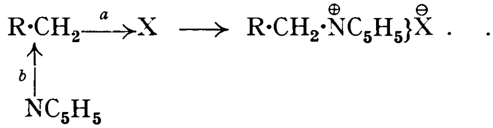
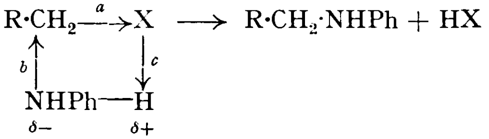
267. Anomalies in the Reactivities of Side-chain Halogens with Special Reference to Reaction Mechanism.

By John W. Baker.

It has already been pointed out (Baker, J., 1932, 1148, 2361) that in the reaction between benzyl and phenacyl halides with pyridine (1) there are at least two factors which may affect the velocity of formation of the quaternary salt: (*a*) the ease of anionisation of the halogen atom, and (*b*) the electrostriction of the pyridine molecule by means of the unshared nitrogen electrons to the methylene group.



$$\underset{\substack{\uparrow b\\ \mathrm{NC_5H_5}}}{\mathrm{R{\cdot}CH_2}}\xrightarrow{a}\mathrm{X}\longrightarrow \mathrm{R{\cdot}CH_2{\cdot}\overset{\oplus}{N}C_5H_5\}\overset{\ominus}{X}} \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$



$$\underset{\substack{\uparrow b\\ \mathrm{NHPh}\\ \delta-}}{\mathrm{R{\cdot}CH_2}}\xrightarrow{a}\underset{\substack{\downarrow c\\ \mathrm{H}\\ \delta+}}{\mathrm{X}}\longrightarrow \mathrm{R{\cdot}CH_2{\cdot}NHPh + HX} \quad . \quad . \quad . \quad . \quad (2)$$

In the corresponding reaction with the primary base aniline (2), there is, in addition, a third factor (*c*) which may influence the velocity of the reaction, *viz.*, the affinity of the unshared halogen electrons for the positively polarised hydrogen of the attacking aniline molecule.* Of these various factors, (*a*) and (*c*) should be facilitated by electron accession to the side chain, whereas (*b*) requires electron recession therefrom. In Table I the values of the pseudo-unimolecular velocity coefficients for the reactions between substituted benzyl and phenacyl bromides with 10 mols. of pyridine or aniline in $M/40$-solution in 90% ethyl alcohol at 30·5° are summarised.

TABLE I.

Reactions between $\mathrm{R{\cdot}CH_2Br}$ and (1) pyridine or (2) aniline, in $M/40$-solution in 90% ethyl alcohol at 30·5°.

Reaction type.*	Y =	MeO.	Me.	H.	I.	Br.	Cl.	NO_2.	(m-NO_2).
R = p-Y·C_6H_4.									
1A	10^3k, min.$^{-1}$	∞	9·5	4·4	3·3	3·0	3·2	1·56	1·36
2A	10^3k, min.$^{-1}$	—	87	35	45	41	44	22	30·4
R = p-Y·C_6H_4·CO.									
1B	10^3k, min.$^{-1}$	—	5·49	6·5	—	7·17	7·22	10·4	11·3
2B	10^3k, min.$^{-1}$	(10) †	11·4	14·5	—	19·4	19·3	35	44

* For convenience in reference reactions with pyridine and aniline are numbered 1 and 2 respectively, those requiring electron accession (*i.e.* benzyl halides) are denoted by the suffix A, and those requiring electron recession (phenacyl halides) by the suffix B.

† For ω-iodo compound.

Considering, for the moment, only the effect of *p*-substituents of the unipolar type $+I$(Me) and $-I(NO_2)$ it is evident that the reaction between benzyl halides and pyridine (1A) or aniline (2A) is facilitated by a *p*-methyl and retarded by a *p*-nitro-substituent and is therefore diagnosed as one requiring electron accession to the side chain (Ingold and Rothstein's type A). On the other hand, the analogous reactions with phenacyl halides (1B and 2B) are retarded by a methyl and facilitated by a nitro-substituent, and thus belong to Type B reactions, *i.e.*, they require electron recession from the side chain.

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* For evidence in support of the intervention of this factor, which is not further discussed here, see Baker, *loc. cit.*

Thus under identical experimental conditions it is seen that the nature of the group R attached to the CH_2Br group determines by which type of mechanism the reaction proceeds, *i.e.*, the nature of R predisposes the molecule to react in accordance with either one or the other type of mechanism.

There has been a tendency in the past to assume that such an experimental diagnosis determines which of the several theoretical factors is the *sole* rate-determining stage in the reaction. Thus in reactions 1A and 2A, which require electron accession to the side chain, the initial anionisation of the halogen atom has been postulated as the rate-determining stage, whereas in the opposite type of reaction, 1B and 2B, this rôle has been ascribed to the initial electrostriction of the base to the adjacent methylene carbon atom. It appears to the author that such an assumption may not be justifiable; a more valid deduction from such an experimental diagnosis would be that the electronic structure of the unsubstituted parent molecule is such that, of the number of collisions between either the reactant molecules and/or the solvent molecules, a far larger proportion of those which can result in, say, the separation of the halogen as a halide ion will come to fruition, than of those which would result in the initial co-ordination of the nitrogen atom, and *vice versa*. In any one experiment, however, both types of mechanism may occur side by side, and the diagnosis based on the effect of substituent groups on the resultant velocity merely indicates that a far larger proportion of the total molecules reacts in accordance with one particular mechanism than with the other.

The results discussed above clearly suggest that alteration of the nature of the group R attached to the CH_2Br residue definitely changes the balance from one type of mechanism to another, and hence the presence of substituents in R, which, of course, alters the nature of this group, may alter the balance between the number of molecules reacting by one or the other type of mechanism. Hence, in interpreting velocity data it may be necessary to consider the effect of the substituent group on all the possible rate-affecting factors, and, since these are of opposite polar types, one requiring electron accession and the other electron recession, the resultant effect on the total velocity of reaction is likely to be complex. This may be so even when the substituent is of a unipolar type, since it affects the two factors in opposite senses, but an even more complicated situation arises when the substituent is of an ambipolar type such as $-I+T$. In such a case the inductive and electromeric effects not only oppositely influence the various rate-determining factors in opposite senses, but they will do so by different mechanisms.

With the exception of the mobility of triad prototropic systems discussed by Dr. Shoppee (this vol., p. 1117), almost all the reactions which have been studied kinetically with a view to elucidating the effect of substitution contain at least two possible rate-affecting factors, and can be represented in a precisely similar manner to that employed for the reactions discussed in this communication (1 and 2), and it is well known that it is mainly, if not exclusively, with substituents of an ambipolar character that the many puzzling anomalies occur. Certain experimental evidence is available to support the idea that the velocity of a reaction depends on more than a single factor or mechanism, and this evidence is briefly summarised in the following paragraphs.

(a) *The influence of ambipolar substituents.* The seemingly anomalous effects of nuclear halogen substituents (ambipolar substituents in general) on aromatic side-chain reactions of Types A and B have already been discussed by Dr. C. W. Shoppee (*loc. cit.*), who has shown that an explanation of their effects can be derived on the assumption of two rate-affecting factors of opposite polar types. In the reactions considered in this paper, the velocity measurements summarised in Table I indicate that the balance between the inductive and electromeric effects of the halogens brings them close together near a (flat) maximum or minimum of the theoretical curve. Thus, in both reactions 1A and 2A the velocities for the three *p*-halogenobenzyl bromides are closely similar, but in each case the order is $I > Cl > Br$, the *p*-bromo-compound exhibiting the smallest velocity.* In the reaction with pyridine (1A), however, the velocity order is H > *p*-halogens, whereas in the reaction with aniline (2A, a reaction also requiring electron accession to the side

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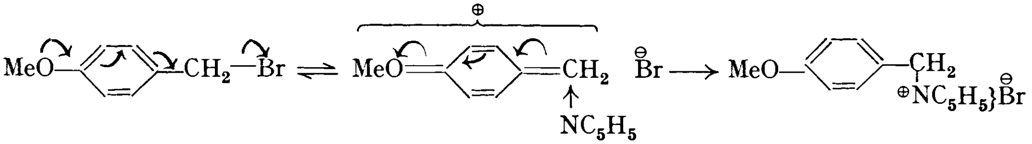
* Cf. curve (Fig. 6) in Dr. Shoppee's communication (*loc. cit.*).

chain) the order is *p*-halogens > H, clearly suggesting the existence of a varying balance between the inductive and electromeric effects of the halogen substituents.

The effect of a *p*-methoxyl substituent on the velocity of interaction of the benzyl halide with pyridine is also striking. In contradistinction to the other substituted benzyl halides, *p*-methoxybenzyl bromide, or even the chloride, reacts almost instantly with the base, and it has been suggested (Baker, J., 1932, 2361) that the powerful $+T$ effect of the methoxyl group enables the molecule to react in an ionised *p*-quinonoid form.



This furnishes an extreme case where the nature of the substituent group completely alters the mechanism of the reaction, which, in this case, is now exactly analogous to the formation of pyridine hydrobromide from pyridine and ionised hydrogen bromide.

(b) *Effect of* m- *and* p-*nitro-substituents on reaction* 1A. The reaction between substituted benzyl halides and pyridine (1A) requires electron accession and will therefore be retarded by both the $-I$ and the $-T$ effect of a substituent nitro-group. Both these retarding effects should be most powerful in the *p*-position, for in the *m*-position the $-I$ effect will be smaller and the $-T$ effect will be largely damped out. Hence if the *sole* rate-determining factor is one which requires electron accession to the side chain, the velocity should decrease in the order $\mathrm{H} > m\text{-}\mathrm{NO_2} > p\text{-}\mathrm{NO_2}$. Actually the velocity of the *m*-nitrobenzyl bromide (1·36) is *less* than that of the para-compound (1·56), suggesting that, in the *p*-position the very powerful $-I$, $-T$ effect of the nitro-group so facilitates the second rate-determining factor (*b*), *viz.*, the initial electrostriction of the base to the methylene carbon atom, that this effect more than counteracts the increased inhibition of the opposite factor (*a*), *i.e.*, the anionisation of the side-chain halogen.

(c) *The relative facilitating and retarding effects of groups.* Examination of the velocity data in the literature shows that it is a fairly general rule that the accelerating influence of any *unipolar* substituent on a reaction of the appropriate polar type is much more marked than is its retarding influence on a reaction of the opposite polar type. Thus, for example, the accelerating influence of a methyl substituent ($+I$) on reactions 1A ($\mathrm{Vel.}_{p\text{-Me}\cdot\mathrm{C_6H_4}\cdot\mathrm{CH_2Br}}/\mathrm{Vel.}_{\mathrm{PhCH_2Br}} = 2{\cdot}16$) and 2A ($\mathrm{Vel.}_{\mathrm{Me}}/\mathrm{Vel.}_{\mathrm{H}} = 2{\cdot}49$), both of which require electron accession, is much greater than its retarding influence on the corresponding reactions 1B ($\mathrm{Vel.}_{\mathrm{PhCO}\cdot\mathrm{CH_2Br}}/\mathrm{Vel.}_{p\text{-Me}\cdot\mathrm{C_6H_4}\cdot\mathrm{CO}\cdot\mathrm{CH_2Br}} = 1{\cdot}2$) and 2B ($\mathrm{Vel.}_{\mathrm{H}}/\mathrm{Vel.}_{\mathrm{Me}} = 1{\cdot}27$), which require electron recession. Similarly the retarding influence of the nitro-group ($-I$) on reaction 2A ($\mathrm{Vel.}_{\mathrm{PhCH_2Br}}/\mathrm{Vel.}_{p\text{-NO_2}\cdot\mathrm{C_6H_4}\cdot\mathrm{CH_2Br}} = 1{\cdot}6$) is smaller than its accelerating influence on reaction 2B ($\mathrm{Vel.}_{\mathrm{NO_2}}/\mathrm{Vel.}_{\mathrm{H}} = 2{\cdot}4$). This point is clearly recognised from the form of the curves obtained by plotting the velocities of the substituted derivatives (relative to that of the unsubstituted derivative as unity) against the dipole moments of the similarly substituted benzenes, a sequence which represents the $-I$ effects of the substituent groups. All reactions of type A (electron accession) give curves similar to that shown in Fig. 1, whilst those of type B (electron recession) are typified by the curve shown in Fig. 2. The greater magnitude of the facilitating influence of the methyl group in Type A reactions than of its retarding influence in Type B reactions is shown by the steeper slope of the portion of the curve to the left of the hydrogen ordinate in Fig. 1 than in Fig. 2. Conversely, the greater slope of the portion of the curve to the right of the hydrogen ordinate in Fig. 2 than in Fig. 1 illustrates the similar point with regard to the nitro-group.

Such behaviour can readily be understood on the basis of a theory of dual mechanistic control such as has been developed in this communication. Where the electronic character of the parent (unsubstituted) molecule is such that most of the molecules react by one particular mechanism, a substituent group which greatly facilitates this mechanism will have only a relatively unimportant retarding effect on those molecules which might react by a mechanism of the opposite type, since these are very few in number. When, however, the substituent is of the type which retards the more important type of mechanism, it will also facilitate the less important one of the opposite polar type, and so increase the possibility of molecules reacting by the latter mechanism. Hence its retarding influence on the more important type of mechanism may be partly counteracted by the increased chance for molecules to react by the second mechanism, and thus its *resultant* retarding effect may be greatly reduced.

FIG. 1.

Type A reactions.

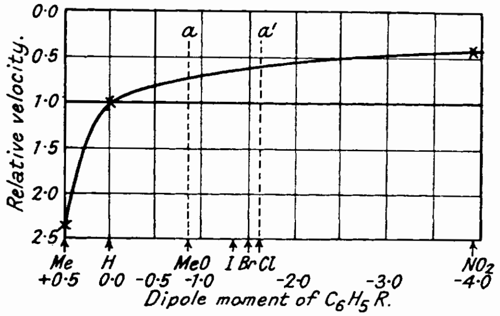
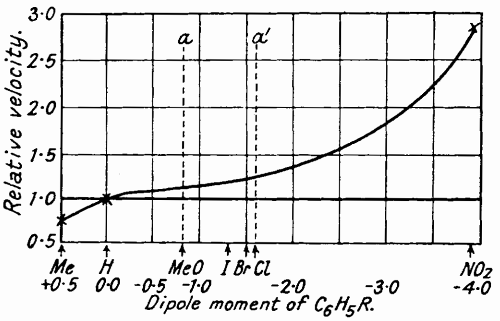


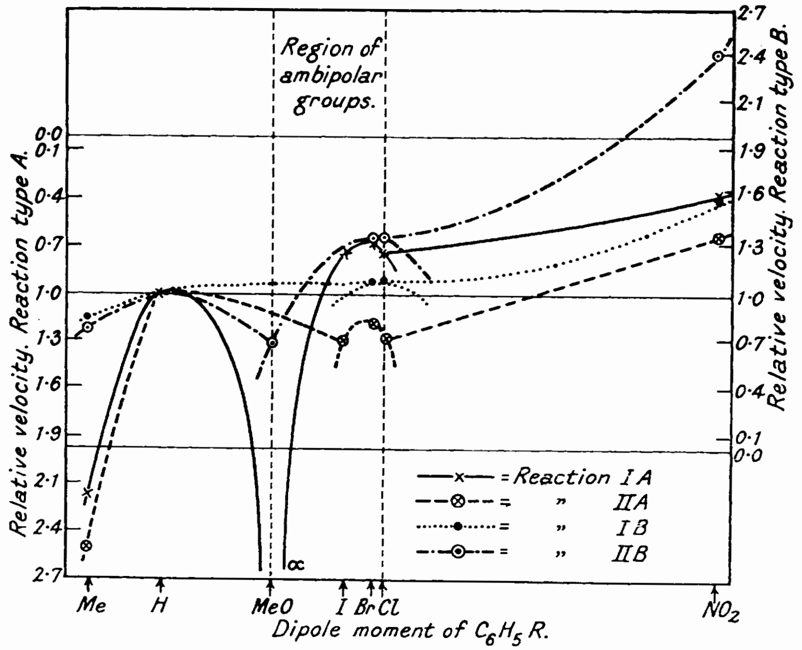
FIG. 2.

Type B reactions.



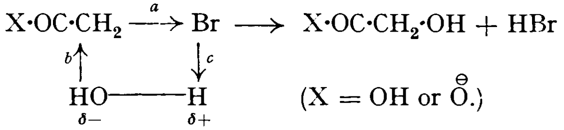
In Figs. 1 and 2 the portion of the curve in the region between *aa'* occupied by ambipolar groups may take any of the forms already discussed by Shoppee, and the interpenetration of these curves into the simple curve which represents the effect of substituent groups of a strictly unipolar character will cause irregularities in the complete curve showing the effects of substituents of *all* polar types. According to the relative positions of the ambipolar groups on the interpenetrating curve (cf. Shoppee, *loc. cit.*), various forms of composite curves can be derived, and examples of all these theoretical types are found in the velocity data recorded in the literature. Such complete composite curves

FIG. 3.



for the reactions between benzyl and phenacyl bromides with pyridine or aniline are shown in Fig. 3.

(*d*) The results of Dawson and Dyson (this vol., pp. **49**, **1133**) have clearly shown that in an apparently simple reaction, which might, but for their investigations, have been represented by



$$\begin{array}{lcl}
\mathrm{X{\cdot}OC{\cdot}CH_2} \xrightarrow{a} \mathrm{Br} & \longrightarrow & \mathrm{X{\cdot}OC{\cdot}CH_2{\cdot}OH + HBr} \\
{}^{b}\!\uparrow \qquad\qquad \downarrow^{c} & & \\
\underset{\delta-}{\mathrm{HO}} \text{———} \underset{\delta+}{\mathrm{H}} & & (\mathrm{X = OH\ or\ \overset{\ominus}{O}.})
\end{array}$$

there are actually four different reactions occurring simultaneously, all giving, ultimately, the same product, and of these the reactions between either the bromoacetic acid or its anion and water are of relatively small importance.

(e) *Effect of the concentration of the base on the velocity of reaction.* Although the reactions between benzyl (1A) and phenacyl (1B) bromide with pyridine are diagnosed as of opposite polar types, the former requiring electron recession from, and the latter electron accession to, the side chain, preliminary experiments summarised in Table II have shown that *both* reactions are dependent to an approximately equal extent on the concentration of the pyridine. Hence both reactions must contain rate-determining factors which are dependent on the concentration of the base.

TABLE II.

Reaction.	Base concentration (mols./mol. of bromide).	10^3k, min.$^{-1}$.
$PhCH_2Br + NC_5H_5$	10	4·4
,, ...	20	8·2
$PhCO{\cdot}CH_2Br + NC_5H_5$	10	6·5
,, ...	20	11

Conclusion.

The evidence summarised above suggests that in most, if not all, of the reactions which have previously been subjected to kinetic study, the presence of at least two rate-determining stages of opposite polar character must be assumed, and that such an assumption provides at least a possible explanation of the various anomalies in the effect of substituents which have been observed (cf. *inter alia*, Baddeley and Bennett, this vol., p. **261**). It therefore appears to be somewhat dangerous to deduce theories regarding the polar character and external fields of substituent groups from such data. The first essential would seem to be a more detailed analysis of the mechanism of some simple reaction on the lines applied so successfully by Dawson to the bromoacetate reaction.

It may thus be possible to circumscribe exactly the mechanism of the simpler of such reactions and then, from a study of the effects of substituents, gain a truer insight into the real nature of their polar character, and investigations on these lines are in hand.

Effects of the side-chain halogen on the velocity. So far, only the effect of different nuclear substituents has been considered. Table III summarises the effect of varying only the nature of the side-chain halogen in the compounds with an unsubstituted phenyl nucleus.

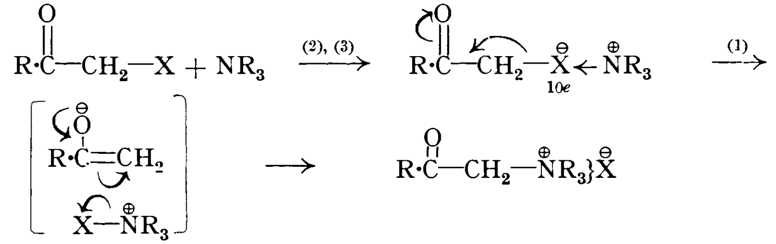
TABLE III.

Reaction type.	10^3k. I.	Br.	Cl.	Relative order of velocities.
1A Electron accession	5·1	4·4	0·09	I > Br>>Cl(> F) *
2A ,, ,, ...	61	35	0·7	I > Br>>Cl
1B Electron recession	5·0	6·5	0·11	Br > I>>Cl
2B ,, ,, ...	14·8	14·5	0·15	(I = Br)>>Cl

* Ingold and Ingold, *loc. cit.*

The anomaly that, in reactions 1A and 2A requiring electron accession to the side chain, the side-chain halogen reactivity decreases in the order I>Br>>Cl, *i.e.*, the order of increasing and not of decreasing — *I* effects, has long been appreciated. Two suggestions have hitherto been made to explain this anomaly. The first, advanced by Ingold and Ingold (J., 1928, 2249), may be briefly summarised by saying that the reactivity of the side-chain halogens depends on the extent to which they are capable of temporary electrical polarisation, *i.e.*, on the relative ease of displaceability of the halogen electrons. The second, due to Bennett (J., 1929, 263), postulates the initial formation of an unstable compound between the base and the halide in which the halogen octet becomes expanded to a decet, $R{\cdot}CH_2{\cdot}\overset{\ominus}{X} \longleftarrow \overset{\oplus}{N}C_5H_5$, the compound subsequently being rearranged to give the ultimate product.

By combining both these suggestions, possible mechanisms for the reactions between benzyl or phenacyl halides with pyridine can be formulated. On the basis of evidence at present available, the necessary conditions which must be satisfied in any mechanism for the reaction with the phenacyl halide are (1) that it requires electron recession from the side chain, (2) that it is dependent on the concentration of the base, and (3) that with different halides it shall become increasingly facile in the order $Cl < Br < I$. The following scheme would satisfy all these requirements :



but such a scheme need not preclude a simultaneous attack of the base directly at the positively polarised methylene group as formulated on p. 1128.

In the reaction with benzyl halides, the necessary conditions relating to the mechanism are (1) that it requires electron accession to the side chain; (2), and with possible minor qualifications (3), as above. The first of these conditions would seem to eliminate the formation of a complex containing a halogen with a 10*e* group as a possible initial step, and in this reaction the initial stage might well be the polarisation of the benzyl halide $R{\cdot}\overset{\delta+}{C}H_2 \rightarrow \overset{\delta-}{X}$. A suitable collision between a pyridine molecule and the positively polarised methylene group could then enable the side-chain halogen to escape with its bonding electrons as a negative halide ion, the depleted octet around the methylene carbon being simultaneously restored by sharing the unshared electron pair on the nitrogen atom. Thus the electrostriction of the base would be a definite rate-determining factor, even although the effect of substituent groups on the velocity suggests that the degree of polarisation of the benzyl halide is the more important consideration.