232. *Mechanism of Aromatic Side-chain Reactions with Special Reference to the Polar Effects of Substituents. Part XIV. The Aldehyde–Cyanohydrin Reaction with Halogeno-benzaldehydes: Polar Effects of Halogen Substituents.*

By John W. Baker and H. B. Hopkins.

As one section of a joint attack, in collaboration with Hughes, Ingold, and Kohnstam, of University College, London, on the problem of the polar effects of halogen substituents (X = F, Cl, Br, I), the values of the equilibrium constants ($K = k_2/k_1$) and of the individual velocity coefficients k_1 and k_2 in the reaction

$$m\text{- or } p\text{-X}\cdot\text{C}_6\text{H}_4\cdot\text{CHO} + \text{HCN} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{X}\cdot\text{C}_6\text{H}_4\cdot\text{CH(OH)}\cdot\text{CN}$$

have been determined in constant boiling-point alcohol as solvent at 20°, using the technique of Baker and Hemming (*J.*, 1942, 191). *m*- and *p*-Nitrobenzaldehydes have been included in the investigation, as examples of substituents of unequivocal electron-attraction, earlier data for alkyl substituents providing information regarding electron-release substituents.

The values of K decrease in the order, p-alkyl $>$ p-F $>$ H $>$ p-Cl $>$ p-NO_2 $>$ p-Br $>$ p-I $>$ m-NO_2 $\sim$ m-F $>$ m-I $>$ m-Cl $>$ m-Br, *p*-F thus exhibiting an overall electron-*release* effect, whilst the remaining halogens (including *m*-F) show an overall electron-attraction which is in the reverse order to that required by the operation of the $-I$ effect alone. Analysis of the data proves that the halogens exhibit both inductive ($-I$) and mesomeric ($+M$) effects which decrease in the order F $\gg$ Cl $>$ Br $>$ I, and that there is considerable second-order relay of the $+M$ effect from the *m*-position.

The velocity data for both k_1 and k_2 show that all the halogens (fluorine included) exert an overall electron-attraction in both the *m*- and the *p*-position but that again the inductive order is inverted or upset by the superimposition of a mesomeric electron-release, reduced both in the transition state and in the cyanohydrin owing to the diminution of unsaturation in the side chain.

Although the results can be satisfactorily interpreted on the basis of the operation of these two polar effects alone, yet the incidence of an inductomeric electron-*attraction*, decreasing in the order I $>$ Br $>$ Cl $>$ F, is not excluded as an alternative explanation of the k_2 sequence.

The present position regarding our understanding of the polar effects of halogen substituents is far from satisfactory. A comprehensive review has been given by one of us elsewhere (Hopkins, Thesis, University of Leeds, 1948).

There is general agreement, based on fairly extensive physical and chemical evidence, for the operation of an electron-attracting inductive ($-I$) effect, derived from the dipole $\overset{\delta+}{\text{C}}\text{–}\overset{\delta-}{\text{Hal}}$, which decreases in the order, originally postulated by Ingold (*Chem. Reviews*, 1934, **15**, 237), F $>$ Cl $>$ Br $>$ I.

Information regarding any corresponding polarizability (inductomeric) effect is more meagre, but it is highly probable that the polarizability of the C–Hal bond decreases in the reverse order I $>$ Br $>$ Cl $>$ F: the decreasing molecular refractivities of this bond, *viz.*, Hal = I, 14·51: Br, 9·47: Cl, 6·57: F, 1·82 c.c. (Remick, "Electronic Interpretations of Organic Chemistry," p. 79), may be cited as one piece of evidence for this conclusion.

Superimposed on these electrostatic effects is the tautomeric electron-release by halogen substituents arising from conjugation of the unshared electron-pairs with attached, unsaturated centres. The original suggestion that both the permanent (mesomeric) and polarizability (electromeric) effects should increase in the order F $<$ Cl $<$ Br $<$ I (Ingold, *loc. cit.*, p. 242) has required modification in the light of later work and there is sound evidence, which is fully substantiated by the present investigation, for the conclusion that the order of mesomeric electron-release follows the reverse sequence F $>$ Cl $>$ Br $>$ I. On the physical side, an accurate determination of the mesomeric moments of the halogenobenzenes by Audsley and Goss (*J.*, 1942, 497) gave the values F, 1·04; Cl, 0·95; Br, 0·75; I, 0·51 D., thus confirming the order obtained earlier by Groves and Sugden (*J.*, 1937, 1992) on a somewhat different basis of computation. The same order of mesomeric electron-release was revealed by an examination of the dissociation constants of halogenated phenols and anilines by Bennett, Brooks, and Glasstone, (*J.*, 1935, 1821), who, in one case (that of *p*-fluorophenol which is a weaker acid than phenol itself) found that fluorine exhibited an overall electron-release, the $+M$ effect being sufficiently powerful to reverse the direction of the polarization arising from the strong $-I$ effect of this substituent.

In the examination of the effect of halogen substituents on the velocity of side-chain reactions a complex situation is present. Quite apart from the possible incidence of duplex polar requirements (*e.g.*, the electrostriction of a nucleophilic reagent and the elimination of an anion) when the reaction is of the S_N2 type, the observed polar effects of halogen substituents may be the resultant of both polarization and polarizability effects originating from both tautomeric (electron-release) and inductive (electron-attraction) mechanisms. Examination of the more important data (Baddeley and Bennett, *J.*, 1933, 261; 1935, 1819; Olivier, *Rec. Trav. chim.*, 1922, **41**, 301, 646; 1923, **42**, 516, 775; Bennett and Brynmor Jones, *J.*, 1935, 1815; Norris, Fasce, and Staud, *J. Amer. Chem. Soc.*, 1935, **57**, 1415; Nixon and Branch, *ibid.*, 1936, **58**, 492, 2499; Ingold and Nathan, *J.*, 1936, 222; Kindler, *Annalen*, 1926, **450**, 1; Baker, *J.*, 1936, 1448; Davies and Lewis, *J.*, 1934, 1599; Braude and Stern, *J.*, 1947, 1096) shows that, with but two minor exceptions (referred to below), the overall effect of all halogen substituents, as a group, in both *m*- and *p*-positions, is always one of electron-*attraction*. Regarding the relative effects of individual halogens within the group, it is found that the order of overall electron-attraction, as revealed by the velocity order (sometimes confirmed by the Arrhenius *E* values for the reaction), may be either a complete *reversal* of the $-I$ order, F > Cl > Br > I, or, more often, a partly inverted, " mixed " order. In the hydrolysis of *p*-halogeno-benzyl chlorides in 50% aqueous acetone (Bennett and Jones, *loc. cit.*) the *p*-fluoro-compound, unlike the other halogen derivatives, was found to undergo hydrolysis at a faster rate than the parent, unsubstituted compound, indicating, in this case, an overall electron-release by fluorine. It has, however, already been pointed out (Baker, *Trans. Faraday Soc.*, 1941, **37**, 632) that, under the conditions employed, the reaction is probably largely unimolecular (S_N1) and hence the operation of a large electromeric electron-release effect by fluorine might be expected. The second reaction in which *all* the halogens apparently exhibit a small, overall electron-release effect is the addition of pyridine to the halogenobenzyl bromides in dry acetone (Baker, *loc. cit.*). This reaction was proved to be bimolecular (S_N2) and one in which a minimum velocity occurs in a graded polar series of substituents showing increasing electron-release. Moreover the velocity differences are so small (maximum range $10^4k^{20^\circ}$ = H, 1·22; F, 1·48) that it is unsafe to draw definite conclusions from them.

Examination of the effect of halogen substituents on the velocity of electrophilic substitution in the same aromatic nucleus, *e.g.*, the nitration of halogenobenzenes (Bird and Ingold, *J.*, 1938, 918) and the halogenation of halogenobenzenes and 1-halogenonaphthalenes (De la Mare and Robertson, *J.*, 1948, 100) reveals the incidence of a polarizability electron-release effect by the halogen substituent which seems to decrease in the order I > Br > Cl > F. This effect was originally regarded by Bird and Ingold as an electromeric (+ *E*) effect, whilst De la Mare and Robertson recognised also the alternative possibility that an inductomeric effect might be responsible. Unpublished data of Hughes, Ingold, and Kohnstam (see below) have cast further doubt upon the interpretation given by Bird and Ingold and, at present, the nature of this polarizability effect is best left an open question.

This brief review of the present position reveals a close analogy to that which pertained to the polar effects of alkyl groups before the introduction, by Baker and Nathan (*J.*, 1935, 1844), of the concept of partial conjugation of the shared electrons of a C–H bond with an attached unsaturated centre—the phenomenon now generally known as hyperconjugation. In the search for conclusive experimental evidence for this new concept two types of reaction were proved to be of great value. Hughes, Ingold, and Taher (*J.*, 1940, 949) found, in the unimolecular solvolysis of *p*-alkylbenzhydryl chlorides, a reaction which is very favourable for the dominant operation of the electromeric electron-release effect, and Baker and Hemming (*J.*, 1942, 191) showed that a clear-cut verification of the theoretical order of mesomeric electron-release could be derived from a study of the cyanohydrin equilibria of *p*-alkylbenzaldehydes. It was considered that these same two reactions, applied to the corresponding halogen-substituted compounds, might provide similarly clear-cut evidence regarding the order of the electromeric (+ *E*) and mesomeric (+ *M*) effects, respectively, of the halogens. Accordingly, by mutual arrangement, a joint attack on the halogen problem was planned with Professors Ingold and Hughes, and the present communication describes the results of an investigation of both the position of equilibrium, $K = k_2/k_1$, and the separate values of k_1 and k_2 in the reaction

$$\mathrm{X{\cdot}C_6H_4{\cdot}CHO + HCN \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X{\cdot}C_6H_4{\cdot}CH(OH){\cdot}CN},$$

where X = F, Cl, Br, and I in the *m*- and *p*-positions. The complementary examination of the solvolysis of the *m*- and *p*-halogenobenzhydryl chlorides will be published in due course by Hughes, Ingold, and Kohnstam.

The experimental technique employed and the method for the evaluation of k_1 and k_2 are those previously described by Baker and Hemming (*loc. cit.*). Since, theoretically, the resultant polar effect of halogen substituents might be one either of electron-release or of electron-attraction, it is obviously desirable to " bracket " the halogen group by a study of the effects of unequivocally electron-releasing and electron-attracting substituents. Data for the former are already available from the earlier study of *p*-alkylbenzaldehydes, and information regarding the latter has been obtained by inculsion of *m*- and *p*-nitrobenzaldehydes in the present investigation. Values for K (but not for k_1 and k_2) for the cyanohydrin formation of these two aldehydes have previously been published by Lapworth and Manske (*J.*, 1928, 2533), but we find that, in these cases, the cyanohydrin reaction is complicated by side reactions (possibly of the aldol condensation type). With both *m*- and *p*-nitrobenzaldehyde, addition of only *one* drop of tri-*n*-propylamine catalyst causes the rapid development of an intense orange-yellow colour, and the concentration of free hydrogen cyanide at first diminishes to a minimum value and thereafter rises continually. Obviously a true equilibrium is not attained. Better results were obtained by using the less powerful " velocity " catalyst (0·01M-pyridine + 0·01M-pyridinium benzoate) and, under such conditions, true equilibrium is attained (and maintained) with the *m*-nitro-compound, and the value quoted in Table I was thus determined. With *p*-nitrobenzaldehyde a slower, but definite increase in free hydrogen cyanide concentration still occurs after the minimum value is reached, but with the weaker catalyst, this upward drift is approximately linear with time and the " equilibrium " concentration of free hydrogen cyanide was estimated by extrapolation of this straight-line portion to zero time. The value so obtained was slightly lower than the experimentally observed minimum concentration. The value of 10^3K thus obtained for the *m*-nitrobenzaldehyde equilibrium (2·10) is rather lower than that recorded by Lapworth and Manske (2·74), but the discrepancy is in the same direction and of the same order of magnitude as has been observed for all the K values we have determined, which are consistently rather lower than those of Lapworth and Manske (cf. also results in the *p*-alkyl series, *loc. cit.*). Our value for the *p*-nitro-compound (3·4) differs greatly from that of Lapworth and Manske (18·1). These authors, using one drop of tri-*n*-propylamine as catalyst, made no mention of any " drift " in the hydrogen cyanide concentration; indeed they state that " among all the cases . . . . 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* " (italics ours). In our experience the complicating side reactions would, in such a period, have released free hydrogen cyanide far in excess of the minimum and, presumably, true cyanohydrin equilibrium concentration (see Experimental, p. 1097), and would thus account for their much larger value of K.

TABLE I.

Data for the reaction $X{\cdot}C_6H_4{\cdot}CHO+HCN \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X{\cdot}C_6H_4{\cdot}CH(OH){\cdot}CN$ in constant-boiling alcohol at 20°. Equilibrium catalyst = 2 drops (~0·02 g.) of NPr_3 in 50 ml. of a solution initially ~2M with respect to both aldehyde and HCN. Velocity catalyst = 0·01M-pyridine + 0·01M-pyridinium benzoate. Units : g.-mol. l.$^{-1}$ sec.$^{-1}$.

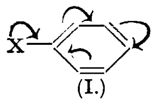
X =	*p*-Me.	H.	F.		Cl.		Br.		I.		NO_2.	
			p.	*m*.	*p*.	*m*.	*p*.	*m*.	*p*.	*m*.	*p*.	*m*.
10^3K, g.-mol. l.$^{-1}$	8·98 ±0·13	4·45 ±0·13	6·30 ±0·13	2·13 ±0·02	3·85 ±0·12	1·97 ±0·01	3·26 ±0·05	1·88 ±0·02	3·13 ±0·04	2·02 ±0·04	3·4	2·1
$10^{-2}\Delta F$, cals.	27·5	31·6	29·5	35·9	32·4	36·3	33·4	36·6	33·6	36·2	33·1	35·9
10^8k_1, g.-mol. l^{-1}. sec.$^{-1}$	0·82* —	1·65* ±0·02	3·59 ±0·01	10·22 ±0·02	6·94 ±0·04	12·45 ±0·02	9·14 ±0·07	14·32 ±0·16	9·38 ±0·09	14·5 ±0·3	37·0	58·4
$10^{10}k_2$, sec.$^{-1}$	0·74*	0·74*	2·26	2·18	2·67	2·45	2·98	2·69	2·94	2·92	12·6	12·3
	(*p*-Bu^t 0·57*)											

* The value now obtained for k_1 for benzaldehyde itself is rather lower than that (1·96) previously recorded by Baker and Hemming; hence, to make the k_1 and k_2 values for the *p*-Me compound comparable with the new data, their value has been multiplied by the factor 1·65/1·96. This correction does not alter the relative position of the values for alkyl groups in the graded polar series.

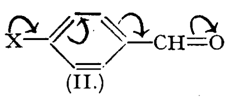
The values obtained for the equilibrium constants K and the velocity coefficients k_1 and k_2 for all the compounds now studied are collected in Table I, earlier data for benzaldehyde and *p*-tolualdehyde being included for purposes of comparison.

DISCUSSION.

Equilibrium Data.—It is important to recognise that the mesomeric effect of a halogen substituent in the benzene ring, although a permanent polarization, will vary in magnitude from compound to compound. The delocalisation of the unshared electrons on a halogen in a monohalogenobenzene (I), where conjugation is restricted to the limits of the benzene ring, will be less than in (II), where a group in the *p*-position (such as $-\text{CH}{:}\text{O}$) extends the conjugation to the limits of the side chain since, in the latter case, the electrons can occupy greater configurational space with the consequent lowering of their energy and resonance stabilisation of the molecule. Thus, by arguments exactly similar to those given by Baker and Hemming (*loc. cit.*), the $+M$ effect of a *p*-halogen substituent should stabilise the free aldehyde (II) relative to benzaldehyde itself, to a greater extent than it does the cyanohydrin (III) relative to benzaldehyde cyanohydrin, with a resultant increase in the value of $K = k_2/k_1$. The greater the mesomeric effect of the halogen the larger should be the value of K and the smaller the value of the free-energy change calculated from the usual relationship $\Delta F = -\boldsymbol{R}T \ln K$.



(I.)



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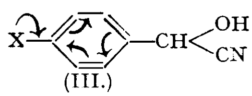
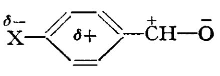


(III.)

Superimposed on the mesomeric effect will be the inductive electron-attraction ($-I$) of the halogen. This gives rise to a fractional positive charge in the benzene ring which will oppose electron-duplet displacements $\overset{\curvearrowright}{\text{C}{=}\text{O}}$ in the aldehyde side chain. Consequently, structures of the general types (IV) and (V) will be of smaller significance in the structure of the halogenobenzaldehyde (X = halogen) than they are in benzaldehyde itself (X = H). Thus the $-I$ effect of the *p*-halogen should be to destabilise the free aldehyde relatively to the parent benzaldehyde. In the cyanohydrin (VI) the $-I$ effect of the halogen might stabilise the molecule (relatively to benzaldehyde cyanohydrin) by increasing the energy required for the separation of CN as an anion, or it might destabilise it by lowering the energy necessary for proton separation from the OH group. In either case its effect on the cyanohydrin is likely to be much less significant than is its destabilising effect on the free aldehyde, so that the $-I$ effect of the halogen should decrease the value of K relatively to that of benzaldehyde.



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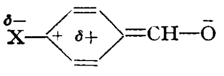

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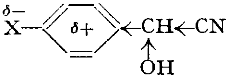
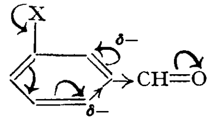


(VI.)

The data in Table I show an order of K = *p*-Me > *p*-F > H > *p*-Cl > *p*-Br > *p*-I $\sim$ *p*-NO_2. Hence, of the four halogens in the *p*-position, Cl, Br, and I exhibit an overall electron-*attraction*, which decreases in the order I > Br > Cl, but fluorine exhibits an overall electron-*release* since, like alkyl substituents, it has a K value > H. Hence the $+M$ effect of fluorine must be sufficiently large to overcome and reverse the polarization of its strong $-I$ effect. Similar arguments apply to the *m*-halogeno-substituted benzaldehydes, except that the $-I$ effect should be of smaller magnitude whilst the $+M$ effect would be greatly reduced since it cannot now reach the aldehyde side chain directly. There may, however, be a second-order effect arising from a relay of permanent, fractional negative charges on the two *o*-carbon atoms of the ring:



The data in Table I indicate that such second-order relay of the mesomeric effect, whilst not sufficient, even with fluorine, to reverse the overall electron-attraction due to the $-I$ effect (as it *does* in the *p*-fluoro-compound), does upset the $-I$ order of electron-attraction by the halogen substituents. Thus the K values for the *m*-series are in the order H > *m*-NO_2 $\sim$ *m*-F > *m*-I > *m*-Cl > *m*-Br. Since all the halogens have K values < H, they must exhibit an overall electron-attraction which decreases in the order *m*-Br > Cl > I > F. The probable value of K for the *p*-nitro-derivative is greater than that for *m*-nitro-. It is difficult to conceive that the electron-attraction of a *p*-NO_2 group is weaker than that of *m*-NO_2, and a more plausible explanation is found in the suggestion by Lapworth and Manske (cf. Ingold, *Ann. Reports*, 1928, **25**, 147) that there is a minimum value for K, now located at the m-bromo-compound, and that further increase in electron-attraction (m- and p-NO_2) again causes an increase in K. The overall electron-release of p-F makes it unlikely that its position in the m-series (close to m-NO_2) is due to strong electron-attraction. A much more satisfactory and consistent explanation is that the strong second-order relay of the large $+M$ effect of fluorine from the m-position, whilst not sufficient to reverse the direction of polarisation due to its $-I$ effect, *is* able to diminish its overall electron-attraction to such an extent that it becomes the least strongly electron-attracting of all the halogens in the m-position. Similarly the $+M$ effect of chlorine displaces it relatively to its neighbour bromine. On this view we have a self-consistent series of increasing electron attraction :

$$\underbrace{p\text{-alkyl} < p\text{-F}}_{\text{Electron release}} < \text{H} < p\text{-Cl} < p\text{-Br} < p\text{-I} < m\text{-F} < m\text{-I} < m\text{-Cl} < \underset{\text{Min. } K}{m\text{-Br}} > m\text{-NO}_2 < p\text{-NO}_2$$

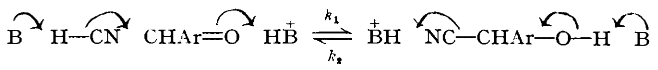
in which the inductive order of electron-attraction by halogens is completely reversed in the p-position by the superimposition of a strong $+M$ effect, and, in the m-position, becomes partly inverted and " mixed " owing to the modifying influences of a second-order relay of the $+M$ effect.

From the arguments developed above it is evident that the value of K_p/K_m should be larger the greater is the $+M$ effect of the halogen substituent. The experimental values of this ratio are :

X =	H.	F.	Cl.	Br.	I.
K_p/K_m =	1	2·98	1·96	1·73	1·55

a clear-cut proof that the order of the $+M$ effect is F > Cl > Br > I.

Velocity Data.—Interpretation of the velocity data is, of necessity, more complex since account must now be taken of relevant polarizability effects. The overall, base-catalysed reactions may be formulated



$$\text{B}\ \ \text{H—CN}\ \ \text{CHAr=O}\ \ \overset{+}{\text{H}}\text{B} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \overset{+}{\text{B}}\text{H}\ \ \text{NC—CHAr—O—H}\ \ \text{B}$$

In the forward reaction (left to right), the more difficult, rate-determining factor might be either the formation of the C–CN bond or the polarization of the C=O group, the former being facilitated by electron-attraction by the aryl group and the latter by its electron-release, especially by the tautomeric mechanism. The experimental values for k_1 (Table I) show that the forward reaction is retarded by electron-releasing alkyl groups and strongly accelerated by electron-attracting nitro-groups. Hence it may be safely assumed that the electrostriction of the CN′ ion is the more important energy requirement.

In the p-series the order $k_1 = p\text{-Me} < \text{H} < \text{F} < \text{Cl} < \text{Br} \gtrless \text{I} \ll \text{NO}_2$ shows that the halogens, fluorine included, all exhibit an overall electron-attraction which decreases in the order I $\gtrless$ Br > Cl > F, which is the reverse of that required by their $-I$ effects. Hence, as in the equilibrium data, there is a superimposed electron-release effect which must decrease in the order F > Cl > Br > I and which, although unable to reverse the polarisation due to the $-I$ effect, is able so to reduce it that fluorine shows a resultant minimum electron-attraction and, in the other halogens, completely inverts the inductive order. Such electron-release effect must be either tautomeric or inductomeric in character, but since the latter almost certainly decreases in the order I > Br > Cl > F (cf. p. 1089) the effect here operative is most probably tautomeric in character. In any reaction of the type A + B ⟶ C the transition state much more closely resembles C than it does A + B, *i.e.*, the transition state in the cyanohydrin reaction, $\text{Ar·}\underset{\vdots \atop \text{CN}\delta-}{\text{CH}}\text{------}\overset{\delta-}{\text{O}}$ will approximate more closely to that of the cyanohydrin $\text{Ar·}\underset{| \atop \text{CN}}{\text{CH}}\text{—}\bar{\text{O}}$ in which the conjugation of the p-halogen substituent is largely restricted to the confines of the benzene ring (III). Hence the magnitude of the $+M$ effect in the p-halogenobenzaldehydes themselves probably approximates to a maximum displacement of the unshared electron-pair so that, in the transition state, it becomes greatly reduced, *i.e.*, in the reaction the halogens are exhibiting a kind of $-(+E)$ effect. The resultant tautomeric effect still decreases in the order F > Cl > Br > I.

In the *m*-series the $-I$ effects will be somewhat reduced and the tautomeric effect greatly reduced, the argument being similar to that already given for the equilibrium data. The observed order is k_1 = H < F < Cl < Br $\gtrsim$ I $\ll$ NO_2, which again reveals an over-all electron-attraction by all halogen substituents, decreasing in the order I $\gtrsim$ Br > Cl > F, the $-I$ order being inverted by superimposition of a second-order relay of the mesomeric effect. The ratio k_1^m/k_1^p should be larger the larger is this second-order relay: the values are as follows:

X =	H.	F.	Cl.	Br.	I.
k_1^m/k_1^p =	1	2·86	1·79	1·56	1·54

a series which clearly resembles that for K_p/K_m (p. 1093) and confirms the order of mesomeric electron-release F > Cl > Br > I.

Before leaving discussion of the k_1 data, it should be noted that the very strong electron-attraction of the *p*-NO_2 substituent causes a *decrease* in the value of k_1 relatively to that of the *m*-nitro-compound. It is evident that, in the latter compound, a condition has been reached when the induced positive charge on the carbonyl carbon has become so great that the polarization of the carbonyl group $C\overset{\curvearrowright}{=}O$ is now the more important factor energetically. Further increase in this induced positive charge, in the *p*-nitro-compound, thus causes a decrease in the velocity of the forward reaction. This constitutes another example of the condition where, in a graded polar series, the substituent acts first as if it is facilitating one requirement in an S_N2 mechanism and then, beyond a certain point, as if it were hindering the other (cf. Baker, *Trans. Faraday Soc.*, 1941, **37**, 637; Hughes, Ingold, and Shapiro, *J.*, 1936, 228).

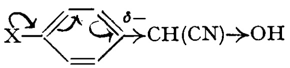
Considerable caution is necessary in any attempt to interpret the significance of the k_2 data. In the first place, the experimental values themselves are likely to be less accurate since, from their method of determination $k_2 = Kk_1$, all the errors in both k_1 and K are incorporated as their products. A second difficulty is the uncertainty of ascertaining what is, energetically, the determining factor in the back reaction. Experimentally, the velocity coefficient k_1 is determined by the loss in concentration of free cyanide ion, and this ion ceases to be precipitated as silver cyanide as soon as it has become united in the ion Ar·CH(CN)·$\bar{O}$ of the cyanohydrin. Since the cyanohydrin is, presumably, a very weak acid, the anion would be expected rapidly to attack a proton, but this would have no further effect on the concentration of free cyanide ion present in the system. Theoretically, however, there must exist the equilibrium Ar·CH(CN)·$\bar{O}$ + $\overset{+}{H}$ $\rightleftharpoons$ Ar·CH(CN)·OH, even though this equilibrium may be displaced well to the right. If the rate of decomposition of the *ion* of the cyanohydrin into cyanide ion and free aldehyde is very rapid compared with the rate of its formation by ionisation of the cyanohydrin, this latter equilibrium may never be attained during the course of the formation of the cyanohydrin from the free aldehyde, and the factor which is most important in determining the value of k_2 might thus become the ionisation of hydrogen from the OH group of the cyanohydrin. The alternative possibility would be that the rate-determining factor is the breaking of the C–CN bond to give free cyanide ion. On the first hypothesis k_2 should be increased by electron-attraction in the aryl group, but on the second the back reaction should be facilitated by electron-release.

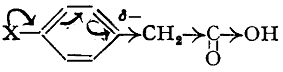
The data in Table I show that k_2 increases in the order *p*-alkyl $\ll$ H < *m*- and *p*-halogen < *m*-NO_2 < *p*-NO_2, a sequence which clearly suggests facilitation by electron-attracting substituents in the phenyl nucleus and which thus makes it extremely improbable that the main energetic requirement could be the breaking of the C–CN bond. In fact, in its broad outlines, the sequence is exactly the same as that found for k_1 where *electrostriction* of the cyanide ion is the important feature. It can therefore be concluded that the main energetic requisite for the back reaction is the ionisation of the hydrogen from the OH bond in the cyanohydrin, the energy required for the rupture of the C–CN bond being derived largely from the covalency sharing of the unshared electron-pair on the oxygen atom in the ion of the cyanohydrin $\overset{-\curvearrowright}{O}\overset{\curvearrowright}{—C—}CN$. Quite apart from such a theoretical interpretation, the experimental sequence clearly shows that all the halogens, in both *m*- and *p*-positions, are exerting an overall electron-attraction. The differences between the k_2 values for the various halogens, however, are very much smaller than are those for k_1 and, moreover, very little differentiation is observed between halogen substitution in either the *m*- or the *p*-position. In so far as the small velocity differences are significant, the orders of the k_2 values are :

$$m\text{-halogen}: \ \mathrm{I} > \mathrm{Br} > \mathrm{Cl} > \mathrm{F} > \mathrm{H}$$
$$p\text{-halogen}: \ \mathrm{I} \sim \mathrm{Br} > \mathrm{Cl} > \mathrm{F} > \mathrm{H}$$

which, in both cases, must also represent the order of decreasing overall electron-attraction. This order is precisely the same (though with much smaller differences) as that deduced for the k_1 values which has been shown (p. 1093) to receive a consistent explanation on the basis of a $+T$ effect decreasing in the order F > Cl > Br > I superimposed on the $-I$ effect which decreases in the same order. On the basis of the hypothesis that the important factor is the breaking of the O–H bond, any $+T$ effect would be one of inhibition and hence must be mesomeric and not electromeric in character. The only way in which such a mesomeric effect could reach the O–H bond in the cyanohydrin would be by inductive relay along the side chain from the phenyl nucleus (VII), and it would thus suffer very appreciable damping and could, possibly, so modify the electron-attracting influence of the halogens that the differences in their $-I$ effects were more or less obliterated, all halogens thus exerting an overall electron-attraction of closely similar magnitudes from either the *m*- or *p*-positions. It is not without significance that there are only small differences between the effect of the various halogens and between their effects in the *m*- and *p*-positions, on the dissociation constants of the phenylacetic acid series given in Table II (Dippy, *Chem. Reviews*, 1939, **25**, 207). In this closely similar system (VIII) the analogy extends to the nitro-group.

(VII.)





(VIII.)

TABLE II.

Values of 10^5K *for halogeno-substituted phenylacetic acids in aqueous solution.*

Position of substituent.	H.	F.	Cl.	Br.	I.	NO_2.
m	4·88	—	7·24	—	6·93	10·8
p	4·88	5·68	6·45	6·49	6·64	14·1

There is, however, an alternative, possible explanation of the k_2 values. For reasons already given, the mesomeric effect may be of little importance in the cyanohydrin so that the k_2 values might be influenced mainly by electron-attracting, electrostatic effects, inductive and inductomeric. Both these would be facilitating polar influences and hence a large inductomeric effect might be called into play in the transition state. Since the order of the inductive effect is F > Cl > Br > I, and that of the inductomeric is I > Br > Cl > F, their combined operation might well approximately equalise the overall electron-attracting power of the four halogens in the transition state and thus, in agreement with experiment, give rise to k_2 values of closely similar magnitudes. Moreover, the relative damping of the two effects in the *m*-position would probably be approximately the same so that both *m*- and *p*-values would be similar. The present experimental data do not permit any decision between these two explanations and more precise information regarding polarizability effects should accrue from the parallel study of the solvolysis of halogenobenzhydryl chlorides, to which reference has already been made.

Summarising the conclusions derived from this investigation, it is evident that the halogens exert strong inductive ($-I$) and mesomeric ($+M$) effects, both of which decrease in the order F > Cl > Br > I, and that there is considerable second-order relay of the $+M$ effect from the *m*-position. The results could be satisfactorily accounted for on the basis of these two polar influences alone if the $+M$ effect is modified (as indeed it must be) by the degree and extent of the unsaturation in the system to which it is attached. If an inductomeric effect is operative, it must be one of electron-*attraction*, which decreases in the reverse order I > Br > Cl > F. The magnitude of the $+M$ effect in the halogenobenzaldehydes would seem to preclude the incidence of any additional electromeric ($+E$) effect in the forward reaction (the only stage at which it might be called into play) and, in fact, the electron-release by this mechanism is smaller in the transition state than it is in the original aldehyde.

Discussion of Bird and Ingold's results (*loc. cit.*) for the nitration of the halogenobenzenes, where iodine and fluorine exhibit comparable electron-release effects, both greater than those of chlorine and bromine, is best deferred until the results of the parallel series of investigations are available, but the present data do suggest that the polarizability electron-*release* effect responsible for *op*-orientation by the halogens may be inductomeric in character rather than electromeric, as was originally postulated by those authors.

EXPERIMENTAL.

Preparation of Materials.—m- *and* p-*Halogenobenzaldehydes.* Although in their initial preparation each aldehyde was found to require its own special method (see below), a standard method of purification was used. This consisted of converting the distilled aldehyde into its bisulphite compound from which, after washing with ether, the aldehyde was regenerated, steam-distilled, and converted into its semicarbazone. This derivative was purified by repeated crystallisation, usually from methyl alcohol, to a sharp, constant m. p. (standard rate of heating essential) and the aldehyde was regenerated from the pure semicarbazone by steam-distillation with aqueous oxalic acid in a current of carbon dioxide. The collected aldehyde was dried in ether solution and then carefully fractionated under reduced pressure (nitrogen), the fraction of constant b. p. being retained. Since both *m*- and *p*-iodobenzaldehyde tended to lose iodine during distillation they were finally purified by crystallisation from ligroin (b. p. 40—60°). All aldehydes were stored in small dark bottles under nitrogen and were freshly redistilled in nitrogen under reduced pressure (or recrystallised) immediately before use. The data given refer to the m. p. and b. p. of pure specimens of the aldehydes and their derivatives.

p-*Chlorobenzaldehyde.* Dry chlorine was passed into boiling, pure *p*-chlorotoluene (b. p. 66·5—67°/29 mm.) illuminated by a 150-watt lamp, and under a reflux condenser partly filled with small glass beads. Fractionation of the product gave *p*-chlorobenzyl chloride, b. p. 96—96·5°/14 mm., which was converted into the aldehyde by refluxing with an equimolecular weight of hexamethylenetetramine in aqueous alcohol for 2 hours in a current of carbon dioxide. After removal of the alcohol by distillation, the aldehyde was distilled in steam (carbon dioxide stream), extracted with ether, and converted directly into its bisulphite compound for purification: semicarbazone, m. p. 227°; *p*-chlorobenzaldehyde, b. p. 92°/16 mm., m. p. 48°.

p-*Bromobenzaldehyde.* Side-chain bromination of 128 g. of *p*-bromotoluene, b. p. 64—65°/14 mm. (from *p*-toluidine), with 120 g. of dry bromine was effected by a procedure similar to that described in *Org. Synth.* (Coll. Vol. 2, 89) with strong illumination and at 110° for the first hour, the temperature then being raised to 150° during the second hour. The resulting *p*-bromobenzyl bromide, b. p. 130—131°/16—17 mm., m. p. 61·5°, was converted into the aldehyde by the hexamine method; semicarbazone m. p. 226°; *p*-bromobenzaldehyde, b. p. 109°/16 mm., m. p. 58°.

p-*Iodobenzaldehyde.* Dry bromine (1 mol.) was added during 2 hours to 50—60 g. of *p*-iodotoluene, b. p. 89—90°/12 mm., at 140° but without illumination. Fractionation of the product gave *p*-iodobenzyl bromide, b. p. 115—120°/0·6 mm., m. p. 77—77·5°, which was converted into the aldehyde as before. The last traces of *p*-iodobenzyl bromide are retained in a considerable tarry residue and require stronger heating for their removal. The yield is very poor; semicarbazone, m. p. 224°; *p*-iodobenzaldehyde, b. p. 98°/1·4 mm., m. p. 76°.

p-*Fluorobenzaldehyde.* *p*-Fluorotoluene (Messrs. British Drug Houses, Ltd.) was chlorinated as described for *p*-chlorotoluene, but without illumination, until the b. p. of the liquid registered by a thermometer below the liquid surface reached 160°. Repeated fractionation of the product gave *p*-fluorobenzyl chloride, b. p. 70—71°/16 mm., for conversion into the aldehyde; b. p. 70°/20 mm.; semicarbazone, m. p. 216°.

m-*Chlorobenzaldehyde.* A purified sample of *m*-nitrobenzaldehyde, b. p. 146—147°/14 mm., was reduced to the amino-aldehyde with A. R. stannous chloride in hydrochloric acid (*Org. Synth.*, Vol. 13, 28) which was diazotised without isolation and converted by cuprous chloride into *m*-chlorobenzaldehyde, b. p. 90°/14 mm.; semicarbazone, m. p. 226°.

m-*Bromobenzaldehyde.* The method analogous to that used for the *m*-chloro-compound gave a product appreciably contaminated with *m*-chlorobenzaldehyde, which could not be removed by repeated crystallisation of its semicarbazone or by fractional distillation. *m*-Nitrobenzaldehyde was reduced with sodium dithionite at 80° (Hodgson and Beard, *J. Soc. Chem. Ind.*, 1926, **45**, 91T), the reduced solution was cooled, acidified with sulphuric acid, diazotised, and treated with a solution of cuprous bromide. The purified *m*-bromobenzaldehyde had b. p. 101°/11 mm.; semicarbazone, m. p. 225°.

m-*Iodobenzaldehyde.* The methods used for the *m*-bromo- and *m*-chloro-compounds proved unsuccessful when applied to the *m*-iodo-derivative. *m*-Iodotoluene, b. p. 96°/21 mm. (from *m*-toluidine), was brominated under the conditions used for *p*-iodotoluene except that a temperature of 180° was employed. The product fraction of b. p. 153—156°/12 mm. was purified by repeated crystallisation from ligroin (b. p. 40—60°) to give *m*-iodobenzyl bromide, m. p. 49—49·5°, which was converted by the hexamine method into *m*-iodobenzaldehyde, b. p. 124—125°/13 mm., m. p. 57°; semicarbazone, m. p. 224°.

m-*Fluorobenzaldehyde.* Chlorination of *m*-fluorotoluene under the conditions used for the *p*-compound gave a product, b. p. 152—156°/20 mm., with a blue fluorescence which was not *m*-fluorobenzyl chloride. Chlorination was successfully effected when carried out with strong illumination by a 500-watt lamp. Repeated fractionation of the main fraction gave *m*-fluorobenzyl chloride, b. p. 69·5—72·5°/21 mm. This was converted as usual into *m*-fluorobenzaldehyde, b. p. 67°/19 mm.; semicarbazone, m. p. 212·5°.

Benzaldehyde. An " extra pure " specimen (Messrs. British Drug Houses, Ltd.) was put through the usual purification, the sample used having b. p. 74°/24 mm.

m-*Nitrobenzaldehyde.* A purchased sample was steam distilled to remove a yellow pigment, and converted into its semicarbazone which was crystallised from glacial acetic acid; m. p. 246°. The aldehyde was regenerated by steam-distillation with 50% sulphuric acid and purified by repeated crystallisation from ligroin (b. p. 40—60°) to give a sample, m. p. 56·5°.

p-*Nitrobenzaldehyde.* This was best purified by sublimation under reduced pressure (17 mm.), followed by repeated crystallisation from carbon tetrachloride, to give a specimen, m. p. 104·5—105°.

Liquid hydrogen cyanide from a cylinder, kindly supplied by Messrs. Imperial Chemical Industries Ltd., was carefully distilled from phosphoric oxide in an all-glass apparatus fitted with an anti-splash head. The stock solution was prepared by dissolving 16 ml. of the pure distillate in 400 ml. of constant-b. p. alcohol to give an approximately M-solution, which was stored in dark bottles with well-ground glass stoppers sealed with paraffin wax.

The constant-boiling alcohol solvent, catalysts, and standard solutions were prepared, and apparatus calibrated, as described by Baker and Hemming (*loc. cit.*).

Equilibria and Velocity Determinations.—These were carried out by means of the microtechnique described by Baker and Hemming in thermostats controlled to 20° ± 0·02°. The consistency of the determinations is shown by the following summary of the results of individual experiments, from which the final mean data in Table I were obtained.

Summary of experimental data for the reaction

$$X{\cdot}C_6H_4{\cdot}CHO + HCN \underset{k_2}{\overset{k_1}{\rightleftharpoons}} X{\cdot}C_6H_4{\cdot}CH(OH){\cdot}CN$$

in constant-b. p. alcohol at 20° ± 0·02°.

Velocity catalyst = 0·01M-pyridine + 0·01M-pyridinium benzoate.
Equilibrium ,, = 2 drops (~0·02 g.) of NPr_3 per 50 ml.

X.	Individual values of 10^3K, g.-mol. l.$^{-1}$.	Mean 10^3K.	Individual values of 10^8k_1, g.-mol.$^{-1}$ l. sec.$^{-1}$.	Mean 10^8k_1.
H	4·53, 4·67, 4·27, 4·23, 4·44, 4·37, 4·66, 4·39	4·45 ± 0·13 *	1·63, 1·66	1·65 ± 0·02
p-F	6·44, 6·33, 6·44, 6·11, 6·10, 6·40 †	6·30 ± 0·13	3·60, 3·59	3·59 ± 0·01
p-Cl	3·90, 3·62, 4·02, 3·86	3·85 ± 0·12	6·98, 6·90	6·94 ± 0·04
p-Br	3·26, 3·31, 3·17, 3·31	3·26 ± 0·05	9·07, 9·20	9·14 ± 0·07
p-I	3·18, 3·08, 3·12	3·13 ± 0·04	9·29, 9·46	9·38 ± 0·09
m-F	2·11, 2·16, 2·11	2·13 ± 0·02	10·20, 10·23	10·22 ± 0·02
m-Cl	1·95, 1·97, 1·98	1·97 ± 0·01	12·43, 12·47	12·45 ± 0·02
m-Br	1·90, 1·86	1·88 ± 0·02	14·16, 14·48	14·32 ± 0·16
m-I	2·08, 2·03, 1·96	2·02 ± 0·04	14·01, 14·97, 14·47	14·5 ± 0·3

* Mean deviation from the mean value.
† From a " velocity " experiment allowed to attain equilibrium.

m- and *p*-*Nitrobenzaldehydes.*—The upward drift in the hydrogen cyanide concentration, subsequent to reaching its minimum value, when the catalyst used was one drop of tri-*n*-propylamine, is illustrated by the following calculated values of the " equilibrium " constant at progressive time intervals from the commencement of the experiments.

m-	10^3K	(1) 3·70. (2) 4·20.	(1) 5·16. (2) 6·00.
	Time, hrs.	*ca.* 3	*ca.* 24

p-	10^3K	12·5	10·0	7·4	7·94	11·3	15·7	26·5	34·3
	Time, hrs.	0·67	1·17	2·67	4·67	22·0	29·75	50·67	68·17

With 0·01M-pyridine + 0·01M-pyridinium benzoate as catalyst, the corresponding drift is shown in the following table, which records the number of ml. (y) of 0·05N-ammonium thiocyanate required for the excess of 0·05N-silver nitrate after addition of 10 ml. of the silver nitrate to a 2-ml. sample of the reaction mixture :

m-NO_2	y, ml.	9·10	9·11	9·11, 9·12	whence 10^3K = 2·10 g.-mol. l.$^{-1}$.
	Time, hrs. ...	24	46	100	

p-NO_2	y, ml.	7·94	8·05	8·16	*8·86*	8·80	8·76	8·64	8·27	8·16
	Time, hrs. ...	6·80	7·58	8·23	24	32	54	72	125	150

Extrapolation to zero time of the straight line obtained by plotting the values of y against time over the period 24—150 hrs. gave an estimated value of $y_{max.}$ = 9·07 ml., whence 10^3K = 3·4 g.-mol. l^{-1}.

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