# 292. *Studies of the* ortho-*Effect. Part I. The Influence of Substituents in the* ortho-*Position upon the Chemical Characters of Carboxylic Acids and their Derivatives.*

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In this series of papers, an attempt is made to throw further light upon the peculiar effects of groups in the *o*-position upon reactivity and upon the strengths of acids and bases. Victor Meyer's conception of steric hindrance does not provide a complete explanation of the observed phenomena, although a geometrical effect of this character cannot be neglected as a possible contributory factor, while in some cases it may be the most important cause. It is significant, however, that the *ortho*-effect appears to operate only when the reacting group contains an electron-donating atom (*e.g.*, $-$COR, $-NR_2$), and a consideration of available evidence, together with some new results recorded in the two following papers, leads to the conclusion that in many carboxylic acids and derivatives there may be an interaction of the *o*-substituent with the unshared electrons of this group to form a hydrogen bond or a co-ordinate linkage as visualised by Sidgwick and Callow in their consideration of the physical properties of *o*-substituted phenols. Certain difficult examples are shown to be not inconsistent with this view. At the same time, the probable intervention of other factors is fully realised.

The relative inertness of many *o*- and di-*o*-substituted benzene derivatives has frequently been demonstrated in reactions such as the formation of quaternary ammonium salts by anilines and of oximes and phenylhydrazones by ketones, the esterification of carboxylic acids, and the hydrolysis of esters, nitriles, acid chlorides, and amides (see summary in Cohen, " Organic Chemistry," Vol. 1, Ch. V). The usual polar effects of substituents will operate from the *o*-position not less than from the *p*-position, but in the *o*-substituted compounds there is evidence of some additional factor which is absent in the isomeric derivatives.

In the course of an extensive series of investigations (for summary and refs., see Lloyd and Sudborough, J., 1899, **75**, 580), Victor Meyer, Sudborough, and their collaborators found that di-*o*-substituted benzoic acids gave no ester when their alcoholic solutions were saturated with hydrogen chloride at 0° or treated by the Fischer–Speier method; even when the boiling solutions were saturated with hydrogen chloride for prolonged periods, the esterification was either not detectable (with $NO_2$, Cl, Br, or I as substituents) or very slight (with alkyl groups, OH, or F). Moreover, the esters and other derivatives of these acids were unusually stable to hydrolytic agents. The retardation of esterification and hydrolysis by one *o*-substituent was also demonstrated (compare also Goldschmidt, *Ber.*, 1895, **28**, 3218; Kellas, *Z. physikal. Chem.*, 1897, **24**, 221; Kindler, *Annalen*, 1928, **464**, 278). Analogous effects in aliphatic compounds are illustrated by the order of velocities $CH_3{\cdot}CO_2H > CH_2X{\cdot}CO_2H > CHX_2{\cdot}CO_2H > CX_3{\cdot}CO_2H$ for the esterification of *all* series of substituted acetic acids independently of the nature of X (Sudborough and Lloyd, J., 1899, **75**, 467) and the different rates of esterification of *cis*- and *trans*-substituted acrylic acids (Sudborough *et al.*, J., 1898, **73**, 81; 1905, **87**, 1840). The strengths of aromatic acids and bases are also profoundly influenced by substituents in the *o*-position, and analogies are found in phenomena such as the greater strength of *allo*cinnamic than of cinnamic acid (compare Dippy and Lewis, this vol., p. 1008). The classical dissociation constants of Ostwald and others indicate that *all* *o*-substituted benzoic acids are stronger than benzoic itself, and often very considerably stronger than their *m*- and *p*-isomerides; this is confirmed by recently measured thermodynamic constants, a table of which, referred to $K_{\text{therm.}}$ for benzoic acid as unity, is included in Part II (following paper). Very few values for di-*o*-substituted benzoic acids are available, but in at least two cases (2 : 6-dihydroxy- and 2 : 6-dinitro-) the presence of the second *o*-substituent leads to a further large increase in the dissociation constant. Groups in the *o*-position decrease the strengths of anilines, and confer increased stability upon benzaldehydecyanohydrins (Lapworth and Manske, J., 1928, 2533).

Meyer emphasised the fact that the *ortho*-effect does not depend upon the chemical nature of the substituent (thus, *o*-F is not comparable with the other halogens), but appears rather to be governed by its size (as measured, according to him, by the weights of the atoms). Moreover, the effect does not operate if the reacting group is separated from the nucleus by one or more carbon atoms (as, *e.g.*, in mesitylacetic acid); this has been confirmed more recently by measurements of the strengths of phenylacetic acids (Part II) and of the rates of hydrolysis of cinnamic esters (Kindler, *loc. cit.*). The conception of steric hindrance was based upon observations of this type. There is, however, no definite relationship, even of a qualitative nature, between the influence of a group in the *o*-position and its weight or volume (*e.g.*, $NO_2$ is usually more effective than I). Flürscheim (J., 1909, **95**, 725) interpreted the relatively high dissociation constants of *o*-substituted acids in the light of Meyer's theory, and his suggestion, when modified in accordance with present views of ionisation, may be expressed by saying that since, in the equilibrium $R{\cdot}CO_2H + H_2O \rightleftarrows R{\cdot}CO_2^{\ominus} + H_3O^{\oplus}$ (in dilute aqueous solution) the acid is in continual contact with water molecules, steric hindrance will not influence the ionisation perceptibly but will retard the reassociation process. Applied to the equilibrium $R{\cdot}NH_2 + H_2O \rightleftarrows R{\cdot}NH_3^{\oplus} + OH^{\ominus}$, however, this would lead to the expectation of increased strength in *o*-substituted bases, for here again only the reversed change will be influenced unfavourably; actually a marked decrease in strength is observed. While, therefore, steric hindrance in the Victor Meyer sense may frequently be an important factor (compare also the restricted rotation in *o*-substituted diphenyls and analogous compounds), the problem of the *ortho*-effect is one of great complexity, and the observations cannot be explained completely in terms of a purely geometrical effect (compare Davis, J., 1900, **77**, 33; Kindler, *loc. cit.*). The work to be described in this series of communications has been undertaken in an attempt to trace the origin of the *ortho*-effect in different systems, and the results of some measurements of the dissociation constants of *o*-substituted benzoic acids and of the velocities of hydrolysis of their esters are considered in this, the first part. A detailed account of the experimental results follows in Parts II and III.

The first fact upon which we wish to lay emphasis is that the *ortho*-effect is by no means a general one, for it is not observed in all aromatic compounds where the substituents are suitably placed with respect to the reacting group. It appears to operate, in fact, only when the latter contains an atom which is known to be a powerful electron-donor, *e.g.*, COR, $CO_2R$, $NR_2$. This is illustrated by the relative effects of two bromine atoms in *o*-positions in benzoyl chloride and benzyl chloride severally; the velocities of hydrolysis of 2 : 6- and 3 : 5-dibromobenzoyl chlorides, referred to that of the unsubstituted compound as unity, are 0·0112 and 13·5, while the figures for the corresponding benzyl chlorides are 0·12 and 0·07 (Olivier, *Rec. trav. chim.*, 1929, **48**, 227). The *ortho*-effect is never detectable, indeed, in the reactions of benzyl chlorides (cf. *idem, ibid.*, 1930, **49**, 697; Bennett and Jones, J., 1935, 1815). Again, Branch, Yabroff, and Bettmann (*J. Amer. Chem. Soc.*, 1934, **56**, 937, 1865) find no increase in strength in *o*-substituted phenylboric acids, $C_6H_4X{\cdot}B(OH)_2$, as compared with their isomerides. The characters of *o*-substituted phenols and their derivatives, moreover, do not indicate an effect of any magnitude; they are not more strongly acidic than the isomeric *m*- and *p*-substituted compounds, nor are they appreciably less reactive (*e.g.*, Boyd *et al.*, J., 1914, **105**, 2117; 1919, **115**, 1239; Burkhardt *et al.*, J., 1936, 17; the influences recorded by Davis, *loc. cit.*, in the reactions of alcohols with 1-substituted β-naphthols are probably inductive effects), and it may be noted in this connection that hydroxyl is predominantly an electron-accepting group.

Secondly, even among reactions of *o*-substituted carboxylic acids and their derivatives, there are instances where no unusual feature is observed. The data for the speeds of hydrolysis and alcoholysis of benzoyl chlorides with one *o*-substituent are rather conflicting (Berger and Olivier, *Rec. trav. chim.*, 1927, **46**, 516; Norris *et al.*, *J. Amer. Chem. Soc.*, 1935, **57**, 1415); these reactions are of a complicated character, and the effects of substituents in any position are difficult to interpret (Ingold, *Ann. Reports*, 1927, **24**, 157). Two notable examples of the definite absence of the *ortho*-effect are found, however, in the reactions of *o*-substituted benzoic acids with di-*p*-tolyldiazomethane (Norris and Strain, *J. Amer. Chem. Soc.*, 1935, **57**, 187) and of the corresponding methyl esters with trimethylamine (Hammett and Pfluger, *ibid.*, 1933, **55**, 4079) :

$$R{\cdot}CO_2H + N_2C(C_6H_4{\cdot}CH_3)_2 \longrightarrow N_2 + R{\cdot}CO_2CH(C_6H_4{\cdot}CH_3)_2$$

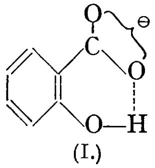
$$R{\cdot}CO_2CH_3 + N(CH_3)_3 \longrightarrow R{\cdot}CO_2^{\ominus} + N(CH_3)_4^{\oplus}$$

Yet, as pointed out above, the ionic equilibria and esterification reactions of these acids and the alkaline hydrolyses of the esters show marked *ortho*-effects. The value of the dissociation constant of *s*-trimethylbenzoic acid ($10^5K = 3{\cdot}75$, as compared with 6·6 for benzoic acid) leads to the conclusion that the *o*-methyl groups are exerting only their normal inductive effects, and the same is true of trimethylacetic acid ($10^5K = 0{\cdot}98$; cf. 1·8 for acetic acid) where also an " *ortho*-effect " might be expected. Nevertheless, when these acids are esterified, the energies of activation are very high in comparison with those for benzoic and acetic acids respectively (Hinshelwood and Legard, J., 1935, 587, 1588); the operation of an " *ortho*-effect " is thus indicated in the acid-catalysed reactions, although not in the strengths of the acids themselves.

Thirdly, our investigation of the alkaline hydrolysis of *o*-substituted benzoic esters (Part III) has shown that the relatively low speeds are to be ascribed to a decrease of approximately a power of 10 in the probability factor $P$ of the kinetic equation $k = PZe^{-E/RT}$; the energies of activation are actually slightly less (appreciably less in ethyl *o*-chlorobenzoate) than those for the isomeric *m*- and *p*-substituted esters. Newling and Hinshelwood (J., 1936, 1357) have obtained similar results for the alkaline hydrolysis of ethyl *iso*butyrate. On the other hand, an " *ortho*-effect " in acid-catalysed esterification involves an *increase* in $E$, and usually an *increase* in $P$ also (Hinshelwood and Legard, *loc. cit.*).

In seeking a solution of the problems presented by the above observations, we are fully aware that steric hindrance of the Victor Meyer type cannot be neglected as a possible cause of the peculiarities shown by *o*-substituted compounds. It may, for example, be entirely or almost entirely responsible for the relatively high dissociation constants of *o*-phenyl- and *o*-phenoxy-benzoic acids (see Part II), and it may also be a contributory factor in many other instances. We believe, nevertheless, that the *ortho*-effect frequently originates, to a great extent, in chelation processes similar to those which produce abnormalities in the physical properties of certain *o*-substituted phenols (Sidgwick and Callow, J., 1924, **125**, 527). At the same time, we do not suggest that this is ever the *sole* cause of the effect, or that other factors should be excluded.

The relatively high dissociation constant of salicylic acid ($10^5K = 105$) cannot be due entirely to steric hindrance by so small a group as hydroxyl, particularly in view of the fact that methoxyl does not lead to any striking increase in the constant, and Branch and Yabroff (*J. Amer. Chem. Soc.*, 1934, **56**, 2568) have postulated the formation of a hydrogen bond between the hydroxyl and carboxyl groups. The positions of the atoms in salicylic acid are peculiarly favourable to hydrogen-bond formation (see Sidgwick and Callow, *loc. cit.*; Sidgwick, "The Electronic Theory of Valency," Oxford University Press, 1927, Ch. XIV), and the resonance to which the bond is due is facilitated by electronic rearrangements [see (II) and (III)]. It is to be anticipated that negatively-charged carboxyl (carboxylate ion) will form such a bond more readily than the undissociated group, and the high acidity may therefore arise almost entirely from the occurrence in the *ion* of the process represented in (I) [the unperturbed structures are (II) and (III)]. This will decrease the electron-availability of the $-CO_2^{\ominus}$ group, and will thus militate against reassociation. Baker has suggested (*Nature*, 1936, **137**, 236) that the further large increase in strength in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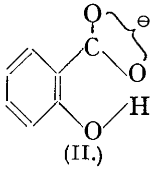
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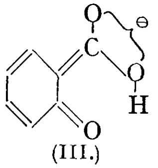
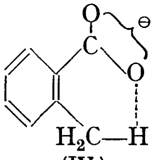

(III.)

2 : 6-dihydroxybenzoic acid ($K = 5 \times 10^{-2}$) is due to the formation of hydrogen bonds by *both* oxygens of carboxyl.

It is probable that an alkyl group can form a hydrogen bond, provided that an electron-donating atom is suitably placed with respect to it, and that the resonance (which involves what is virtually an ionisation process) is made possible by a neighbouring electron-attractive group (*e.g.*, in *o*-nitrotoluene, Sidgwick and Callow, *loc. cit.*; cf. also Evans, J., 1936, 785). The fact that *o*-toluic acid ($10^5K = 12{\cdot}35$) is appreciably stronger that its *m*- and *p*-isomerides (and than benzoic acid itself) may therefore be attributed to the formation, to a limited extent, of a hydrogen bond as in (IV). Comparison of the strengths of salicylic and *o*-toluic acids shows that in the latter the average state must approach the unperturbed structure (V) far more closely than (VI). The same interpretation is not applicable to *o-tert.*-butylbenzoic acid, which is markedly stronger than *o*-toluic acid ($10^5K = 35$; Shoesmith and Mackie, J., 1936, 300), although hydrogen-bond formation is not possible. Other effects must operate here.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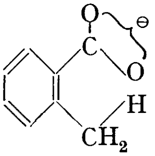
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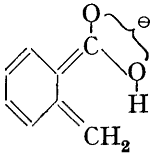
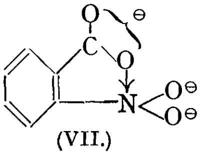
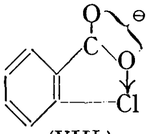

(VI.)

In *o*-nitro- and the *o*-halogeno-benzoic acids (excluding *o*-F), an oxygen of the carboxyl group may act as electron donor in the formation of a co-ordinate bond of the normal type. Chlorine, bromine, and iodine can expand their valency groups beyond eight electrons (the rather high value of $K$ for *o*-fluorobenzoic acid must be accounted for otherwise), and Bennett and Willis (J., 1929, 256), in their formulation of the additive products of nitro-compounds with amines and hydrocarbons, ascribe electron-acceptor properties to the nitrogen atom of the nitro-group. Structures (VII) and (VIII) are therefore suggested for the ions of *o*-nitro- and *o*-chloro-benzoic acids; a five-membered ring is postulated here (cf. examples in the papers by Sidgwick and Callow and by Evans, already referred to). In the *o*-substituted phenylacetic and cinnamic acids, and in *o*-methoxybenzoic acid, the positions of the atoms are unsuitable for chelation, and there is no great increase in the dissociation constant.

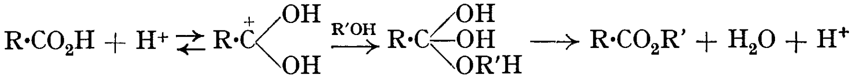

(VII.)


(VIII.)

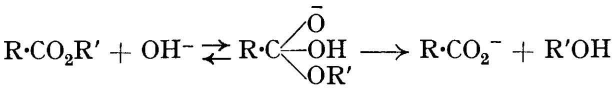
If the *ortho*-effect has its origin very largely in phenomena of this kind, the necessity that the reacting group should be electron-donating is understood; the chelation processes suggested above could not occur, for example, in *o*-substituted benzyl chlorides, and hydrogen-bond formation in a phenol (OH acting as acceptor, OH ←—, compare Sidgwick and Callow, *loc. cit.*) would not be expected to have much influence upon its dissociation or upon the electron-availability of the oxygen.

The second point which has been emphasised, *viz.*, the absence of an *ortho*-effect in certain processes involving *o*-substituted acids and esters, has next to be considered. It has already been pointed out that, on our view, the high dissociation constants of acids are due principally to decreased facility of the reassociation, since chelation will occur most extensively in the ion. In reactions such as those formulated on p. 1423, the un-ionised acid (or ester), and not the anion, is the reacting entity, and it is therefore not surprising that the *ortho*-effect becomes small or negligible. In *s*-trimethylbenzoic and trimethylacetic acids, where the dissociation constants do not indicate an *ortho*-effect, it must be supposed that some factor inhibits the formation of the hydrogen bond, and it is not possible at present to determine whether the inductive effects of the additional methyl groups are to any extent responsible for this.

Chelation in the anion of the acid does not account for *ortho*-effects in esterification processes, or in the hydrolysis of esters. In accordance with a previous suggestion (Evans, Morgan, and Watson, J., 1935, 1171), we represent these processes as follows :



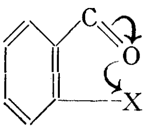
$$R{\cdot}CO_2H + H^+ \rightleftarrows R{\cdot}\overset{+}{C}\begin{matrix}\diagup OH\\ \diagdown OH\end{matrix} \xrightarrow{R'OH} R{\cdot}C\begin{matrix}\diagup OH\\ -OH\\ \diagdown OR'H\end{matrix} \longrightarrow R{\cdot}CO_2R' + H_2O + H^+$$



$$R{\cdot}CO_2R' + OH^- \rightleftarrows R{\cdot}C\begin{matrix}\diagup \bar{O}\\ -OH\\ \diagdown OR'\end{matrix} \longrightarrow R{\cdot}CO_2^- + R'OH$$

The carboxyl and carbethoxyl groups have resonance energies of about 1·2 v.e. (Pauling and Sherman, *J. Chem. Physics*, 1933, **1**, 606), and in the complex formed on collision with the catalyst the resonance is destroyed. The electrons are now in higher energy levels and consequently more reactive. If, therefore, other atoms are suitably placed, chelation or hydrogen-bond formation is likely to occur *simultaneously* with the attack of the catalyst as represented in (IX). For acid-catalysed esterification the resulting decrease in electron-availability of the oxygen will lead to a high energy of activation (compare the prototropy of propiophenone; Evans, *loc. cit.*), but in alkaline hydrolysis (where the catalyst is added at carbon and not at oxygen) there will be no such effect; the slightly low value of *E* may be due to the facilitation of the electromeric change $\overset{\curvearrowright}{C{=}O}$.

If the complex is highly chelated, its constitution will be as represented in (X) (for esterification) or (XI) (for hydrolysis). The effect of the chelation is a drift of electrons away from carbon, and in esterification the subsequent change, *viz.*, addition of R'OH, will thereby be facilitated, whereas in hydrolysis, which requires the elimination of –OR', the process will be rendered more difficult. This explains the effect of *o*-substituents upon the *P* factor if, as suggested in Part III, this factor is governed largely by the second stage of the complete change.



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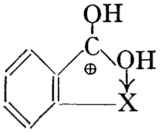
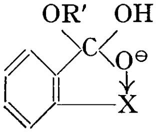


(X.)



(XI.)

Finally, the behaviour of ethyl *o*-fluorobenzoate on alkaline hydrolysis is in complete harmony with an interpretation of this type. The values of *E* and *P* are here almost the same as those found for the isomeric *p*-substituted ester. The formation of a co-ordinate bond is impossible, since fluorine cannot increase its valency group, and this enforced absence of chelation is accompanied by the complete non-existence of all the criteria of the *ortho*-effect.

A satisfactory interpretation of a number of phenomena is thus found along the lines indicated. Nevertheless, other important factors may also be involved, and in no case is the absence of these assumed. The study of the *ortho*-effect is being continued in these laboratories.

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