60. *The Mechanism of the Reaction of (—)Phenylalkylcarbinols with Hydrogen Bromide.*

By C. L. Arcus.

Levene and Rothen (*J. Biol. Chem.*, 1939, **127**, 237), having determined the rotations of the bromides produced by the action of hydrogen bromide on (—)phenyl-methyl-, -ethyl-, and -*n*-propyl-carbinols at temperatures from —80° to +20°, expressed the view that the three mechanisms of substitution known as S_Ni, S_N2, and S_N1 do not suffice to explain these curves. An explanation is now put forward in which the participation of each mechanism in the total reaction is represented by a distribution curve about a maximum at a certain temperature, and it is found that the algebraic sum of the optical results of the three mechanisms reproduces the experimental curves.

The " domain " of each mechanism, represented by the area between its distribution curve and the temperature axis, has been calculated for the three reactions.

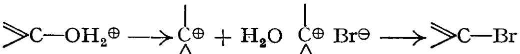
Levene and Rothen (*loc. cit.*) have determined the sign and magnitude of the rotation of the α-phenyl-ethyl, -*n*-propyl, and -*n*-butyl bromides produced by the action of hydrogen bromide, in the absence of solvent, on (—)phenyl-methyl-, -ethyl-, and -*n*-propyl-carbinols, at temperatures from —80° to +20°. The percentage optical purity of these bromides varies with temperature of reaction according to Fig. 1 for α-phenylethyl-bromide (the propyl analogue gives a very similar curve) and to Fig. 2 for the *n*-butyl compound. Values for the first two compounds approach large negative limits at —80°; with increasing temperature they fall to zero, and then rise to a positive maximum, from which they slowly fall. The (—)α-phenyl-*n*-butyl bromide produced at –80° appears to have reached a limiting negative optical purity; with increasing temperature a curve is followed similar in shape to those of the other two, but which is always negative.

The method employed was the same throughout. Dry hydrogen bromide was introduced very slowly into an evacuated flask containing the carbinol and maintained at the required temperature. The reaction was allowed to proceed substantially to completion. The excess hydrogen bromide was pumped off, and the bromide isolated and distilled. Hence, for a single carbinol the only variable is the reaction temperature, and for different carbinols reacting at the same temperature the only variable is the structure of the carbinol.

Three mechanisms of substitution applicable to these reactions have been described. A bimolecular mechanism leading to complete inversion has been proposed by Kenyon and Phillips (*Trans. Faraday Soc.*, 1930, **26**, 451) and investigated kinetically by Hughes, Ingold, and Masterman (J., 1937, 1196). For the reaction of an alcohol with hydrogen bromide this mechanism (S_N2) is

$$>\!C—OH + HBr \longrightarrow Br^{\ominus}\ >\!C—OH_2^{\oplus} \xrightarrow{\frown} Br—C\!< + H_2O$$

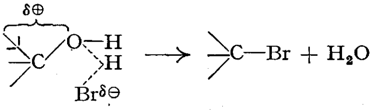
A unimolecular mechanism was proposed by Hughes and Ingold (J., 1935, 244), in which the molecule undergoing substitution slowly ionises and the carbonium cation reacts with the entering group (S_N1) :



$$>\!C—OH_2^{\oplus} \longrightarrow C^{\oplus} + H_2O\quad C^{\oplus}\ Br^{\ominus} \longrightarrow >\!C—Br$$

The carbonium cation is flat, but it is shielded from attack by the withdrawing group, whence the inverted configuration preponderates. Hughes, Ingold, and Scott (J., 1937, 1201) found the hydrolysis of α-phenylethyl chloride in water and aqueous acetone to be unimolecular and to result in 2—17·5% excess of the inverted configuration.

A third mechanism (S_Ni) for the replacement of hydroxyl by halogen has been described (Cowdrey, Hughes, Ingold, Masterman, and Scott, J., 1937, 1252; Hughes, Ingold, and Whitfield, *Nature*, 1941, **147**, 206); an addition compound is formed, and if sufficient electron release is available to the carbon atom undergoing substitution, a rearrangement leading to retention of configuration occurs.



The addition compound is probably formed by hydrogen bonding. The valency angle of the hydrogen bond is 180°, but bending to 120° is known in the *o*-nitrophenols, and bending to a quasi-cyclic structure by electrostatic attraction between the bromine and the carbon atoms may occur as a preliminary to reaction.

From the literature, Hughes, Ingold, and Scott (*loc. cit.*) concluded that when phenylmethylcarbinol and α-phenylethyl bromide have the same sign of rotation they are of the same configuration; Levene and Rothen (*loc. cit.*) further concluded from an analysis of the rotatory dispersions of these compounds that phenyl-methyl-, -ethyl-, and -*n*-propyl-carbinols with the same sign of rotation have the same configuration, and similarly for the three bromides. Hence, for all three reactions retention of sign means retention of configuration.

At low temperatures, the retention of configuration in all three reactions, together with the formation of a white crystalline addition compound in the reaction with the ethyl carbinol, indicates that S_Ni predominates at such temperatures. This is superseded, with rising temperature, by replacement with inversion until –30°, –27·5°, and –17·5°, respectively, are reached for the three reactions, whereupon movement in the direction of retention occurs. Since this movement results in larger rotatory powers for α-phenyl-*n*-butyl bromide, Levene and Rothen concluded that the change is due, not to the commencement of racemisation, but to the coming into play of a second mechanism leading to retention and that " consequently the mechanisms (above) do not suffice . . . since, of the three only one proceeds with retention, whereas the present observations point to two mechanisms connected with retention."

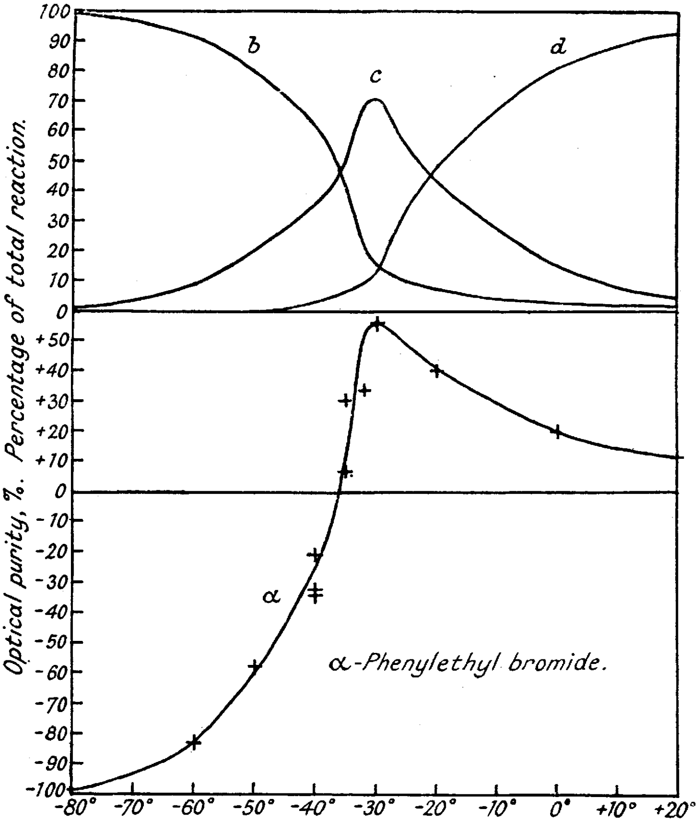
It is now shown that, on certain assumptions, these three mechanisms suffice to explain the form of the rotation–temperature curves.

Mechanism S_N2 is considered to result in complete inversion; for S_N1, 10% inversion is estimated as an approximate value in the light of the results of Hughes, Ingold, and Scott (*loc. cit.*). The intramolecular mechanism S_Ni is considered to give complete retention. This is supported, for the phenylalkylcarbinols, by the almost complete retention observed during the (intramolecular) Hofmann and Curtius rearrangements

$$CHMePh{\cdot}CO{\cdot}NH_2 \longrightarrow CHMePh{\cdot}NH_2 \text{ and } CHMePh{\cdot}CO{\cdot}N_3 \longrightarrow CHMePh{\cdot}NH_2$$

in which the radical CHMePh· migrates (Arcus and Kenyon, J., 1939, 916; Kenyon and Young, J., 1941, 263). Then, considering the reaction of one carbinol with hydrogen bromide at one temperature, the phenylalkyl bromide is assumed to result from a combination of the three mechanisms, there being no experimental evidence for the existence of further mechanisms, applicable to the reaction conditions, of substitution of OH by Br. Since each mechanism has a characteristic optical result, it should be possible to determine, from the optical purity of the bromide, the percentage of the total reaction due to each mechanism. The bromide isolated was the product of the completed reaction, and hence these percentages refer to the reaction as a whole. The composition of the reaction medium changes as the reaction proceeds and the relative importance of the mechanisms may vary with time during the reaction; this aspect, however, is not discussed, and no assumptions are made about it. The percentages deduced are averages over the whole reaction period and their variations with changes in temperature and structure are described.

FIG. 1.



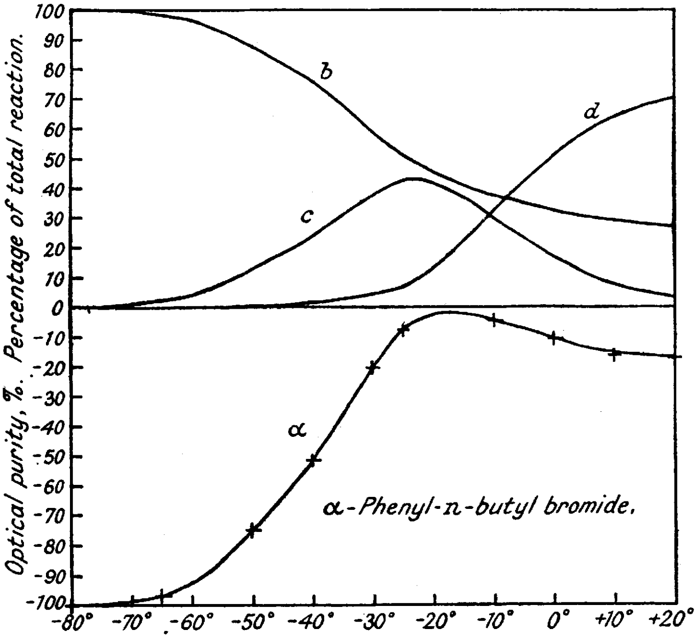
Finally, the assumption was made that the plot against temperature of the participation of any mechanism in the total reaction would, in general, be a distribution curve diminishing in a sigmoid curve on either side of a maximum at a certain temperature. (If one mechanism were to gain total control of the reaction above or below a certain temperature, then its maximum would be extended as a straight line over the range of total control.) Such a distribution curve represents the variation with temperature of the probability (the average probability over the whole reaction period) that a molecule of carbinol, when several mechanisms of reaction are possible to it, will react by one given mechanism.

The rotations of optically pure bromides were taken from the graphs of Levene and Rothen, small extrapolations being necessary for the methyl and the ethyl carbinol. The experimental rotations were then converted from $[M]_{5780}$ to percentage optical purity, and smooth curves were drawn through the resulting values; then, if b, c, and d are the percentages of the total reaction proceeding by mechanisms S_Ni, S_N2, and S_N1, respectively, and α is the percentage optical purity of the product, at a given temperature,

$$b + c + d = 100 \text{ and } \alpha = -(b - c - 0{\cdot}1d)$$

A third relation is supplied by the assumption that the curves b, c, and d are distribution curves which are always positive and have only one point of inflection between successive stationary points. It was then found by successive trial that if these conditions were to be satisfied the range of permissible variation is small. Representative values of b, c, and d have been calculated for 16 values of α for each bromide, and these values for α-phenyl-ethyl and -n-butyl bromide are plotted in Figs. 1 and 2, respectively.

FIG. 2.



Thus the three mechanisms S_Ni, S_N2, and S_N1, leading respectively to retention, inversion, and to much racemisation with some inversion (estimated at 10%), when their participations in the total reaction vary according to the distribution curves b, c, and d, yield bromides whose optical purity varies with temperature according to the experimental curves.

S_Ni approaches or attains a maximum at −80°, indicating that formation of the addition complex is favoured at low temperatures. S_N1 tends towards a maximum at above +20°, showing ionic fission of $R{\cdot}OH_2^{\oplus}$ to be predominant at higher temperatures. S_N2 is at a maximum at intermediate temperatures, approximately −25° to −30°, which are presumably low enough to check ionisation and high enough to diminish the addition of hydrogen bromide which yields the complex of S_Ni.

In view of the assumptions made, the distribution curves are not numerically exact, but the following relationships may be noted. The " domain " of each mechanism between the temperatures considered, −80° to +20°, can be represented by the area between its distribution curve and the axis of temperature; these areas, expressed as % of the total area, are :

Carbinol :	CHMePh·OH.	CHEtPh·OH.	CHPr^{a}Ph·OH.
S_Ni	41·3	43·2	62·4
S_N2	23·6	22·1	17·6
S_N1	35·2	34·6	20·0

With increasing electron release by the methyl, ethyl, and *n*-propyl groups, the domain of S_N2 diminishes, that of S_Ni is markedly increased, and that of S_N1 decreases. The last two mechanisms are both known to be promoted by electron release by groups attached to the carbon atom undergoing substitution (Hughes, Ingold, *et al., locc. cit.*), and it is inferred that when, as here, conditions permit these two mechanisms to compete, S_Ni is promoted more strongly by electron release than is S_N1. This can be seen in the region 0° to +20° in Figs. 1 and 2; here S_N2 is of relatively little importance and, with increasing electron release, S_Ni competes successfully with S_N1. This situation is entirely compatible with the known effect of electron release in promoting S_N1 over S_N2 when these two mechanisms compete in the absence of S_Ni.

The author wishes to thank Drs. J. Kenyon, M. P. Balfe, and J. W. Smith for reading the MS. of this paper.

BATTERSEA POLYTECHNIC, LONDON, S.W.11. [*Received, December* 14*th*, 1943.]