by its quantitative and electropolar factors just balance one another. The authors' views on the appearance of the nitro-group in quite unusual company have already been stated (pp. 2535, 2538).

(2) m-*Substitution*.—Here the sequence among the substituents examined is :

Substituent	CH_3	$\underbrace{\text{HO and H}}$	OCH_3	NO_2	Cl
$\Delta F \times 10^{-2}$	−30·0	−31·0	−32·0	−34·0	−35·0

This order bears apparently no relation whatever to the quantitative sequence, but definitely indicates that the electropolar effect is the dominant one. Even the methyl group takes its correct position with respect to hydrogen, although the authors admit that this may be fortuitous, for in this relation, as with that of OCH_3 to H, the difference is approaching the probable limits of experimental error. The order of NO_2 and Cl suggests that possibly NO_2, even in the meta-position, increases the extent of non-polar conjugation (Thiele effect) between the carbonyl group and the nucleus.

It seems highly significant that if the value of the expression $10^{-2} \times (\Delta F_{\text{para}} - \Delta F_{\text{meta}})$, that is, of $10^{-2} \times (RT \log_e K_{\text{para}} - RT \log_e K_{\text{meta}})$, be calculated for any of the single-bonded substituents measured both in para- and in meta-positions, the results obtained are as follows :

Substituent	OH	OCH_3	Cl	CH_3	H
Difference	+16	+12	+4	+3	±0

The agreement with Flürscheim's quantitative sequence (J., 1909, **95**, 726) is remarkable, in spite of the opposite and very widely different electropolar factors of Cl and CH_3. The coincidence cannot fail to suggest that the electropolar effects produced by the substituents are nearly the same at the meta- as at the para-position. If this indeed be so, separation of the quantitative and electropolar factors is greatly simplified.

(3) o-*Substitution*.—The sequence now is :

Substituent	OH	H	OCH_3	Cl	NO_2
$\Delta F \times 10^{-2}$	−24·0	−31·0	−35·0	−40·0	−42·0

The position of OH in this list is almost certainly attributable, not to its quantitative factor, but to the circumstance that *o*-hydroxybenzaldehyde is not comparable with other substituted benzaldehydes, the true hydroxy-compound existing largely as a more stable form where there is chelation between the hydroxyl and carbonyl groups, as Sidgwick and his co-workers have shown (J., 1924, **125**, 527; 1925, **127**, 907). Such an occurrence as this must have the effect of reducing the apparent stability of the cyanohydrin. The other groups, OCH_3, Cl, and NO_2, when in the ortho-position all act so as to increase the stability of the cyanohydrin relatively to that of the aldehyde. In view of the opposite effect which OCH_3 exercises when in the para-position, the large gap between the values of ΔF for ortho-situated OCH_3 and Cl may well be due to the opposite signs of the quantitative factors of these two substituents.

o-Methylbenzaldehyde could not be obtained for examination, but comparison of the numbers found for 2- and for 3-methyl-4-methoxybenzaldehyde show that in the ortho-position, CH_3, like OCH_3, Cl, and NO_2, raises the stability of the cyanohydrin in comparison with that of the aldehyde.

Discussion of Results in Table II.

Here are given a number of dissociation constants for cyanohydrins of cyclic ketones and (in parentheses) of some corresponding open-chain compounds. The effect of ring formation may be roughly shown by subtracting from the value of ΔF for the cyclic ketone that for its open-chain analogue. In the following list the name of the former only is given and the numbers represent the gains

TABLE II.

Constants of Cyanohydrins of some Cyclic (and Related) Ketones.

Ketone.	No. of determinations.	$K \times 10^2$.	% Error.	$\Delta F \times 10^{-2}$.
*cyclo*Pentanone	4	1·49	2·8	−24
(Methyl *n*-propyl ketone)	4	3·54	2·3	−19
*cyclo*Hexanone	4	0·092	4·3	−41
(Methyl *n*-butyl ketone)	4	3·22	1·2	−20
2-Methyl*cyclo*hexanone	5	0·059	5·4	−43
3- ,, ,, ,,	4	0·30	1·1	−34
4- ,, ,, ,,	4	0·127	2·0	−39
Menthone	4	6·54	1·8	−16
*cyclo*Heptanone	4	7·96	1·0	−15
Camphor	(No appreciable cyanohydrin formation.)			>>+10
α-Hydrindone	3	610·0	9·0	+11
(Phenyl ethyl ketone)	5	59·4	1·7	− 3
α-Ketotetrahydronaphthalene	3	806·0	10·0	+10·2
(Phenyl *n*-propyl ketone)	5	89·4	1·2	− 0·65
Fluorenone	3	146·0	0·6	+ 2·3
(Benzophenone)	(No appreciable cyanohydrin formation.)			>>+10
Anthrone and Xanthrone	(No appreciable cyanohydrin formation.)			>>+10

in the free energy of dissociation ($\Delta F \times 10^{-2}$) consequent upon ring closure :

*cyclo*Pentanone	−5·0	α-Hydrindone	+13·5
*cyclo*Hexanone	−20·7	α-Ketotetrahydronaphthalene	+10·9
*cyclo*Heptanone	+*ca.* 6·5	Fluorenone	very large and negative

In some cases, then, and more especially in those of *cyclo*hexanone and fluorenone, ring formation in effect greatly increases the stability of the addition compound, and, with *cyclo*hexanone and its methyl derivatives, the result is to render the corresponding ketone-cyanohydrins the most stable known. In some cases, on the other hand, ring formation has the opposite result, and this is especially remarkable in the case of α-hydrindone, where ortho-substitution such as is involved in the ring formation would ordinarily tend to stabilise the cyanohydrin.

The effects of introducing methyl groups into *cyclo*hexanone have the appearance of an induced alternate effect, but this can scarcely be more than a coincidence. It seems much more probable that the normal electron-releasing electropolar effect of methyl is larger in the 3- than in the 4-position, whilst in the 2-methyl derivative an electron-restraining effect (similar to that produced by ortho-situated methyl in aromatic acids and aldehydes) enters, dominating all others.

The very large depressant effect of the *iso*propyl group in position 2- in 3-methyl-2-*iso*propylhexanone (menthone) is most striking, for methyl in that position has the opposite effect. Possibly this may be a true case of interference by configurational strain in the cyanohydrin due to crowding. It has always appeared probable that the so-called steric effects are associated with, and therefore conditioned by, the amount of branching of chains.

Summary.

The constants for the dissociation

$$R^1{\cdot}C(OH)(CN){\cdot}R^2 \longleftrightarrow R^1{\cdot}CO{\cdot}R^2 + HCN$$

of a number of cyanohydrins derived from aldehydes and ketones have been determined in 96% alcohol at 20° ± 0·5°.

The dissociation constants of cyanohydrins derived from benzaldehyde and its substitution derivatives appear to be affected by the same factors which influence the ionisation constants of benzoic acid and its substitution derivatives (Flürscheim, J., 1909, **95**, 726), although (i) the " electropolar " factor appears to be of relatively less importance in the para-substituted cyanohydrins, and (ii) the " quantitative " factor has little if any influence in the meta-substituted cyanohydrins. The effects of ortho-substituents examined (other than HO) are such as to depress the dissociation constants of the cyanohydrin, and this is in direct contrast to the result to be anticipated from the classical " space-occupation " hypothesis so frequently used to account for other effects associated with ortho-substitution. Ring closure (with elimination of two atoms of hydrogen) in a chain comprising a carbonyl carbon atom leads sometimes to a large increase and sometimes to a large decrease in the dissociation constant of the derived cyanohydrin.

The results obtained are discussed from the point of view of the electronic theory, and it is suggested that possibly the additive capacity of carbonyl carbon and ethylenic carbon, considered from the standpoint of entropy, does not increase continuously with the restraint on its electrons but reaches a maximum and then declines, just as in the series, boron, carbon, nitrogen, and oxygen, the capacity to form stable compounds, in which the element exercises a co-ordination number of 4, attains a maximum at carbon.

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