362. *Aliphatic Substitution and the Walden Inversion. Part I.*

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In most of the numerous theories proposed in explanation of the Walden inversion, it is assumed that inversion takes place when the entrant group attaches itself to the side of the asymmetric carbon atom opposite that occupied by the group to be expelled (Werner, *Ber.*, 1911, **44**, 873; *Annalen*, 1912, **386**, 70; Lowry, Conseil de Chimie Solvay, 1925, 40; Meisenheimer, *Annalen*, 1927, **456**, 126; and others). The racemisation of organic halides by halogen ions was explained by Holmberg (*J. pr. Chem.*, 1913, **88**, 580) as caused by substitution accompanied by inversion. These views have recently been given a more detailed physical foundation by Polanyi and by Olsen (Meer and Polanyi, *Z. physikal. Chem.*, 1932, *B*, **19**, 164; Bergmann, Polanyi, and Szabo, *ibid.*, 1933, *B*, **20**, 161; Olson, *J. Chem. Physics*, 1933, **1**, 418; Olson and Long, *J. Amer. Chem. Soc.*, 1934, **56**, 1294). The main conclusion is that the negative ion approaches the carbon–halogen dipole at its positive end, a process leading to an inverted product, or if the reaction is reversible, as in the special case of substitution by like ions, to an ultimately racemic product.

Olson and Long (*loc. cit.*), from an analysis of their data for the set of simultaneous and consecutive reactions occurring when *l*-bromosuccinic acid and chloride ion interact, have concluded that in these reactions replacement of one halogen by the other does not take place without inversion.

A very direct experimental test of the hypothesis that stereochemical inversion occurs when, and only when, substitution takes place, is possible by means of a radioactive halogen isotope. It is only necessary to compare the velocity of halogen interchange between a suitable organic halide and the corresponding isotopic halogen ion with the speed of racemisation of the optically active molecule under identical conditions. The racemisation has, in principle, the advantage over an actual inversion, that it is not necessary to know the relationship between sign of rotation and configuration, or the actual rotatory power of the pure isomeride. We have therefore studied (*a*) the interchange reaction of *dl-sec.*-octyl iodide with sodium iodide in acetone solution, and (*b*) the racemisation of the *d*-iodide.

Measurement of the interchange reaction is possible by means of the radioactive isotope of iodine. Sodium iodide containing a small proportion of the isotopic iodide ion (distinguished by an asterisk) is prepared by neutron bombardment. The extent of the substitution reaction $RI + NaI^* \rightleftharpoons RI^* + NaI$ is determined at the end of a period of reaction by measuring the relative intensities of radioactivity of the RI* produced and of the NaI* remaining.

The total amounts of organic iodide and of sodium iodide remain constant during the reaction, and so therefore do the state of ionisation of the sodium iodide and all "medium effects." † Without restricting ourselves to any special mechanism of the chemical reaction, we can formulate a comparison by experiment of the rates of (*a*) and (*b*) on the following statistical basis.

In a particular solution, after a period of reaction t secs., the composition is specified by the following number of mols. of each solute species: $RI^* = x$; $RI = A - x$; $NaI^* = B\beta - x$; $NaI = B(1 - \beta) + x$; $d\text{-}RI = A\delta - y$; $l\text{-}RI = A(1 - \delta) + y$. Here A is the total amount of organic iodide, B that of sodium iodide, δ is the fraction of organic iodide in the *d*-form, and β the fraction of sodium iodide in the isotopic form, all at $t = 0$ when also

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† There are, of course, small energy changes during the reaction arising in (*a*) from the zero-point energy difference of the isotopic molecules, and in (*b*) from the collisions of two *d*-RI molecules. The effect of the first of these upon the reaction rate is certainly infinitesimal. The effect of the second could not be appreciable unless the intermediate activated state for substitution involved a collision complex containing more than one molecule of RI, which is improbable; in any case the constancy of the first-order velocity constants through each polarimeter experiment shows that no detectable effect arises from the different potential energy surfaces of pairs of RI molecules, of similar or of dissimilar configuration, in collision. It follows that it is legitimate to compare the isotope exchange in the racemic solution with the racemisation of the optically active solution.

$x = y = 0$. The symbols RI and RI* without prefix stand for organic iodide or isotopic iodide molecules irrespective of *d*- or *l*-configuration.

In the solution considered, let N_s be the total rate of the substitution reaction (the four types which occur simultaneously being *added*), and N_i the total rate of stereochemical inversion, in both directions, in the units mols./sec. N_s and N_i are constant rates.

For the exchange reaction, we have

$$\frac{dx}{dt} = N_s\left\{1 - \frac{x}{B\beta}\left(\frac{A+B}{A}\right)\right\}\beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

which follows, after algebraic simplification, by multiplying the total number of mols. reacting by the probability that any unit act of substitution chosen at random will be of the type RI $\longrightarrow$ RI*, and subtracting the corresponding product for the type RI* $\longrightarrow$ RI. Integration of (1) gives

$$N_s = \frac{1}{t}\cdot\frac{AB}{A+B}\log_e\frac{A}{A - x(A+B)/B\beta} \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Experimentally the quantity $x/B\beta$ is measured by the ratio γ of the activity (*i.e.*, the atoms disintegrating per mol. in unit time) of the organic iodide to that of the sodium iodide. We have

$$x/B\beta = \gamma/(\gamma + B/A) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and by substitution of (3) into (2)

$$N_s = \frac{1}{t}\cdot\frac{AB}{A+B}\log_e\frac{1+\gamma A/B}{1-\gamma} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

For the inversion we have, by analogous consideration of the probabilities of a unit act of inversion being in the direction *d*-RI $\longrightarrow$ *l*-RI or the reverse :

$$dy/dt = N_i\,.\,2\{(\delta - \tfrac{1}{2}) - y/A\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Since the angle of rotation α is proportional to the quantity $\{(\delta - \frac{1}{2}) - y/A\}$, integration of (5) and substitution of α_0 and α gives

$$N_i = (A/2t)\log_e \alpha_0/\alpha \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

A decision whether substitution and inversion are the same process can be reached by determining N_s and N_i from measurements of α and γ in solutions of the same concentration of total organic iodide and total sodium iodide.

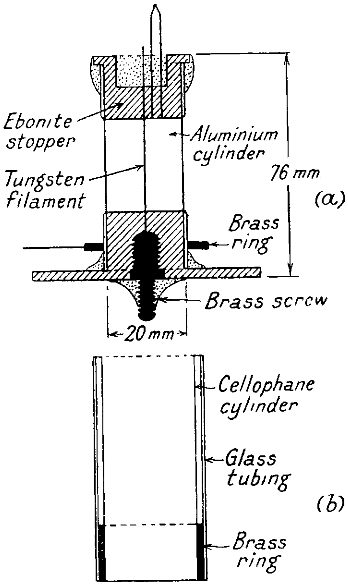
EXPERIMENTAL.

(a) *The Exchange Reaction* (F. Juliusburger, B. Topley, and J. Weiss).—The sodium iodide, *dl-sec.*-octyl iodide, and acetone were prepared and purified as described under (*b*) below. Weighed quantities of sodium iodide were sealed up in glass tubes and sunk in a large paraffin block close to a radon–beryllium neutron source of about 150 millicuries strength. The activated sodium iodide was dissolved in a known volume of acetone kept at 30°, and a measured volume of the racemic iodide added. The reaction was stopped after a suitable interval by addition of water and crushed ice. The racemic iodide was extracted from the resulting emulsion by shaking with carbon tetrachloride, and the aqueous solution of sodium iodide separated from the heavy layer. The aqueous solution was washed once with carbon tetrachloride to remove residual traces of racemic iodide, and the carbon tetrachloride solution three times with ice-cold distilled water to remove traces of sodium iodide. The iodine was precipitated as silver iodide from both solutions (in the case of the carbon tetrachloride solution, by means of boiling alcoholic silver nitrate followed by heating with aqueous silver nitrate). It was not necessary that the precipitation should be quantitatively complete. The physical condition of the silver iodide from the organic iodide differs from that of the precipitate from the aqueous solution, even after it has been washed with alcohol and ether and dried in an oven at 200° ; but by heating nearly to the m.p. and grinding the sintered product in an agate mortar, the two specimens can be reduced to the same physical form in about 10 mins. For the comparative measurements of their radioactivities, this precaution is essential.

The activities of standard samples of the two silver iodide precipitates were determined with a Geiger–Müller counter, operating a telephone counter *via* a two-stage amplifier and thyratron set up in the usual form of circuit. The construction of the discharge chamber used is shown in Fig. 1 (*a*). A piece of seamless aluminium tubing is turned down for a length of 40 mm. in the middle to a wall thickness of 0·1 mm., and polished internally. Two ebonite stoppers fit closely into the ends; their purpose is clear from the diagram. A smooth tungsten wire 0·040 mm. in diameter is soldered on to a brass screw at its lower end. It is stretched between the stoppers and held by a highly insulating wax (rosin and beeswax). The same wax makes the cylinder gas-tight. The wax is shown by dotted shading, and the ebonite parts by line shading. The discharge chamber is dried out by evacuation over-night, and filled with dry air at about 80 mm. pressure of mercury. Electrical contact with the cylinder is made through a brass ring round the lower section of the aluminium tube; the ring also acts as the support for the container of the active material.

It is necessary to expose the discharge chamber to the active material in a geometrically reproducible manner. The arrangement used to ensure this is shown in section in Fig. 1 (*b*). The container for the silver iodide consists of an outer tube of soda-glass and an inner cylinder of thin cellophane, separated by a brass ring.

FIG. 1.



(a) *Geiger–Müller counter discharge chamber.*
(b) *Cylindrical container for radio-active substances.*

The silver iodide, after the treatment described above, was poured into the annular space of the container, and packed down by means of a closely fitting brass plunger of semicircular section. The uniformity of the "packing" was checked several times by weighing the silver iodide filling the container up to a measured height, and found to be satisfactory. For comparison of the activity, the containers were filled as nearly as possible up to the same height; the deviations were kept below ± 10% and were allowed for by assuming proportionality between height and the number of pulses per minute in the counter; this was found by special tests to be justified. The number of pulses recorded was corrected for the background measured with the empty container round the discharge chamber, and, by the usual quadratic formula, for the proportion of coincident impulses. The electrical steadiness of the counter was checked from time to time during the measurements by a standard consisting of one of the containers filled with potassium chloride; the sensitivity of the counter was usually such that the radioactivity of this salt gave 170 impulses per min. The activities of the two silver iodide preparations were measured one after the other, and reduced to the same time by means of the known half-life period of radio-iodine (24 mins.). The ratio γ of these activities is also the ratio of the molar activities of the organic iodide and sodium iodide at the end of the period of reaction.

The details of the five experiments at 30·0° are given in Table I (the results of Expt. 5, at 30·9°, have been corrected to 30·0° by means of the temperature coefficient given in the next section). The concentration A of RI was in each experiment 0·1377M. The reaction rates N_s given in col. 4 are calculated by equation (4). B is the molar concentration of sodium iodide.

TABLE I.

Expt.	Temp.	B.	$N_s \times 10^5$.	Expt.	Temp.	B.	$N_s \times 10^5$.
1	30·0°	0·1706	3·20	4	30·0°	0·1889	3·49
2	,,	0·2053	3·82	5	(30·9)	0·1668	(3·74)
3	,,	0·1634	2·47		30·0	,,	3·43

(b) *The Racemisation* (E. D. Hughes and S. Masterman).—The rate of racemisation of *d-sec.*-octyl iodide has not hitherto been measured, but the analogous reactions of *d-sec.*-amyl iodide and *d-sec.*-butyl iodide with sodium iodide in acetone solution have been studied by Bergmann, Polanyi, and Szabo (*loc. cit.*). Since the sodium iodide concentration does not change during the racemisation, the reaction is reduced to one of the first order. These authors found that the first-order constants increase with the sodium iodide concentration, but rather less than linearly, and our results confirm this. For comparison with other data on similar reactions, we have made measurements at four different temperatures, and have recorded the results (Table II) as second-order velocity constants calculated from the expression $k = 2{\cdot}303/2Bt\,.\,\log_{10}\alpha_0/\alpha$, where α_0 and α are respectively the rotations initially and after t secs.' reaction.

TABLE II.

Expt.	Temp.	*B*.	$k \times 10^3$.	Expt.	Temp.	*B*.	$k \times 10^3$.
6	10·0°	0·163	0·152	8	29·85°	0·182	1·26
7	19·85	0·163	0·454	9	39·80	0·161	3·21

The plot of log k against $1/T$ is a straight line, giving $\log_e k = 22{\cdot}84 - 17{,}800/RT$. Comparison of these results with those of Bergmann, Polanyi, and Szabo under similar conditions gives the approximate relative rates : *sec.*-amyl : *sec.*-octyl : *sec.*-butyl (iodides) = 1·1 : 1·0 : 1·15. The direction of such small velocity differences need not be discussed here, but it may be noted that the close agreement accords with the general principle that alkyl substitution has a negligible effect when the substituent is removed by three or more carbon atoms from the seat of the reaction.

Preparation of sec.*-Octyl Iodides.*—*r-sec.*-Octyl alcohol was saturated with dry hydrogen iodide at 0° and kept at this temperature for 15 hrs. The product, which had separated into two layers, was extracted with ether, washed successively with water, dilute sodium bicarbonate, sodium bisulphite, and water, dried over anhydrous sodium sulphate, and distilled. Two fractions were collected : (1) b.p. 77—94°/16 mm., (2) b.p. 94—95°/16 mm. Fraction (1), which contained unchanged alcohol, was again saturated with hydrogen iodide and treated as above. The combined iodide fractions were redistilled before use; b.p. 95°/16 mm.; yield 65%.

d-sec.-Octyl iodide was prepared from *l-sec.*-octyl alcohol (" Organic Syntheses," Vol. 6, p. 68) as described above (compare Pickard and Kenyon, J., 1911, **99**, 45). The alcohol used had $[\alpha]_D^{21^\circ}$ − 8·8°; the iodide obtained had $[\alpha]_D^{20^\circ}$ + 38·5°.

Purification of Materials.—Acetone was purified as described by Conant and Kirner (*J. Amer. Chem. Soc.*, 1924, **46**, 246). Sodium iodide was recrystallised and dried.

TABLE III.

Expt. 6. 10·0°.
$A = 0{\cdot}118$; $B = 0{\cdot}163$.

t.	α.	$N_i \times 10^6$.
0	2·36°	—
633	2·29	2·79
1523	2·19	2·89
1945	2·14	2·95
2718	2·05	3·05
4214	1·92	2·89
5378	1·80	2·97
7163	1·65	2·93
9231	1·51	2·83
13332	1·18	3·05
	Average	2·93

Expt. 7. 19·85°.
$A = 0{\cdot}0897$; $B = 0{\cdot}163$.

t.	α.	$N_i \times 10^6$.
0	1·80°	—
345	1·71	6·67
702	1·62	6·73
1368	1·47	6·64
2071	1·32	6·68
2904	1·19	6·39
4824	0·87	6·74
6344	0·69	6·77
7564	0·59	6·60
9794	0·42	6·65
	Average	6·65

Expt. 8. 29·85°.
$A = 0{\cdot}0764$; $B = 0{\cdot}182$.

t.	α.	$N_i \times 10^5$.
0	1·48°	—
248	1·32	1·76
620	1·11	1·77
925	0·99	1·64
1553	0·72	1·77
2093	0·57	1·74
2721	0·42	1·77
3227	0·34	1·74
5360	0·12	1·80
	Average	1·75

Expt. 9. 39·8°.
$A = 0{\cdot}130$; $B = 0{\cdot}161$.

t.	α.	$N_i \times 10^5$.
0	1·41°	—
299	1·05	6·41
421	0·89	7·07
549	0·80	6·71
747	0·65	6·73
872	0·56	6·87
1072	0·46	6·79
1186	0·41	6·75
1436	0·31	6·85
	Average	6·78

Expt. 10. 29·6°.
$A = 0{\cdot}0819$; $B = 0{\cdot}102$.

t.	α.	$N_i \times 10^5$.
0	1·88°	—
357	1·70	1·16
835	1·48	1·17
1211	1·33	1·17
1692	1·17	1·14
2129	1·03	1·16
2634	0·90	1·15
3006	0·80	1·15
3657	0·67	1·16
4565	0·52	1·16
5250	0·43	1·16
6334	0·32	1·15
9055	0·15	1·15
	Average	1·16

Expt. 11. 29·5°.
$A = 0{\cdot}0790$; $B = 0{\cdot}106$.

t.	α.	$N_i \times 10^5$.
0	1·51°	—
278	1·40	1·08
583	1·28	1·12
762	1·21	1·14
1018	1·12	1·17
1443	0·99	1·14
1806	0·90	1·13
2490	0·73	1·14
3493	0·52	1·15
4866	0·35	1·17
5383	0·32	1·13
6412	0·24	1·13
7987	0·15	1·03
	Average	1·13

Method.—Weighed quantities of the reagents were dissolved separately in acetone, and the solutions made up to volume at the temperature of the experiment. Equal volumes were then mixed, and the mixture introduced quickly into a jacketed 2-dm. polarimeter tube of the usual type maintained within ± 0·05° of the working temperature.

In Table III, N_i is the total rate of inversion (in mols./l./sec.) calculated by means of equation (6).

DISCUSSION.

The concentrations actually used in the exchange measurements were not quite the same as those in the racemisation measurements, and before collation of the absolute rates they have to be put upon a common basis. The assumption that the reaction is of the first order with respect to the octyl iodide and that no " medium effect " need be allowed for at the small mol.-fraction of octyl iodide ($< 0{\cdot}01$) presents no difficulty. The work of Bergmann, Polanyi, and Szabo (*loc. cit.*) shows that the rate increases with sodium iodide concentration less rapidly than with the first power; and since the absolute rates in their measurements and ours are almost identical, we can safely assume the same dependence upon sodium iodide concentration. The data in their paper are amplified by Szabo (*Diss.*, Berlin, 1933); and we find that the results for *sec.*-butyl iodide at 30·0° are correctly reproduced in the range of sodium iodide concentration 0·1—0·3*M* by the expression $k = k'\{B/0{\cdot}16\}^{0{\cdot}78}$, where k is the first-order constant for a concentration B of sodium iodide, and k' is the constant for $B = 0{\cdot}1600$.

In Table IV, the relevant experimental data for 30·0° are collected; both N_s and N_i have been reduced by the above expression to a sodium iodide concentration of 0·1600*M*. Also the values of N_i have been reduced to the *sec.*-octyl iodide concentration used in all the substitution experiments, *viz.*, 0·1377*M*. The fractions of a degree by which the experimental temperatures differed from 30·00° have been allowed for by means of the measured temperature coefficient.

TABLE IV.

	$N_s \times 10^5$.					$N_i \times 10^5$.		
Expt.	1.	2.	3.	4.	5.	10.	11.	8.
	3·04	3·15	2·43	3·06	3·32	2·88	2·86	2·89
	Average $N_s = 3{\cdot}00 \pm 0{\cdot}25$					Average $N_i = 2{\cdot}88 \pm 0{\cdot}03$		

The absolute rates N_s and N_i agree to within 4%, which is within the experimental uncertainty of the measurements with the radioactive indicator. It follows as a necessary conclusion that in this reaction the inversion is directly caused by the substitution.

SUMMARY.

By means of the radioactive isotope of iodine, the velocity in acetone solution of the substitution of iodine for iodine in *sec.*-octyl iodide has been measured, and also the velocity of racemisation of *d-sec.*-octyl iodide by sodium iodide under similar conditions. The absolute rates of the two processes are the same within the experimental error of the measurements of the radioactivity (10%). The result confirms in the most direct way possible the causal connexion between aliphatic substitution and optical inversion, in reactions of this type.

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