257. *Reaction Kinetics and the Walden Inversion. Part VI. Relation of Steric Orientation to Mechanism in Substitutions involving Halogen Atoms and Simple or Substituted Hydroxyl Groups.*

By W. A. Cowdrey, E. D. Hughes, C. K. Ingold, S. Masterman, and A. D. Scott.

The known relationships between the mechanism of aliphatic substitution and the structures of the compounds substituted form a starting point for the investigation of the laws governing the steric orientation of substitution. As a result of work reported in the preceding papers, certain general principles relating to the orientation of substitution are advanced. Detailed discussion is confined to the reciprocal replacements of ·Hal and ·OR, and within this field previously recorded stereochemical observations are to a large extent rationalised. A fuller statement of the conclusions is given on p. 1270.

Notwithstanding the large number of investigations that have been carried out since Walden's discovery of the inversion known by his name, much uncertainty still attaches to the rules and conditions that control the steric course of substitution at a saturated carbon atom. This is due partly to the difficulty of relating sign of rotation to molecular configuration. But a still more important cause is that the conditions controlling steric orientation are intimately dependent on the mechanism of substitution, and it is only within comparatively recent years that mechanism in aliphatic substitution has been fruitfully studied. In this field, mechanism has been elucidated principally through the examination of reaction kinetics, by means of which an intelligible relationship has been traced between mechanism, on the one hand, and the chemical structures of reactants, and the physical conditions of reaction, on the other. It was an obvious sequel to apply kinetics in order to elucidate the factors controlling the steric course of substitution; and the procedure has two advantages. First, we can often decide the steric orientation of a reaction by comparison on the basis of mechanism (which kinetic results help to establish) with some other reaction whose steric course is known. Secondly, it should be possible to establish an *empirical* connexion between steric orientation and kinetics; and thus, using our present knowledge of the relation of kinetics to mechanism, to link steric orientation with mechanism and its determining factors, chemical structure and physical conditions. We have therefore studied the optical effect of substitution at an asymmetric carbon atom under conditions, not chosen haphazard, but defined by parallel studies of kinetics. It is our view that much of the previous work on the Walden inversion requires repetition with this form of control (cf. Cowdrey, Hughes, and Ingold, *Nature*, 1936, **138**, 759).

In the present paper we set forth conclusions based largely on the experimental studies recorded in the previous five papers. We deal here only with the reciprocal replacements of ·Hal and ·OR, and this only in a preliminary way : extensions of the study in this field, and likewise our investigations on the substitutions which involve $\cdot NR_2$, will be described in future groups of papers.

On the theoretical side our starting point is the general survey given by Hughes and Ingold (J., 1935, 244) of aliphatic substitution from the point of view of kinetics and mechanism. In section (A) we shall summarise such of the conclusions and applications of this theory as will be needed. It happens that one of the applications, one which we shall particularly require, was not mentioned in Hughes and Ingold's paper : this relates to the effect of modifications of the carboxyl group, including especially the carboxylate ion, on the mechanism of substitution at an adjoining carbon atom. Accordingly, we include a fuller reference to this point than would otherwise have been necessary in the following preface to our stereochemical discussion.

(*A*) *Preliminary Remarks on Kinetics and Mechanism.*

(1) *General Principles.*—Reactions in which ·Hal is replaced by ·OR are " nucleophilic substitutions " : replacement is characterised by electron transfers from the reagent to the seat of substitution and from the latter to the extruded group. They are also classified as belonging to the " three-atom problem " : only one bond is broken and only one is formed —in short, one bond only is exchanged. For such substitutions two mechanisms are established. If the bond is exchanged in one act, the substitution is called bimolecular (S_N2) ; and in most cases it will be kinetically of the second order. Alternatively, if the bond is broken and reconstituted in separate acts, the substitution is said to be unimolecular (S_N1) ; and, if as usual bond-fission controls the rate, it will be kinetically of the first order. The two mechanisms are formulated for the example of hydrolysis :

$$\overset{-}{\mathrm{O}}\mathrm{H} + \mathrm{Alk{\cdot}Hal} \longrightarrow \mathrm{OH{\cdot}Alk} + \overset{-}{\mathrm{Hal}} \quad . \; . \; . \; . \; . \; . \; . \quad (S_N2)$$

$$\left.\begin{aligned} \mathrm{Alk{\cdot}Hal} &\longrightarrow \overset{+}{\mathrm{Alk}} + \overset{-}{\mathrm{Hal}} \\ \overset{+}{\mathrm{Alk}} + \mathrm{H_2O} &\longrightarrow \mathrm{Alk{\cdot}OH} + \overset{+}{\mathrm{H}} \end{aligned}\right\} \quad . \; . \; . \; . \; . \; . \; . \; . \quad (S_N1)$$

Which of these mechanisms will operate in a given example depends *inter alia* on structure, *i.e.*, on the groups attached to the seat of substitution. Groups which withdraw electrons thereby facilitate the approach of the nucleophilic reägent, the presence of which is necessary for reaction by mechanism S_N2. Groups which supply electrons favour the dissociation, which is the rate-determining stage of mechanism S_N1. Our stereochemical argument will require the consideration of four kinds of groups, *viz.*, alkyl, aryl, carboxyl and carboxylate-ion groups, the effect of which on the mechanism of substitution will now be summarised.

(2) *Alkyl Groups.*—The replacements of ·Hal by ·OR in methyl halides is exclusively bimolecular (S_N2). Alkyl groups release electrons more strongly than hydrogen ; and hence the progressive replacement of the three hydrogen atoms in a methyl halide by alkyl groups will tend to replace mechanism S_N2 by mechanism S_N1. It is established that this happens (Hughes, J. 1935, 255; Hughes, Ingold, and Shapiro, J., 1936, 225; Hughes and Shapiro, this vol., pp. 1177, 1192 ; Cooper and Hughes, *ibid.*, p. 1183 ; Bateman and Hughes, *ibid.*, p. 1187) : in the replacement of ·Hal by ·OR in Alk·Hal, where Alk = Me, Et, Pr^{β}, Bu^{γ}, in aqueous or alcoholic solvents, reaction proceeds by mechanism S_N2, with successively diminishing speeds, in the first three members of the series ; and by mechanism S_N1, with increasing speeds, in the last two members ; in the third the two mechanisms are of comparable facility and operate side by side. The majority of known optically active halides are secondary ; but the proved similarity of *iso*propyl and β-*n*-octyl halides with regard to mechanism of substitution shows that the behaviour of the *iso*propyl group may be assumed to be typical of that of all purely aliphatic *sec.*-alkyl groups.

(3) *Aryl Groups.*—These behave similarly, except that, because they are highly polarisable, the large electron demand created by the otherwise uncompensated electron transference in the rate-controlling (first) step of mechanism S_N1 calls forth a peculiarly strong electromeric electron-release. Aryl substitutents at the seat of substitution therefore facilitate mechanism S_N1 much more strongly than do alkyl groups. In the series Alk = CH_3, CH_2Ph, $CHPh_2$, CPh_3, the two mechanisms are of nearly comparable importance at the second member (Olivier and Weber, *Rec. trav. chim.*, 1934, **53**, 869, 891) ; whilst at the third, mechanism S_N1 has taken full control (Ward, J., 1927, 2285). The " mixed " aralphyl group Alk = CHMePh has the expected intermediate character between $CHMe_2$ and $CHPh_2$: in aqueous solvents mechanism S_N1 assumes control (Ward, J., 1927, 445), but in less ionising, dry alcoholic solvents the two mechanisms can be observed simultaneously (Hughes, Ingold, and Scott, this vol., p. 1201).

(4) *Carboxyl Groups.*—Groups of the form ·CO_2R—which include not only carboxylic

ester and carboxylamide groups, but also the undissociated carboxyl groups of free carboxylic acids and the metal-carboxylate groups of undissociated metallic salts—were not discussed by Hughes and Ingold. Being electron attractors, their introduction in such series as Alk = CH_3, $CH_2\cdot CO_2R$, $CH(CO_2R)_2$, $C(CO_2R)_3$ and Alk = CH_2Me, $CHMe\cdot CO_2R$, $CMe(CO_2R)_2$ will serve more firmly to establish mechanism S_N2, to the exclusion of S_N1; and this will remain true unless and until the cumulative effect of several electron-attracting groups sufficed to reverse the direction of the electron transferences, and thus to remove the reaction from the category of nucleophilic substitutions.* As evidence we may refer to Cowdrey, Hughes, and Ingold's deduction from their kinetic and optical studies (this vol., p. 1208) that halides for which Alk = $CHMe\cdot CO_2R$, although " secondary," undergo hydrolysis and alcoholysis by mechanism S_N2, under conditions in which mechanism S_N1 alone would have operated for simple secondary alkyl halides.

(5) *Carboxylate-ion Group.*—The ionic group $\cdot\overset{-}{CO_2}$ is of particular interest since, like alkyl groups, it repels electrons : in a series such as Alk = CH_3, $CH_2(\overset{-}{CO_2})$, $CH(\overset{-}{CO_2})_2$, $C(\overset{-}{CO_2})_3$ we may expect a transition from mechanism S_N2 to mechanism S_N1, just as in series involving the progressive accumulation of alkyl groups. In series such as Alk = CH_3, $CH_2\cdot\overset{-}{CO_2}$, $CHMe\cdot\overset{-}{CO_2}$, $CMe_2\cdot\overset{-}{CO_2}$, in which alkyl and carboxylate-ion groups collectively accumulate at the seat of substitution, and in the analogous "mixed" series Alk = CH_3, $CH_2\cdot\overset{-}{CO_2}$, $CHPh\cdot\overset{-}{CO_2}$, $CPh_2\cdot\overset{-}{CO_2}$, we may likewise anticipate mechanistic change from S_N2 to S_N1. As effects arising from the carboxylate-ion group were not treated previously, the available evidence concerning these theoretical expectations will briefly be reviewed.

Reference has already been made to the first member, methyl halide, of each of the above series. The hydrolysis of bromoacetic acid, the anion of which is the second member, has been investigated by Dawson and Dyson (J., 1933, 49, 1133) and Brooke and Dawson (J., 1936, 497). In summarising their results the last-named authors gave a list of ten reactions which might conceivably participate in the elimination of bromide during the aqueous hydrolysis of bromoacetic acid. Of these ten reactions, four were shown to have zero velocity—a fact which is readily understood, because in these four cases the assumed substituting agents are electrophilic and not nucleophilic. The other six reactions had speeds which, calculated as second-order rate constants for 25° (units : 10^{-6}. min.$^{-1}$ g.-mol.$^{-1}$ l.) may be summarised as follows :

	Reagent.	$CH_2(OH)\cdot CO_2^-$.	$CH_2Br\cdot CO_2^-$.	H_2O.
Compound substituted	$CH_2Br\cdot CO_2H$	136	72	0·041
	$CH_2Br\cdot CO_2^-$	35	19·3	0·059

For convenience we separate the interacting entities into " compounds substituted " and " reagents." The reactions whose speeds are calculated as of bimolecular reactions with water are kinetically of the first order, and might *a priori* be either bimolecular or unimolecular (S_N2 or S_N1); the other reactions are, of course, demonstrably bimolecular (S_N2). Let us for the moment assume that *all* the reactions are bimolecular. Then since the reagents are nucleophilic, the velocities of substitution for *the same compound substituted* should decrease with decreasing basicity of the reagent; and this appears from the figures. Furthermore, the gaps between the speeds for the first two reagents should be small, since the difference of basicity is small, whilst those between the speeds for the second and third reagent should be large, corresponding to the large difference of basicity; this is also shown by the figures. [Acidity increases in the series $CH_2(OH)\cdot CO_2H < CH_2Br\cdot CO_2H \ll H_3O^+$, and basicity decreases analogously in the conjugate bases.] Again, for *the same reagent*, the bromoacetate anion should substitute more slowly than the undissociated bromoacetic acid molecule, because the greater electron density at the seat of substitution in the former should impede the attack of the nucleophilic reagent. The observed differences are in the right direction for the first two reagents, but not for water; for this reagent the reactivity of the bromoacetate ion is relatively too great : and we take this to mean that part of the

---

* The reaction is then no longer a hydroxylation, or anything analogous, but a reduction.

calculated second-order rate constant for the action of water on the bromoacetate ion does not belong to the bimolecular process (S_N2), but arises from the incursion of the unimolecular reaction (S_N1). As the truly bimolecular rate constant, estimated from the other figures in the table, is only 0·011, whereas the experimental constant is 0·059, we may say that the main mode of hydrolysis of the bromoacetate ion by water is probably the unimolecular process, the speed of which is determined by halogen ionisation (S_N1). It appears therefore that in the example Alk = $CH_2{\cdot}CO_2^-$ a mechanistic transition from S_N2 to S_N1 is in progress, although a very careful investigation such as Dawson's is necessary in order to detect it.

If this be so the unimolecular mechanism should be well developed in the next member, Alk = $CHMe{\cdot}CO_2^-$, of the "mixed" alkyl-carboxylate series; and it certainly is. Senter and Wood showed (J., 1909, **95**, 1827; 1915, **107**, 1070; 1916, **109**, 681) and Cowdrey, Hughes, and Ingold confirmed (*loc. cit.*) that, in the hydrolysis and alcoholysis of the α-bromopropionate ion, unimolecular substitution proceeds at rates comparable to those with which the bimolecular reactions take place in the presence of considerable concentrations of hydroxide or alkoxide ions. The α-bromo-*n*-butyrate ion exhibits qualitatively similar phenomena, and the relative importance of the unimolecular process in hydrolysis is even greater in this case. Senter gives the following values for the rate constants (time units = min.) for aqueous hydrolysis at 52·4° of the anions of the first three α-bromo-aliphatic acids :

	$Br{\cdot}CH_2{\cdot}CO_2^-$.	$Br{\cdot}CHMe{\cdot}CO_2^-$.	$Br{\cdot}CHEt{\cdot}CO_2^-$.
First order (10^4k_1)	1	14	26
Second order (10^4k_2)	65	9	8

The α-bromo-β-phenylpropionate ion, $Br{\cdot}CH(CH_2Ph){\cdot}CO_2^-$, also behaves similarly to the α-bromopropionate and α-bromo-*n*-butyrate ions, but the formation of cinnamic acid by a side reaction complicates quantitative study (Senter and Martin, J., 1917, **111**, 44).

The unimolecular mechanism should be still more prominent in the "mixed" aryl-carboxylate example, Alk = $CHPh{\cdot}CO_2^-$, on account of the electromeric effect of the phenyl substituent. The facts are that the unimolecular mechanism exclusively controls the aqueous hydrolysis of α-chloro- and α-bromo-phenylacetate ions (Senter and Tucker, J., 1915, **107**, 908; 1916, **109**, 690).*

(*B*) *Steric Orientation in the Replacement of* ·Hal *by* ·OR.

(1) *General Principles*.—Most of the earlier theories of the steric course of substitution, notably those of E. Fischer (*Annalen*, 1911, **381**, 126), Werner (*Ber.*, 1911, **44**, 873; *Annalen*, 1912, **386**, 70), and Pfeiffer (*ibid.*, 1911, **383**, 123), postulate the prior formation of an addition product, in which the entering group attaches itself to the asymmetric carbon atom either on the side of the group to be replaced or on the opposite side; the theories of Gadamer (*J. pr. Chem.*, 1913, **87**, 372) and Meisenheimer (*Annalen*, 1927, **456**, 126) are elaborated forms of the same general view. The idea that addition is not previous to but synchronises with dissociation seems to have been introduced into the theory by Le Bel (*J. Chim. physique*, 1911, **9**, 323), but it was first stated in an acceptable form by G. N. Lewis ("Valence and the Structure of Atoms and Molecules," 1923, p. 113). The remaining alternative, prior dissociation, was assumed by Lowry (*Conseil de Chimie Solvay*, 1925, 130), who suggested that substitution through an intermediate "carbonium" ion might proceed with predominating retention of form; and by Kenyon and Phillips (*Trans. Faraday Soc.*, 1930, **26**, 451; with Lipscomb, J., 1930, 415), who supposed, on the contrary, that it would tend to produce inversion.

More recent hypotheses concerning the laws which govern the steric orientation of substitution have been advanced by Olson (*J. Chem. Physics*, 1933, **1**, 418), Meer and

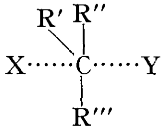
---

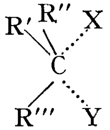
* (*Note added in proof.*) A study of the hydrolysis of bromomalonic acid, methylbromomalonic acid, and the corresponding anions has just been completed by N. A. Taher. The reaction of the bromomalonate ion is unimolecular in dilute solutions of alkali, while that of its methyl derivative remains unimolecular even in moderately concentrated solutions. The velocity relationships, moreover, are in harmony with the predictions made above. The results will be published in conjunction with other similar investigations now in progress.

Polanyi (*Z. physikal. Chem.*, 1932, *B*, **19**, 164), and two of the present authors. Olson and Meer and Polanyi use only the theory of synchronous addition and dissociation. Olson assumes that every substitution in which only one bond is exchanged involves inversion. Meer and Polanyi distinguished between substitutions effected by an anionic reagent (" negative mechanism ") and those in which the attack is by a cation (" positive mechanism ") ; and they suggested that the former involve inversion whilst the latter do not : some reserve has, however, been expressed with respect to certain examples held to belong to the positive mechanism (Polanyi, " Atomic Reactions," p. 63). Hughes and Ingold (*loc. cit.*) employ the theories of synchronous addition and dissociation and of prior dissociation in conjunction; and they do not make the net charges of the interacting species a primary basis for the classification of substitutions. Treating substitutions as either bimolecular or unimolecular and either nucleophilic or electrophilic (S_N2, S_E2, S_N1, S_E1), they suggested that bimolecular substitutions (S_N2 and S_E2) are invariably accompanied by steric inversion, whilst unimolecular substitutions (S_N1 and S_E1) may involve inversion, racemisation or retention of form, depending on circumstances which have to be considered in detail. Since negative mechanism substitutions are always nucleophilic and bimolecular, there is agreement as to these with Meer and Polanyi's theory; and, of course, with Olson's.

Inversion of configuration is presumed to be the rule for bimolecular substitutions (S_N2 and S_E2) primarily because the transition state (I), which leads to inversion, will have a smaller energy than that (II) which corresponds to retention of stereochemical form :

(I.)



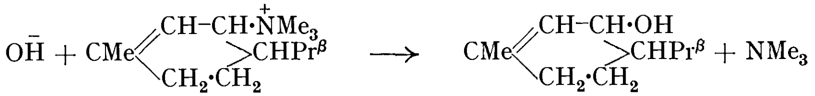


(II.)

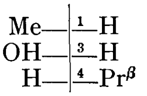
We assess the relative energies of these transition states by application of the exclusion principle; *i.e.*, we consider the conditions which would minimise the repulsive, exchange energy integrals. In either transition state the " split " bond X···C···Y can be described as a state of resonance between the structures X C—Y and X—C Y. In state (I) the charge-cloud of this split bond has a nodal surface which is either a plane (if X = Y) or a very obtuse-angled cone; and the repulsive integrals are minimised if the maxima of electron density due to the bonds CR_3 lie in this surface. In state (II) the nodal surface is not a figure of revolution, and it is unlikely that the CR_3-bonds will be able to conform to it; indeed the electron density due to the system $.\mathrm{C}{<}^{X}_{Y}$ would in general be considerable over the space occupied by the rather sharp-angled pyramid which the CR_3-group must constitute. State (I) will thus correspond to a smaller energy of activation than state (II).

Meer and Polanyi have pointed out that the dipole field in a link such as C—Cl would preferentially direct an anionic reagent such as OH^- to the position leading to inversion; the corresponding statement concerning the transition state is that the repulsion of quasi-ionic charges (δ —)OH···C···Cl(δ —) must be smaller for configuration (I) than for (II). This electrostatic factor must, of course, make a definite contribution to the difference between the theoretical rates of the alternative processes; but we think that the effect arising from the exclusion principle is likely to be more important, and, indeed, in all ordinary cases, determinative. An experimental basis for decision between the two factors can be found, because, although they favour the same stereochemical result in the hydrolysis of alkyl halides, this agreement is fortuitous and does not extend to substitutions generally : in the hydrolysis of 'onium cations, for example, the two factors oppose each other. In the attack of $\overset{-}{\mathrm{O}}\mathrm{H}$ on $\mathrm{C—}\overset{+}{\mathrm{N}}\mathrm{R_3}$ the electrostatic forces direct the anion to the side of the displaced group; and in the transition state the quasi-ionic charges attract each other, so that the closer they are together the smaller is their mutual electrostatic energy; thus the electrostatic factor favours transition state (II), $\mathrm{C}{<}^{\mathrm{OH}(\delta\,-)}_{\mathrm{NR_3}(\delta\,+)}$, and, therefore, substitution with a retained configuration. On the other hand, the exclusion principle still favours transition state (I), and substitution with an inverted configuration. Hence considerable interest attached to an experimental determination of the steric course of such a reaction.

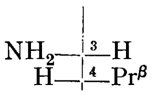
A determination of this kind has been recorded by Read and Walker (J., 1934, 308; cf. Read, " A Chapter in the Chemistry of Essential Oils," Institute of Chemistry, 1936, p. 21). These authors converted *l*-piperityltrimethylammonium hydroxide into piperitols, and showed that the principal isomeride formed was *d-neo*piperitol :



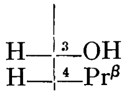
The original piperitylamine belonged to the stable (ordinary) series, and the piperitol to the labile (*neo*-) series; and hence an inversion must have accompanied the substitution. Read's configurations for these compounds, and for two related menthols as reference structures, are as follows :



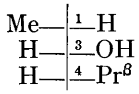
l-Menthol.



l-Piperitylamine.

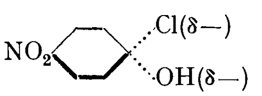


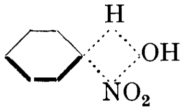
*d-neo*Piperitol.



*d-neo*Menthol.

Digressing, we may remark that the same theory requires that in aromatic substitution the reagent attacks from a direction lateral to the plane of the ring : as the attack proceeds, the original substituent becomes deformed until, in the transition state, the atoms lie in two mutually perpendicular planes, as is illustrated with reference to a three-atom nucleophilic, and a four-atom electrophilic substitution :



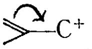


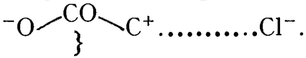
We have now to consider the unimolecular substitutions (S_N1 and S_E1), in which a carbon cation or anion is formed intermediately. The simplest conditions arise in the absence of any group which, on account of either unsaturation or charge, tends strongly to influence the configuration of the carbon ion. Then for nucleophilic substitutions, if the ion is long-lived, either by reason of an intrinsically small reactivity, or on account of the lack of reactivity of the medium, or of the great dilution of the reagent, the substitution product will be racemised (Hughes and Ingold, *loc. cit.*) ; this follows because the carbon cation is flat. Frequently, however, the length of life of a carbon cation in a reactive medium is comparable to the period of molecular oscillation or libration of the solute within the enclosing solvent ; and in this case the recession of the ion ejected from its former partner will produce a dissymmetric shielding of the latter during the period in which the course of substitution is being determined * ; the result will be that substitutions with inversion will outnumber those which retain the original configuration. As an example we may consider the unimolecular hydrolysis (S_N1) of an alkyl halide in a series of solvents ranging from a nearly dry inert solvent to pure water : in the former, racemisation would be most nearly complete, because the great dilution in which water is present affords the ion a comparatively long life; whilst in pure water, inversion would reach its greatest degree of predominance, because under these conditions the ion is short-lived. The theory is the same for electrophilic substitutions if the carbon anion, although its equilibrium configuration is pyramidal, has a plane of symmetry conferred on it by a nuclear resonance effective for the life-time of the ion.† This case, however, is not of much practical importance, since it is hardly possible to produce carbon anions which do not possess stabilising unsaturated substituents.

---

* In unimolecular substitution the ionisation must nevertheless pass over its energy barrier before the reagent intervenes.

† As nuclear resonance has been demonstrated for ammonia, it could probably occur in the carbon anion with its smaller central nuclear charge, at least if one of the attached groups is a hydrogen atom.

The presence of an unsaturated group, such as phenyl, at the seat of substitution introduces mesomerism, a factor which tends to stabilise and at the same time to flatten the ion (cation or anion) :  or . The result will be enhanced racemisation, the situation otherwise being exactly as described in the preceding paragraph.

The presence of a charged group of appropriate sign (negative for the organic cation and positive for the anion) tends to stabilise the ion and to preserve a pyramidal configuration; for the " ion " is now a betaine, which has least potential energy in this form. The example which we shall use in illustration later is that of the carboxylic-ion group in a nucleophilic substitution. During the process of ionisation the charged substituent will be oriented away from the eliminated ion; and it will tend to hold the pyramidal configuration thus produced until a new group enters the position from which the old one left :  $^-O{-}CO{-}C^+ \dots\dots\dots\dots Cl^-$. It may be assumed, as was pointed out to us by Dr. G. W. Wheland, that, contributing to the normal state of the betaine, there should be a canonical structure in which the charges are neutralised at the cost of producing septets, which maintain a tetrahedral character in the orbitals.* The result will be a retention of form, which might be partial or complete. It will be complete if the betaine has sufficient time in which to take up its preferred configuration, but only partial if an external reagent intervenes before this happens.

We can attempt no classification of heterogeneous substitution in general, but in the displacement of halogens from organic halides by means of hydroxyl and similar groups the use of silver oxide and silver salts is of special importance, and therefore merits discussion. In Parts IV and V we showed that the reaction of organic halides with silver oxide was essentially analogous to that with soluble silver salts; and that all such reactions involve a heterogeneous attack by silver ions on the organic halide adsorbed on the surface of an insoluble silver salt (silver halide and/or oxide). We may assume that the adsorption of the halide stretches the carbon–halogen bond (which normally is shorter than the distance between the centres of attraction in the surface of the crystal), and that an adsorbed silver ion takes advantage of this disturbance in order to extract the halogen as an anion. Thus conceived, the substitution process depends on an assisted, heterogeneous ionisation; and the final step must involve the heterogeneous reaction of the carbon cation with an adsorbed, nucleophilic solvent or solute molecule. The general resemblance of the heterogeneous process to homogeneous, unimolecular hydrolysis (S_N1) is obvious, and we may accordingly expect to find certain phenomenological similarities, two of which may be mentioned.

The first relates to the influence of structure on reaction rate. It is evident that if both the S_N1-reaction and the silver-ion reaction depend on a preliminary ionic fission of the halide, the latter reaction, like the former, should be facilitated by access of electrons to the seat of substitution. For instance, the electron-repelling substituent $\cdot CO_2^-$ should accelerate reaction, whilst the electron-attracting groups $\cdot CO_2H$ and $\cdot CO_2Me$ should retard it. The expected effect for both these reactions is the opposite of that normal for the S_N2-reaction, which is facilitated by the withdrawal of electrons from the seat of substitution. The evidence on these matters is contained in Parts III and V. First, with regard to the silver reaction, we show that the hydroxylation of α-bromopropionic acid with aqueous silver nitrate proceeds mainly through the anion of the bromo-acid even in the presence of a 1*N*-concentration of hydrogen ions : this means that the specific rate of substitution of the bromo-anion must be more than 1000 times greater than the rate for the undissociated acid. Secondly, for the homogeneous unimolecular reaction S_N1, we find that the α-bromopropionate ion is methoxylated at 64° in methyl alcohol by this reaction about 20 times faster than methyl α-bromopropionate is methoxylated at 100° by an S_N2-reaction which itself is fast enough completely to mask the S_N1-reaction ; at equal temperatures, therefore, the S_N1-reaction of the anion must be considerably more than 1000 times faster than that of the ester. Thirdly, for contrast, we may take the S_N2-methoxylations of the same substances : it can easily be computed from the recorded data that, at like temperatures, the reaction of the anion must be of the order of 100 times slower than that of the ester.

---

* For reasons mentioned later (p. 1264) we are not prepared to assume the formation of an α-lactone.

Thus, with respect to the effect of structure on rate, the silver-ion reaction resembles the S_N1- rather than the S_N2-process—as it should according to our theory of the mechanism.

The other type of correspondence to be expected between the silver-ion reaction and the homogeneous unimolecular process is concerned with the spatial orientation of substitution. The physical conditions in a surface being different from those obtaining in homogeneous reactions, we can make no quantitative comparisons, in regard, for instance, to the amount of racemisation to be anticipated; but a qualitative similarity should hold. For example, the silver-ion reaction with alkyl halides should exhibit inversion of form with accompanying racemisation; that with aralphyl halides inversion with more extensive racemisation; and that with α-halogeno-carboxylate ions retention of form with racemisation. The evidence is considered in the next sub-section.

Intermolecular rearrangements are difficult to classify, since they have analogies with bimolecular and unimolecular substitutions. It is obvious, however, that we may expect retention of configuration when the point in the rearranging chain at which it is able to recombine is not sufficiently far removed from the point at which it breaks loose to permit the formation of a transition state of type I (with X and Y connected by a chain): a transition state of form II (but cyclic) is then the only possibility.

(2) *Alphyl and Aralphyl Halides* (*Orientation Rules*).—There seems to be no previous record of any investigation of steric orientation in the homogeneous hydrolysis of an alkyl halide under any conditions, and certainly none for hydrolysis under conditions specified with respect to kinetics. We may, however, take β-*n*-octyl bromide as a typical halide containing, besides the halogen, only neutral, saturated substituents at the seat of substitution. In Part I we showed that bimolecular hydrolysis and alcoholysis (S_N2) proceeds with inversion of configuration and a practically quantitative preservation of the optical rotatory power; whilst unimolecular hydrolysis and alcoholysis (S_N1) takes place with a predominating inversion but extensive racemisation. These results accord well with the theory set forth in the preceding sub-section: we may reasonably draw two conclusions. The first is that in all homogeneous substitutions of ·Hal by ·OR in alkyl halides, no matter whether the mechanism is S_N2 or S_N1, the predominating orientation will be inversion: this principle seems so definite that we should be able to use it for the purpose of diagnosing the relationship of molecular configuration to sign of rotation. The second conclusion is that the absence of racemisation in mechanism S_N2, and the extensive racemisation characteristic of mechanism S_N1, afford a basis for an auxiliary diagnosis of mechanism from optical results alone.

Concerning the effect of the presence of a neutral, unsaturated substituent at the seat of substitution, we have again to rely on our own data; but α-phenylethyl chloride may be taken as typical for this case. In Part II we showed that, although the bimolecular hydrolysis of this halide could not be realised, bimolecular alcoholysis (S_N2) proceeded with inversion and a high retention of rotatory power; and that unimolecular hydrolysis and alcoholysis (S_N1) took place with predominating inversion, but with extensive racemisation, which further increased when the water in the medium was diluted with an inert solvent (acetone). These results are qualitatively similar to those obtained for the purely aliphatic halide, and hence we may conclude that aralphyl halides will conform to the generalisations mentioned in the previous paragraph: substitution by either mechanism will give inversion and the two mechanisms will be distinguishable through the racemisation which characterises one of them. The effect of the unsaturated (aryl) substituent is confined to increasing the relative importance of the unimolecular mechanism, and to increasing the amount of racemisation which accompanies its operation: both these effects are expected from our theory (sub-sections A3 and B1). It is also consistent with theory that racemisation in substitution by the unimolecular mechanism is increased when we prolong the life of the organic ion by diluting the reactive with an unreactive solvent (*e.g.*, water with acetone).

As an example of the use of our diagnostic rules, reference may be made to the observation (Part II) that (+)α-phenylethyl chloride, on solution in liquid ammonia, gives (−)α-phenylethylamine. This is obviously a nucleophilic substitution, although it is not a replacement of ·Hal by ·OR; but the same rules will surely apply to replacements of ·Hal by $·NR_2$. No kinetic investigation was carried out, but it is unnecessary to consider whether the mechanism of the reaction is S_N2 or S_N1 in order to decide its steric course: the mechanism must be one or the other, and hence the predominating orientation must be inversion; therefore the (+)chloride and (+)amine are configuratively related.

Inasmuch as the diagnostic rules follow from our theoretical considerations, as well as agreeing with the experimental evidence, we may regard stereochemical classifications reached in the manner now illustrated as having a basis which is independent of the rather elaborate arguments employed in Parts I and II. We can directly use the orientation rule in order to establish configurational analogy with each of the following sets of optically active compounds:

(1) β-n-*Octyl Derivatives*:—(+)Chloride, (+)Bromide, (+)Alcohol, (+)Ethyl ether, (+)Acetate.

(2) *α-Phenylethyl Derivatives*:—(+)Chloride, (+)Bromide, (+)Alcohol, (+)Methyl ether, (+)Ethyl ether, (+)Amine.

Most of the substitutions utilised in making these stereochemical classifications are recorded in Parts I and II, but the direct transformations of β-*n*-octyl halides into the acetate were described by Pickard and Kenyon (J., 1911, **99**, 45). These authors first correctly diagnosed the stereochemical relationship between β-*n*-octyl bromide and the alcohol by comparison of the rotatory dispersion diagrams (*loc. cit.*): the contrary conclusions reached later by Levene and Mikeska are based on quite untenable arguments (*J. Biol. Chem.*, 1924, **59**, 45).

We have still to consider the substitution undergone by alkyl and aralphyl halides under the influence of silver oxide or silver salts in the presence of hydroxylic solvents. In Part IV we showed that the hydroxylation and ethoxylation of β-*n*-octyl bromide by means of silver oxide suspended in aqueous alcohol proceeded with predominating inversion of configuration and considerable accompanying racemisation; and that a like statement is true for the substitutions which were promoted by the soluble silver salts, silver nitrate and silver acetate, in a similar solvent. We showed also that predominating inversion with particularly extensive racemisation characterised the hydrolysis of α-phenylethyl chloride in aqueous solvents. These are the effects to be expected on our view (sub-section B,1) of the reaction with silver salts as a heterogeneous analogue of unimolecular hydrolysis (mechanism S_N1). It would seem that we can safely generalise, postulating a predominating inversion of configuration in all reactions of alkyl or aralphyl halides with silver salts.

(3) *Halogeno-acids and their Esters and Salts* (*Orientation Rules*).—There are no previously recorded observations from which we could with any confidence deduce empirically the rules governing steric orientation in the homogeneous hydrolysis or alcoholysis of halides containing a carboxyl group in its various forms as a substituent at the seat of substitution. We consider, however, that α-bromopropionic acid, its ester and anion are essentially typical of the structures which we wish to treat, and that accordingly generalisations based on the results of Part III are justified.

We may first consider non-ionised forms of the carboxyl substituent. In Part III we investigated two such forms, *viz.*, the ester group $\cdot CO_2Me$, and the undissociated carboxyl group $\cdot CO_2H$ (which was maintained in a non-ionised state by the addition of extraneous hydroxonium ions). The methyl alcoholysis of methyl α-bromopropionate was investigated under alkaline conditions, for which it was possible to prove kinetically that the mechanism was bimolecular, S_N2; and the stereochemical result was inversion without significant racemisation. The methyl alcoholysis of the same ester was also investigated under acid conditions, in which a secondary alkyl halide would have undergone substitution by the unimolecular mechanism S_N1; but, although no strict demonstration of the nature of the mechanism was possible in the case of this ester, the extreme slowness of reaction suggested that the mechanism was bimolecular, S_N2; and the optical result was inversion without appreciable racemisation. Then the acid hydrolysis of undissociated α-bromopropionic acid was examined; again the mechanism could not be demonstrated from the kinetics, but the slow rate suggested that it was bimolecular, S_N2—and again the optical result was inversion with no definitely detectable racemisation. It is, of course, quite in agreement with theory (sub-section A, 4) that non-ionised forms of the carboxyl group, which are strong attractors of electrons, should suppress substitution by mechanism S_N1; and the uniformity of the optical result confirms our assumption that all the above-mentioned substitutions proceed by mechanism S_N2. It would appear to be impossible to realise mechanism S_N1 in the hydrolysis or alcoholysis of a halide (ammonolysis remains to be investigated), in which, besides a non-ionic carboxyl form such as ·CO·OH, ·CO·OR, $\cdot CO\cdot NH_2$, $\cdot CO\cdot NR_2$, etc., only one alkyl group and a hydrogen atom are attached at the seat of substitution. For substitution by mechanism S_N2 the theoretical considerations of sub-section B,1 require just what we find, *viz.*, inversion without substantial racemisation.

In the presence of two alkyl groups or an aryl group, in addition to a non-ionised form of the carboxyl group, *e.g.*, in $CMePhCl\cdot CO_2Me$, it probably would be possible to effect hydrolysis or alcoholysis by mechanism S_N1. Then, since the carbon ion is flat in its equilibrium configuration and intrinsically unstable, we may expect a predominating inversion accompanied by considerable racemisation, which will be further increased by dilution of the hydroxylic with a non-hydroxylic solvent. These theoretical predictions cannot be tested by any of the experimental results we have obtained hitherto, but the planned extensions of this research include the study of examples which should provide the necessary check.

Next we have to consider the carboxylate-ion substituent: this repels electrons and therefore facilitates substitution by mechanism S_N1 (sub-section A, 5). In Part III we describe an investigation of both the methyl alcoholysis and the hydrolysis of the α-bromopropionate ion. Methyl alcoholysis was found to occur in general by both the bimolecular and the unimolecular mechanism, but by suitably choosing the concentrations of the reactants the separate mechanisms, S_N2 and S_N1, could be isolated; and methoxylation by mechanism S_N2 took place with inversion of configuration and with no appreciable racemisation; whilst by mechanism S_N1 it proceeded with a practically quantitative retention of the original stereochemical form. Similar results were obtained for hydrolysis.

Summarising, we may say that in the presence of the carboxylate-ion group, substitution by the bimolecular mechanism, S_N2, leads, as usual, to a substantially complete inversion of configuration. This accords with the requirements of theory (sub-section B, 1). On the other hand, reaction by the unimolecular mechanism, S_N1, produces essentially a retained configuration. This is also in conformity with the theory, which points out that the most stable configuration of the intermediate carbon cation is now, not planar, but pyramidal (*loc. cit.*).

The steric orientation of substitution undergone by α-halogeno-acids and their derivatives under the influence of silver oxide or silver salts in the presence of hydroxylic solvents was considered in Part V. The data relate to derivatives of α-bromopropionic acid, and once again a clear distinction was found between those compounds which contain a formally neutral modification of the carboxyl group in attachment to the seat of substitution, and the α-bromopropionate ion which has a charged carboxyl substituent.

The former case is illustrated by the hydroxylation of an amide by means of silver carbonate and water, and the methoxylation of an ester by silver nitrate in methyl alcohol. In each case the stereochemical outcome was a predominating inversion with accompanying partial racemisation. As is pointed out above, a homogeneous unimolecular substitution (S_N1) of the halogen atom in compounds having neutral modifications of the carboxyl group attached to the asymmetric centre has probably not yet been realised; but it is theoretically expected to lead to inversion with racemisation. Furthermore, our view that the reaction of halides with silver salts is a heterogeneous analogue of unimolecular substitution implies qualitative similarity of steric orientation. Thus the experimental results seem intelligible, and it can probably be accepted as general that the reactions of α-halogeno-esters and -amides with silver salts will proceed with predominating inversion.

The hydrolysis of the α-bromopropionate ion was investigated with silver oxide, and with silver nitrate, in the presence of aqueous solvents. Under all conditions substitution proceeded with a predominating retention of form and some accompanying racemisation. The retention of form constitutes qualitative analogy with the homogeneous unimolecular substitution (S_N1) of the anion. The racemisation, considerable with silver oxide, was small with silver nitrate; it is small at most in the unimolecular substitution (S_N1). On the whole, therefore, the expected qualitative analogy between the silver reactions and the S_N1 process seems well supported; and we may accordingly assume that a predominating retention of configuration will be the normal result of attack by silver ions in a hydroxylic solvent on the anions of α-halogeno-acids (cf. pp. 1243, 1263).

(4) *Halogeno-acids and their Salts* (*Review of Literature*).—There has been so little previous work on the steric course of the hydrolysis of alkyl halides that no further reference to these compounds is necessary. In the field of the halogeno-acids, however, observations have been recorded, which, although unco-ordinated, and often insufficiently precise in the specification of conditions, are numerous enough to justify discussion. In most examples some at least of the recorded observations can be used in conjunction with our orientation rules in order to establish the stereochemical connexion between factors and products.

The example which from a structural point of view most closely resembles our simple one of α-bromopropionic acid is α-bromo-β-phenylpropionic acid: the groups which influence the substitution are the same except that benzyl replaces methyl, and the effect of this change will be merely to increase slightly the tendency towards unimolecular substitution. McKenzie, Wren, and Barrow hydrolysed α-bromo-β-phenylpropionic acid by means of aqueous sodium hydroxide, the maximal alkalinity of which was 0·06*N*, by means of water in the presence of calcium carbonate, by water alone, by water acting on the silver salt of the acid, and by water and excess of silver oxide acting on the silver salt (J., 1910, **97**, 1355; 1911, **99**, 1921). No kinetic study was made, but we can be sure that under all these conditions the dominant mechanism will be either the homogeneous unimolecular mechanism S_N1, or the heterogeneous modification of this already considered, the entity substituted being the anion : the stereochemical outcome should therefore in all cases be a retention of configuration. In all five experiments McKenzie, Wren, and Barrow obtained an α-hydroxy-β-phenylpropionic acid with a retained sign of rotation. It is therefore certain that the bromo- and hydroxy-acids which have like signs of rotation have like configurations. The same authors hydrolysed α-chloro-β-phenylpropionic acid by means of water and calcium carbonate, and obtained a hydroxy-acid with a retained sign of rotation. This proves that chloro- and hydroxy-acids with like signs of rotation also have corresponding configurations.

In the halogenophenylacetic acids the aryl substituent creates an increased tendency to unimolecular substitution (S_N1); and it is known experimentally that the homogeneous hydroxylation of the anions of these halogeno-acids pursues a unimolecular course practically exclusively (sub-section A, 5). The steric course of this reaction must be determined jointly by the carboxylate-ion group and by the phenyl group : the former causes retention of configuration and the latter racemisation, so that the joint effect of the groups should be to produce a predominating retention of form accompanying racemisation.

McKenzie and Clough treated α-chlorophenylacetic acid with water, and its sodium salt with water, aqueous sodium carbonate, and aqueous sodium hydroxide; in each case the mandelic acid which was produced retained the original sign of rotation but was largely racemised (J., 1908, **93**, 811; 1909, **95**, 777). Under all the conditions mentioned the reaction must have consisted essentially in the unimolecular hydrolysis of the anion of the chloro-acid : this is true, on the one hand, for the experiment involving sodium hydroxide because of the strong joint effect of the phenyl and carboxylate-ion groups in favouring unimolecular hydrolysis; and, on the other, for the experiment with the free chloro-acid, because, in spite of the low concentration of the anion, its great reactivity will ensure that hydrolysis goes by that route. Comparing the expected steric orientation of the unimolecular reaction of the anion with the observed effect of substitution on the sign of rotation in the experiments mentioned, we see that chloro- and hydroxy-phenylacetic acids with like signs of rotation are configuratively similar. We can include α-methoxyphenylacetic acid in the same statement on the basis of homogeneous methoxylations of the sodium salt of the chloro-acid, in which also the sign of rotation was retained.

α-Bromophenylacetic acid was investigated by McKenzie and Walker (J., 1915, **107**, 1685; cf. Ward, J., 1926, 1184) who brought about hydroxylation by the action of water on the acid, and by water and by aqueous sodium hydroxide acting on the sodium salt. The products of these experiments were almost inactive, although in the first case small rotations, some with an inverted sign, were observed. Small rotations with a retained sign were obtained when the reaction was complete as judged by the elimination of halogen, although after considerably longer periods inversion of sign occurred. This observation makes it evident that the inversions are due to the interaction of two molecules of the acid (or anion) to form esters (or lactide) which are rapidly produced with, and slowly hydrolysed without, inversion. We assume inversion in the formation of such esters, because the reaction must be essentially bimolecular; and retention of form in their hydrolysis, because the fission would not exchange a bond attached to the asymmetric carbon atom (cf. p. 1265). The methoxylation of α-bromophenylacetic acid, effected by treatment of the sodium salt with methyl alcohol, proceeded with retention of the sign of rotation. The conclusion is that configuratively related bromo-, hydroxy-, and methoxy-phenylacetic acids have like signs of rotation.

McKenzie and his collaborators effected the hydroxylation and methoxylation of chloro- and bromo-phenylacetic acid by the agency of silver salts in the presence of water or methyl alcohol: the hydroxy- or methoxy-acid produced had in each case an inverted sign of rotation. This happened, for instance, when, according to the description given, the silver salt of the halogeno-acid was prepared and subsequently decomposed by means of water or methyl alcohol. The stereochemical result seems anomalous, because, if reaction is determined essentially by an attack of silver ions on the anion of the halogeno-acid, there should be a predominating retention of form, and therefore a retained sign of rotation. Reconciliation arises through our observation, which will be published later, that the preparation of the silver salts of these highly reactive halides is not the simple process imagined, but involves the production of esters by the interaction of two organic molecules; these esters are eventually hydrolysed or alcoholysed, and the over-all result is inversion for the reasons indicated above.

Rather similar conditions apply to α-chloro-α-phenylpropionic acid, which was examined by McKenzie and Clough (J., 1910, **97**, 1016, 2564). Homogeneous hydrolysis, which takes place very rapidly both in acid and in alkaline solution, and is surely unimolecular, leads to a wholly racemised product. Hydrolysis by means of silver salts takes a course similar to that outlined in the preceding paragraph, and leads eventually to an α-hydroxy-acid with an inverted sign of rotation, which we may presume to correspond to an inverted configuration.

The only monobasic aliphatic β-halogeno-acid which has been studied in connexion with the steric course of hydrolysis is β-chlorobutyric acid. Fischer and Scheibler hydrolysed the methyl ester and the free acid with aqueous hydrochloric acid, and the silver salt with silver oxide and water (*Ber.*, 1909, **42**, 1219); in all these experiments they obtained a partly racemised β-hydroxybutyric acid with an inverted sign of rotation. The type to which the first of these experiments, and, more doubtfully, the second and third may be expected to conform is the S_N1 hydrolysis, or its heterogeneous analogue, of a secondary alkyl halide; we expect, therefore, partial racemisation with a predominating inversion of configuration. The conclusion may be drawn that a β-chloro- and a β-hydroxy-butyric acid with like signs of rotation are configuratively similar.

The β-halogeno-β-phenylpropionic acids are in like case, except that the presence of the aryl substituent at the seat of substitution will ensure the domination of unimolecular hydrolysis (S_N1) even in alkaline solution. The hydrolysis of β-chloro- and β-bromo-β-phenylpropionic acid has been investigated by McKenzie and Humphries (J., 1910, **97**, 121), McKenzie and Barrow (J., 1911, **99**, 1921), and Fischer and Scheibler (*Annalen*, 1911, **383**, 337). The bromo-acid on hydrolysis, either with water alone or with aqueous sodium carbonate, gave a β-hydroxy-β-phenylpropionic acid with an inverted sign of rotation, and a similar result was obtained on hydrolysis with silver oxide and water. The chloro-acid on hydrolysis by means of water alone behaved like the bromo-acid. We may conclude that the chloro-, bromo- and hydroxy-acids which have like signs of rotations have corresponding configurations.

The halogenosuccinic acids figured in Walden's original discovery of optical inversion (*Ber.*, 1896, **29**, 133; 1897, **30**, 3146; 1899, **32**, 1833, 1855), and their hydrolysis has since been investigated by Holmberg (*J. pr. Chem.*, 1913, **87**, 456; **88**, 553; *Arkiv Kemi Min.*

Geol., **1916**, **6**, No. 8, 1; 1917, **6**, No. 23, 33; *Ber.*, 1927, **60**, 2194), Bancroft and Davis (*J. Physical Chem.*, 1931, **35**, 1253) and Rördam (J., 1932, 2931; *Ber.*, 1934, **67**, 1595). The presence of an α- and a β-carboxyl group leads to considerable complication, and it is not possible on the basis of the particulars given to interpret unequivocally every detail of the reported experiments. However, the main features are outlined below. Some of the results quoted have been obtained with one, and some with several of the halogenosuccinic acids (chloro-, bromo- and iodo-); but, as there is no evidence of any significant difference of behaviour between them, we shall discuss them collectively.

Hydrolysis by means of an excess of a soluble metallic hydroxide is kinetically of the second order and leads to a malic acid with an inverted sign of rotation. This tells us that the mechanism is bimolecular (S_N2), and that, since such a reaction must invert configuration, those halogenosuccinic and malic acids which have rotations of like sign have similar configurations.

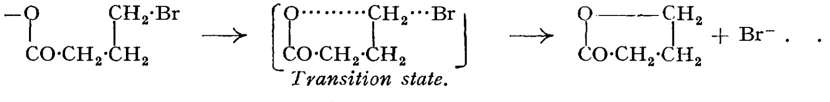
The hydrolysis of the sodium salt in water follows no simple kinetic order, and gives a malic acid with a retained sign of rotation, and therefore a retained configuration. The unimolecular mechanism (S_N1) would produce this stereochemical result; and a simple kinetic order is not to be expected, since under the conditions chosen the liberated hydrogen bromide is continually causing replacement of the halogenosuccinate ion by the much less reactive free acid. (In our experiments on α-bromopropionic acid, we kept an extra equivalent of alkali in the solution in order to avoid this complication.) On the other hand, the observations mentioned below show that there is also another route through which a malic acid with a retained configuration could be produced.

When a halogenosuccinic acid is treated with one equivalent of a soluble silver salt a lactonic acid is formed, which has an inverted sign of rotation. There has been much discussion, first, as to whether this malolactonic acid is an α- or a β-lactone, and secondly, as to whether it is formed with retention or inversion of configuration. In our view a definite answer can be given to both these questions. The substance is a β-lactone, because its production is peculiar to the halogenosuccinic acids, and has not been paralleled for any of the numerous monobasic α-halogeno-acids which have been investigated, some under the definite preconception that an analogue of malolactonic acid would be produced; and furthermore because β-lactones are common substances, particularly well known in the succinic acid series, whereas unpolymerised α-lactones are quite unknown. Malolactonic acid is formed with an inversion of configuration because the most probable reaction mechanism is an "intramolecular variety" of the bimolecular mechanism (S_N2); * and also because a halogenosuccinic acid and the lactonic acid derived from it have separately been converted, both by obviously bimolecular substitutions, into enantiomeric xanthates. It follows that a β-malolactonic acid and a malic acid with rotations of the same sign have like configurations.

β-Malolactonic acid undergoes hydrolysis to malic acid by three distinct mechanisms; in concentrated or dilute alkaline solution reaction is rapid and preserves the configuration; in dilute acid it is slow and inverts configuration; in more concentrated acid it is compara-

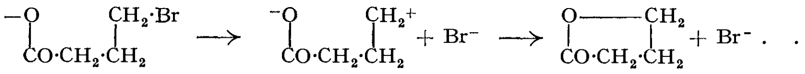
---

* We mean that the carboxylate-ion group attacks the halogen-bearing carbon atom, and we take the same view with regard to the first-order lactonisation of the γ-bromobutyrate ion (Caldin and Wolfenden, J., 1936, 1239):



$$\begin{array}{l}-O \qquad CH_2{\cdot}Br \\ CO{\cdot}CH_2{\cdot}CH_2\end{array} \longrightarrow \underset{\textit{Transition state.}}{\left[\begin{array}{l}O\cdots\cdots CH_2\cdots Br \\ CO{\cdot}CH_2{\cdot}CH_2\end{array}\right]} \longrightarrow \begin{array}{l}O\text{———}CH_2 \\ CO{\cdot}CH_2{\cdot}CH_2\end{array} + Br^- \quad . \quad . \quad (S_N2)$$

Analogy suggests that the alternative of ionic fission of the carbon–halogen bond before intervention of the carboxylate ion:



$$\begin{array}{l}-O \qquad CH_2{\cdot}Br \\ CO{\cdot}CH_2{\cdot}CH_2\end{array} \longrightarrow \begin{array}{l}^-O \qquad CH_2^+ \\ CO{\cdot}CH_2{\cdot}CH_2\end{array} + Br^- \longrightarrow \begin{array}{l}O\text{———}CH_2 \\ CO{\cdot}CH_2{\cdot}CH_2\end{array} + Br^- \quad . \quad . \quad (S_N1)$$

would be relatively very slow. The mechanisms here represented are "intramolecular varieties" of S_N2 and S_N1 respectively. They are kinetically indistinguishable; but in some cases, although not in this, a stereochemical criterion for their distinction could be devised.

tively slow and retains configuration. The first and third of these reactions correspond to the ordinary alkaline and acid hydrolyses of esters. It has been shown by methods based on the use of optical activity (Holmberg, *Ber.*, 1912, **45**, 2997), the principle of mesomerism (Ingold and Ingold, J., 1932, 756), and the isotopes of oxygen (Polanyi and Szabo, *Trans. Faraday Soc.*, 1934, **30**, 508) that, when a carboxylic ester is hydrolysed by acids or alkali, fission takes place between the singly bonded oxygen atom and the carbonyl group; therefore these mechanisms applied to β-malolactonic acid cannot produce inversion. However, in the absence of any alkali, and of sufficient acid to give adequate speed to the intrinsically slow process of acid saponification, it becomes possible to observe a bimolecular displacement of the acyloxy-group by water molecules, a process which involves inversion.

Malic acid with a retained configuration is produced when water is allowed to act not only, as already mentioned, on the sodium salts of halogenosuccinic acids, but also on the silver salts, and on the free acids. In any of these cases it could be supposed, as indeed it has been, that malolactonic acid is first formed with one inversion and then hydrolysed with another. To what extent this double process does in fact contribute to the observed optical results cannot be decided from the existing kinetic data. When silver halogenosuccinates are treated with silver oxide, a much racemised malic acid is formed with an inverted configuration: the most probable cause seems to be the incursion of the alkaline hydrolysis of the lactonic acid. But independently of these details, which only a careful kinetic investigation can clear up, we have a sufficient number of transformations to which the orientation rules can safely be applied in order definitely to establish configurative relationships between the three halogenosuccinic acids, malolactonic acid, and malic acid.

There is similar cause for complicated behaviour in α-chloroglutaric acid, although the hydrolysis of this substance has not been investigated in such detail as has that of bromosuccinic acid. Using aqueous sodium hydroxide, water alone, and silver oxide and water, Fischer and Moreschi hydrolysed α-chloroglutaric acid to α-hydroxyglutaric acid, which in each case had a changed sign of rotation (*Ber.*, 1912, **45**, 2447). Under the first-named conditions the reaction would be essentially of the S_N2 type, and would involve inversion. The reactions with water alone, and with silver oxide and water, probably proceed by way of the very easily formed γ-lactonic acid, which is here produced with inversion and hydrolysed, in the manner of an ordinary carboxylic ester, without inversion. We may conclude that those chloro- and hydroxy-acids which have like signs of rotation have like configurations.

There is one halogeno-acid, *viz.*, α-bromo*iso*valeric acid, which has been hydrolysed to an optically active hydroxy-acid, whose stereochemical relationship to the bromo-acid we are nevertheless unable to assign. The conditions of the recorded experiments (Fischer and Scheibler, *Ber.*, 1908, **41**, 2891) are so similar to those for which we would expect a change of mechanism that we should require to carry out kinetic measurements before venturing to interpret the optical observations.

Our discussion establishes that the following sets of compounds have corresponding configurations *:—

(1) *α-Substituted Propionic Acids:* (+)Chloro-, (+)Bromo-, (+)Iodo-, (+)Methoxy-propionic acid, (−)Lactic acid.
(2) *α-Substituted β-Phenylpropionic Acids:* (+)Chloro-, (+)Bromo-, (+)Hydroxy-β-phenylpropionic acid.
(3) *α-Substituted Phenylacetic Acids:* (+)Chloro-, (+)Bromo-, (+)Methoxy-phenylacetic acid, (+)Mandelic acid.
(4) *α-Substituted α-Phenylpropionic Acids:* (+)Chloro-, (+)Hydroxy-α-phenylpropionic acid.
(5) *β-Substituted* n-*Butyric Acids:* (+)Chloro-, (+)Hydroxy-*n*-butyric acid.
(6) *β-Substituted β-Phenylpropionic Acids:* (+)Chloro-, (+)Bromo-, (+)Hydroxy-β-phenylpropionic acid.

---

* Following common usage, we employ (+) and (−) to signify sign of rotation. Lævorotatory lactic acid gives dextrorotatory salts, *i.e.*, (−)lactic acid and (+)lactate ion belong to the same stereochemical class (*d*-series).

(7) *Substituted Succinic Acids :* (+)Chloro-, (+)Bromo-, (+)Iodo-succinic acid, (+)β-Malolactonic acid, (+)Malic acid.
(8) *α-Substituted Glutaric Acids :* (+)Chloro-, (+)Hydroxy-glutaric acid.

This list agrees well with Frankland's (J., 1913, **103**, 725), but poorly with Clough's (J., 1918, **113**, 526). Previous authors have based their assignments largely on a statistical survey of the recorded optical effects of particular reagents, and Frankland seems to have made a circumspect use of the rule that, when in a large majority of examples a particular reagent causes retention or inversion of the sign of rotation, then the action of that reagent is characterised by retention or inversion of configuration as the case may be. This may be a good general guide, but it takes insufficient account of mechanism : we have seen that the same reagent may behave in stereochemically different ways towards different compounds, and even towards the same compound under different conditions. Our assignment, on the other hand, is based wholly on a consideration of mechanism, and does not make use of any view about the statistical probability that stereochemically analogous structures will have like signs of rotation.

(C) *Steric Orientation in the Replacement of* ·OR *by* ·Hal.

(1) *Replacements by Means of Halides of Phosphorus and Sulphur.*—The configurational relationships established in section (B) enable us to make definite statements concerning the stereochemical behaviour of those reagents which, acting on the hydroxy-compounds, restore a halogen atom. In this sub-section we shall consider replacements effected by means of phosphorus halides and oxyhalides and thionyl halides, either in the absence or in the presence of a tertiary base such as pyridine. The following table contains a list of halogenations the steric course of which can unequivocally be specified on the basis of the conclusions of section (B).

(a) *Substitutions with Inversion of Configuration : Reagents and Hydroxy-compounds.*

Phosphorous Trichloride.—β-*n*-Octyl alcohol (22), α-Phenylethyl alcohol (11), Ethyl β-hydroxy-β-phenylpropionate (24).

Phosphorus Trichloride and Pyridine.—α-Phenylethyl alcohol (21), Ethyl β-hydroxy-β-phenylpropionate (24).

Phosphorus Oxychloride.—β-*n*-Octyl alcohol (22), α-Phenylethyl alcohol (21).

Phosphorus Oxychloride and Pyridine.—α-Phenylethyl alcohol (21), Methyl mandelate (19).

Phosphorus Pentachloride.—β-*n*-Octyl alcohol (22), α-Phenylethyl alcohol (15, 21), Lactic acid (3, 4), Ethyl lactate (5), Malic acid (1), Methyl malate (2), Ethyl malate (2), β-Hydroxy-*n*-butyric acid (8, 12), Methyl β-hydroxy-*n*-butyrate (8, 12), β-Hydroxy-β-phenylpropionic acid (13), Ethyl β-hydroxy-β-phenylpropionate (24), α-Hydroxy-β-phenylpropionic acid (10), Mandelic acid (6, 7), Methyl mandelate (6, 7), Menthyl mandelate (23), α-Hydroxy-α-phenylpropionic acid (11), Ethyl α-hydroxy-α-phenylpropionate (11).

Phosphorus Pentachloride and Pyridine.—β-*n*-Octyl alcohol (22), α-Phenylethyl alcohol (21), Ethyl lactate (25).

Phosphorus Tribromide.—Ethyl β-hydroxy-β-phenylpropionate (24).

Phosphorus Tribromide and Pyridine.—Ethyl β-hydroxy-β-phenylpropionate (24).

Phosphorus Pentabromide.—α-Phenylethyl alcohol (14), Lactic acid (4), Methyl lactate (4), Ethyl lactate (3, 6), Methyl malate (2), Ethyl malate (2), β-Hydroxy-β-phenylpropionic acid (9), Methyl β-hydroxy-β-phenylpropionate (9), Mandelic acid (6), Methyl mandelate (6).

Phosphorus Pentabromide and Pyridine.—Ethyl lactate (25).

Thionyl Chloride.—β-*n*-Octyl alcohol (17), Lactic acid (15), Ethyl lactate (15, 25), Malic acid (13), Ethyl malate (13), Ethyl α-hydroxy-β-phenylpropionate (13).

Thionyl Chloride and Pyridine.—β-*n*-Octyl alcohol (18), α-Phenylethyl alcohol (21), Ethyl lactate (16, 25), Ethyl mandelate (20), Ethyl β-hydroxy-β-phenylpropionate (24).

Thionyl Bromide and Pyridine.—β-*n*-Octyl alcohol (18).

(b) *Substitutions with Retention of Configuration: Reagents and Hydroxy-compounds.*

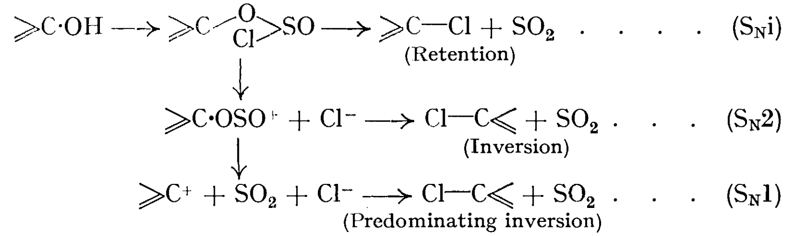
Thionyl Chloride.—α-Phenylethyl alcohol (15), β-Hydroxy-β-phenylpropionic acid (13), Ethyl β-hydroxy-β-phenylpropionate (24), Mandelic acid (13), Methyl mandelate (13), Ethyl mandelate (13), Menthyl mandelate (23), α-Hydroxy-α-phenylpropionic acid (11), Ethyl α-hydroxy-α-phenylpropionate (11).

References.—(1) Walden, *Ber.*, 1893, **26**, 215. (2) *Idem*, *Ber.*, 1895, **28**, 1289. (3) *Idem*, *ibid.*, p. 1293. (4) Walker, J., 1895, **67**, 918. (5) Purdie and Williamson, J., 1896, **69**, 820. (6) Walden, *J. Russ. Phys. Chem. Soc.*, 1898, **30**, 669. (7) McKenzie and Clough, J., 1908, **93**, 811. (8) Fischer and Scheibler, *Ber.*, 1909, **42**, 1219. (9) McKenzie and Humphries, J., 1910, **97**, 121. (10) McKenzie and Wren, *ibid.*, p. 1356. (11) McKenzie and Clough, *ibid.*, pp. 1016, 2564. (12) Fischer and Scheibler, *Annalen*, 1911, **383**, 339. (13) McKenzie and Barrow, J., 1911, **99**, 1910. (14) Holmberg, *Ber.*, 1912, **45**, 997. (15) McKenzie and Clough J., 1913, **103**, 687. (16) Frankland and Garner, J., 1914, **105**, 1101. (17) Levene and Mikeska, *J. Biol. Chem.*, 1924, **59**, 45. (18) McKenzie and Tudhope, *J. Biol. Chem.*, 1924, **62**, 551. (19) Wagner-Jauregg, *Helv. Chim. Acta*, 1929, **12**, 61. (20) Kenyon, Lipscombe, and Phillips, J., 1930, 415. (21) Kenyon, Phillips, and Taylor, J., 1931, 382. (22) Houssa and Phillips, J., 1932, 108. (23) McKenzie and Smith, J., 1923, **123**, 1962. (24) Kenyon, Phillips, and Shutt, J., 1935, 1663. (25) Gerrard, Kenyon, and Phillips, this vol., p. 153.

From these steric orientations we might conclude, with Frankland, that the halides of phosphorus always bring about inversion of configuration, and that thionyl chloride does so unless a phenyl group is attached to the seat of substitution; as Kenyon and Phillips first noticed, this peculiarity of the phenyl substitutent disappears if the reaction with thionyl chloride is carried out in the presence of pyridine.

It is impossible, however, that this statement of the orientation rules is accurate. Their extension and correction require a discussion of mechanism, which we shall give only in outline since further study has been undertaken with the aid of radioactive halogens.

We assume that with all the reagents under consideration the first step is the formation of an ester-halide, $\mathrm{Alk{\cdot}O{\cdot}PCl_2}$, $\mathrm{Alk{\cdot}O{\cdot}SOCl}$, etc.: many such compounds have been isolated. These ester-halides are all capable of ionising one of their halogen atoms; and, as Kenyon and Phillips have suggested (*loc. cit.*), this tendency is increased by pyridine owing to the production of pyridinium halides. The ester-halides can also undergo intramolecular "rearrangement" with the elimination of an organic oxide or oxyhalide. On the whole the phosphorus halides ionise more readily, and rearrange less readily, than the thionyl halides. Contrary to a suggestion of Kenyon and Phillips (*loc. cit.*), the secret of the peculiar behaviour of the phenyl substituent is that, owing to its capacity for electromeric electron-release, it loosens the C·O bond of the ester-halide, and so promotes rearrangement: $\overset{\curvearrowright}{\mathrm{Ph{-}}}\mathrm{C}\overset{\curvearrowright}{\mathrm{{-}O}}\mathrm{{-}}$. Now, ionisation may be followed by either bimolecular or unimolecular substitution ($\mathrm{S_N2}$ or $\mathrm{S_N1}$); which sequel actually obtains may be expected to depend on the structure and the solvent in accordance with established principles; and bimolecular substitution will lead to inversion, whilst unimolecular substitution will produce inversion with racemisation; the alternative is an intramolecular nucleophilic change ($\mathrm{S_Ni}$) which will retain the original configuration (cf. sub-section B, 1). The matter is illustrated with reference to the thionyl chloride reaction *:



$$\geqslant\mathrm{C{\cdot}OH} \longrightarrow \geqslant\mathrm{C}\begin{smallmatrix}\diagup\mathrm{O}\\ \mathrm{Cl}\end{smallmatrix}\!\!>\!\mathrm{SO} \longrightarrow \underset{\text{(Retention)}}{\geqslant\mathrm{C{-}Cl} + \mathrm{SO_2}} \quad .\ .\ .\ .\quad (\mathrm{S_Ni})$$

$$\downarrow$$

$$\geqslant\mathrm{C{\cdot}OSO^+} + \mathrm{Cl^-} \longrightarrow \underset{\text{(Inversion)}}{\mathrm{Cl{-}C}\leqslant + \mathrm{SO_2}} \quad .\ .\ .\quad (\mathrm{S_N2})$$

$$\downarrow$$

$$\geqslant\mathrm{C^+} + \mathrm{SO_2} + \mathrm{Cl^-} \longrightarrow \underset{\text{(Predominating inversion)}}{\mathrm{Cl{-}C}\leqslant + \mathrm{SO_2}} \quad .\ .\ .\quad (\mathrm{S_N1})$$

It will be realised that what we have here referred to as a "rearrangement" is a nucleophilic substitution belonging to the category of the "four-atom problem": two covalencies are exchanged.

---

* The decomposition of alkyl chloroformates may be regarded similarly (read C for S in the above scheme). Harford, Kenyon, and Phillips have shown that configuration is retained when these esters are heated without a basic solvent, but inverted when they are decomposed in pyridine (J., 1933, 179).

These considerations allow us to interpret the optical results of halogenations in a more consistent manner than would have been possible on the basis of an unsupported application of the approximate empirical rules. We give some examples.

α-Hydroxy-α-phenylpropionic acid has been converted into the chloro-acid with change in the sign of rotation by means of phosphorus pentachloride, and without change by means of thionyl chloride; similar results have been obtained by the use of the ethyl esters in place of free acids (McKenzie and Clough, J., 1910, **97**, 1016, 2564). Since a phenyl group is attached at the seat of substitution, this relationship is normal; and the rules tell us that phosphorus pentachloride causes inversion of configuration whilst thionyl chloride does not. Like signs of rotation therefore correspond to like configurations.

Ethyl α-hydroxy-α-naphthylacetate has been shown to yield a chloro-ester with an altered sign of rotation when the reagent is phosphorus pentachloride, and with a retained sign when it is thionyl chloride either alone or with pyridine; similar results have been obtained with the menthyl ester (McKenzie and Gow, J., 1933, **32**, 705). This relationship is abnormal, and is not covered by the rules : we usually find, either that all three reagents behave similarly, or that the first two act alike and the third oppositely : in this case the last two act alike and the first oppositely, so it has to be decided wherein the anomaly lies. As to this, the theory shows that, since the α-naphthyl group releases electrons more strongly than phenyl, the presence of the former group in place of the latter might promote the intramolecular change (S_Ni) in place of the more normal substitution (S_N2 or S_N1), but could not act in the opposite way; hence the anomalous reaction is the one involving thionyl chloride and pyridine, which in this case proceeds by rearrangement with retention of configuration. Therefore, for these compounds also, like signs of rotation signify corresponding configurations.

As a final example we may contrast the behaviour of α-phenylethyl alcohol with its homologue α-phenyl-*n*-amyl alcohol. The former reacts with phosphorus pentachloride with a change in the sign of rotation, and with thionyl chloride without a change; the latter reacts with both chlorinating agents without any change of sign, although the substitution brought about by phosphorus pentachloride is characterised by considerable racemisation (Levene and Mikeska, *J. Biol. Chem.*, 1926, **70**, 355). Now in most cases in which the two reagents behave in an optically similar manner we know that they both cause inversion; but α-phenyl-*n*-amyl alcohol is an exception, as the theory clearly indicates : not only does the amyl group promote better than methyl those electronic conditions which facilitate reaction S_Ni, but also it diminishes the tendency to the ionisation necessary for reactions S_N2 and S_N1. It follows that for the higher homologue the predominating mechanism is S_N1, and that both reagents substitute with preferential retention of configuration; although the racemisation observed with phosphorus pentachloride suggests that in this case the change from substitution to internal rearrangement is far from complete.

By means of these and similar arguments it is possible to establish configurational correspondence within the following sets of compounds :—

(1) β-n-*Butyl Series.*—(+)Alcohol, (+)Chloride, (+)Bromide.
(2) β-n-*Amyl Series.*—(+)Alcohol, (+)Chloride.
(3) α-*Phenyl*-n-*propyl Series.*—(+)Alcohol, (+)Chloride.
(4) α-*Phenyl*-n-*butyl Series.*—(+)Alcohol, (+)Chloride.
(5) α-*Phenyl*iso*butyl Series.*—(+)Alcohol, (+)Chloride.
(6) α-*Phenyl*-n-*amyl Series.*—(+)Alcohol, (+)Chloride.
(7) α-*Substituted* α-*Phenyl*iso*valeric Acids.*—(+)α-Hydroxy-, (+)α-Chloro-.
(8) *Ethyl and Menthyl* α-*Substituted* α-*Naphthylacetates.*—(+)α-Hydroxy-, (+)α-Chloro-.
(9) αα'-*Disubstituted Succinic Esters.*—(+)Methyl tartrate, (+)Ethyl tartrate, (+)Methyl chloromalate, (+)Ethyl chloromalate, (+)Ethyl bromomalate.

References.—(1) Le Bel, *Bull. Soc. chim.*, 1892, **7**, 552; 1893, [iii], **9**, 676; Kenyon, Phillips, and Pittman, J., 1935, 1072. (2) Le Bel, *locc. cit.* (3)—(6) Levene and Mikeska, *locc. cit.* (7) Walden, *Ber.*, 1895, **28**, 2768. (8) McKenzie and Gow, *loc. cit.* (9) Walden, *Z. physikal. Chem.*, 1906, **55**, 42; *J. Russ. Phys. Chem. Soc.*, 1898, **30**, 522.

(2) *Replacements by Means of Hydrogen Halides.*—The configurative relations established in the preceding sections enable us to specify the steric course of a number of reactions in which hydrogen halides have been used in order to introduce halogen in place of hydroxyl. The following is a list of these substitutions. In all cases configuration is inverted; and, where any evidence as to the rotatory power of the optically pure halide exists, the indication is that more or less considerable racemisation occurs.

Substitutions with Inversion : Reagents and Hydroxy-compounds.

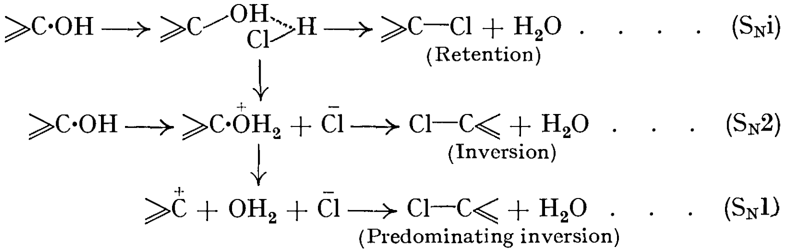
Hydrogen Chloride.—β-*n*-Amyl alcohol (2), β-*n*-Octyl alcohol (2), α-Phenylethyl alcohol (2), α-Phenyl-*n*-propyl alcohol (2), β-Hydroxy-β-phenylpropionic acid (3).

Hydrogen Bromide.—β-*n*-Butyl alcohol (6), β-*n*-Octyl alcohol (2, 4), α-Phenylethyl alcohol (7), α-Phenyl-*n*-propyl alcohol (5), α-Hydroxy-β-phenylpropionic acid (1), Methyl α-hydroxy-β-phenylpropionate (1).

Hydrogen Iodide.—β-*n*-Octyl alcohol (2).

References.—(1) McKenzie and Humphries, *loc. cit.* (2) Pickard and Kenyon, J., 1911, **99**, 45. (3) McKenzie and Barrow, *loc. cit.* (4), (5) Levene and Mikeska, *locc. cit.* (6) Kenyon, Phillips, and Pittman, *loc. cit.* (7) Hughes, Ingold, and Scott, this vol., p. 1201.

The expected mechanisms are quite similar to those illustrated with reference to the halides of phosphorus and sulphur. In the presence of strongly electron-releasing groups, and under conditions inhibitory to ionisation, we may expect a configuration-preserving "rearrangement" of a hydrogen-bond complex; otherwise an oxonium ion should be formed, the bimolecular or unimolecular substitution of which should produce inversion :



$$\geqslant C{\cdot}OH \longrightarrow \geqslant C\begin{smallmatrix}OH\\ Cl\end{smallmatrix}\!\!>\!H \longrightarrow \geqslant C{-}Cl + H_2O \quad . \quad . \quad . \quad . \quad (S_Ni)$$

(Retention)

$$\geqslant C{\cdot}OH \longrightarrow \geqslant C{\cdot}\overset{+}{O}H_2 + \overset{-}{Cl} \longrightarrow Cl{-}C\leqslant + H_2O \quad . \quad . \quad . \quad (S_N2)$$

(Inversion)

$$\geqslant \overset{+}{C} + OH_2 + \overset{-}{Cl} \longrightarrow Cl{-}C\leqslant + H_2O \quad . \quad . \quad . \quad (S_N1)$$

(Predominating inversion)

The bimolecular substitution (S_N2) corresponds to Meer and Polanyi's "positive mechanism," but contrary to these authors, we here represent it as proceeding always and in principle with an inversion of configuration.

From the examples tabulated above it would appear that the internal mechanism (S_Ni) is not at all commonly followed : we hope to realise it, but expect to do so only for specially chosen systems. There can be no doubt that, for all aliphatic, as well as the simpler aromatic, secondary alcohols, inversion is the rule : for these the mechanism is either the bimolecular (S_N2) or the unimolecular (S_N1) substitution of the oxonium ion; *a fortiori* the same statement must be true for primary alcohols.

These two mechanisms should in principle be distinguishable kinetically, the former as a third-order, the latter as a second-order, reaction : the rate of the S_N2 process should be proportional to the product of the activities of the alcohol, hydrogen ions and chloride ions; whilst that of the S_N1 reaction should vary as the product of the activities of the alcohol and hydrogen ions only—if we may assume, as usual, that the final ionic association is rapid. Several kinetic investigations have been carried out, but, in the non-aqueous solvents which are usually employed, the liberated water has a marked effect on the speed, and for this and other reasons the relation of activity to concentration is far from straightforward (Kilpi, *Z. physikal. Chem.*, 1914, **86**, 427; 1929, *A*, **141**, 424; **142**, 195; 1933, *A*, **166**, 285; Norris, *ibid.*, 1927, **130**, 600; *Rec. trav. chim.*, 1929, **45**, 885; Levene and Rothen, *J. Biol. Chem.*, 1929, **81**, 359; Bennett and Mosses, J., 1931, 2956; Bennett and Reynolds, J., 1935, 131; Hinshelwood, *ibid.*, p. 599). (The effect of water is to be expected, since the large energy of hydration of the hydrogen ion must reduce its activity.) It is noteworthy, however, that Kilpi, whose experiments related to the action of hydrogen chloride on ethyl and *n*-propyl alcohols in the absence of a solvent, concluded that his results could be interpreted by assuming that the rate varied as the activities of hydrogen and chloride ions: since the alcohols were present in excess, this indicates a third-order reaction such as S_N2. Bennett and his collaborators, who examined the action of hydrogen bromide on a large number of alcohols in aqueous phenol as solvent, obtained second-order constants such as mechanism S_N1 would require; however, the constants varied so considerably with the initial concentrations of reactants that this indication of mechanism cannot be regarded as conclusive. Bennett showed that the reaction is accelerated by electron accession; but although this must be true for mechanism S_N1, it may also be true for mechanism S_N2.

In spite of these uncertainties sufficient is clear concerning mechanism to enable us to base several further assignments of relative configurations on results which have been obtained in the treatment of optically active alcohols with hydrogen halides:

(1) β-n-*Butyl Series.*—(+)Alcohol, (+)Iodide.
(2) β-n-*Amyl Series.*—(+)Alcohol, (+)Iodide.
(3) β-n-*Hexyl Series.*—(+)Alcohol, (+)Iodide.
(4) γ-n-*Nonyl Series.*—(+)Alcohol, (+)Chloride, (+)Bromide, (+)Iodide.
(5) α-*Phenyl*-n-*propyl Series.*—(+)Alcohol, (+)Bromide.

References.—(1)—(4) Pickard and Kenyon, *loc. cit.* (5) Levene and Mikeska, *J. Biol. Chem.*, 1926, **70**, 355.

SUMMARY.

(1) The known relationships between the mechanism of aliphatic substitution and the structures of the compounds substituted form a starting point for the investigation of the laws governing the steric orientation of substitution. Experimental investigation of the optical effect of substitution at an asymmetric carbon atom is most valuable if the conditions are defined by a previous examination of the reaction kinetics; and, as a result of work carried out on this plan, certain general principles relating to the orientation of substitution are advanced, although detailed discussion is confined to the reciprocal replacements of •Hal and •OR.

(2) The accumulation of electron-releasing alkyl groups, and still more of aryl groups, at the seat of substitution in an organic halide for known reasons causes the suppression of bimolecular nucleophilic substitution and its supersession by the unimolecular reaction dependent on halogen ionisation. The electron-repelling carboxylate-ion group acts quite similarly, and the apparently complicated results recorded by previous workers (*e.g.*, Dawson) on the kinetics of the hydrolysis of halogeno-acids receive a simple explanation on this basis. The electron-attracting carboxyl group (undissociated), and likewise the ester and carboxylamide groups, act oppositely, as would be expected: they favour bimolecular substitution and inhibit the unimolecular process.

(3) Bimolecular substitution (S_N2 or S_E2) leads to inversion normally because of the exclusion principle, and independently of whether the electropolar forces in the compound substituted direct the reagent predominatingly to one side of the molecule or the other. (In aromatic substitution, as an application of the exclusion principle shows, the attack of the reagent must be lateral to the plane of the ring.)

(4) Unimolecular substitution in alkyl compounds leads normally to racemisation, because the intermediate ion has a plane of symmetry; but if the life of the ion is short, racemisation will be incomplete and will accompany a predominating inversion, owing to the circumstance that the separating ions shield each other; and since the life of an ion can be varied by altering the composition of the medium the degree of incompleteness of the racemisation should vary in a predictable way with such changes. An unsaturated substituent (*e.g.*, aryl) at the seat of substitution should increase the tendency to racemisation, because mesomerism confers additional stability on the planar ion. A charged substituent of neutralising sign (*e.g.*, a carboxylate-ion substituent in a cation) may stabilise a pyramidal configuration in the ion, and lead to eventual substitution with retention of form.

(5) Heterogeneous mechanisms of substitution arise in the hydrolysis of organic halogen compounds with silver oxide and silver salts. They appear to depend on a weakening of

the carbon–halogen bond by adsorption on the polar surface of an insoluble silver salt, and subsequent ionic fission of the bond on this surface through the attack of adsorbed silver ions. The stereochemical consequences are similar to those of the homogeneous mechanism dependent on ionisation (S_N1).

(6) Substitution dependent on internal rearrangements may lead to a retention of form if the point in the rearranging chain at which it recombines is insufficiently removed from the point at which it breaks loose to permit a simultaneous linking with both sides of the asymmetric atom.

(7) The rules mentioned in paragraphs (3), (4), and (5) for the steric orientation of nucleophilic aliphatic substitution are confirmed by reference to the hydrolysis and alcoholysis of β-*n*-octyl bromide, α-phenylethyl chloride, and α-bromopropionic acid, its methyl ester, and its anion, the reactions of these compounds having been investigated by the method indicated in paragraph (1).

(8) Previous investigations of the optical effects accompanying the hydrolysis or alcoholysis of optically active halogeno-acids and their derivatives are reviewed. In spite of the general lack of precise information concerning the conditions in which the observations were made, our orientation rules in most cases permit a determination to be made of the stereochemical relationship between factors and products. The assignments of relative configuration thus derived agree well with those of Frankland, who employed different principles.

(9) The assignments of configuration, reached as described above, determine the steric orientation of reactions in which hydroxyl is replaced by a halogen atom. A review of the orientations obtaining in the reactions in which phosphorus and thionyl halides have been employed indicates the general nature of the mechanisms at work. An ester-halide is first formed which may either internally rearrange with retention of stereochemical form, or ionise and thus substitute with inversion. The former mechanism is favoured by the release of electrons (*e.g.*, from aryl groups) to the seat of substitution, and the latter by those conditions which promote ionisation. Apparent anomalies are interpreted on this basis, and further assignments of relative configuration are made.

(10) Similar treatment is accorded to the reactions in which hydrogen halides are used to replace hydroxyl by halogen. The possible mechanisms include internal rearrangement of a hydrogen-bond complex with retention of form, and the ionisation of the complex followed by substitution with inversion. The ionic route is most commonly followed, and its consideration leads to some further assignments of configuration.

University College, London. [*Received, April 24th*, 1937.]