CCCXXIV.—*The Walden Inversion.*

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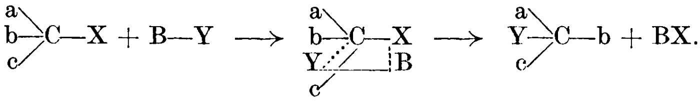
THE discovery by Walden in 1896 of the stereochemical inversion to which his name is now given raised a problem which still remains unsolved. Since the optical isomerides always possess the same chemical properties, the same energy content, the same solubility, etc., and the corresponding reactions consequently have the same affinities, there is no apparent reason why, for instance, silver oxide and water should transform *l*-chlorosuccinic acid into *l*-malic acid, whilst potassium hydroxide converts it into *d*-malic acid.

Also, although Senter (J., 1915, **107**, 638 *et seq.*) has shown that the nature of the solvent can influence the inversion, and Holmberg (*e.g.*, *J. pr. Chem.*, 1913, **87**, 456; **88**, 553) has demonstrated that it is sensitive to the presence of salts and to changes in concentration of the reagents, yet no mechanism has hitherto been suggested which is capable of explaining all the results or of predicting the occurrence of an inversion.

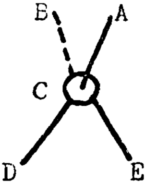
Holmberg (*Ber.*, 1926, **59**, 125; *Svensk Kem. Tidskr.*, 1927, **39**, 1) has suggested a theory according to which the determining factor for a Walden inversion is to be found in what he has termed " the reaction distance," *i.e.*, the distance between the two reacting parts of the molecule or ion acting upon the optically active compound, *e.g.*, the distance between H and OH in a molecule of water or, in general, between B and Y in the reacting molecule B—Y in the reaction :

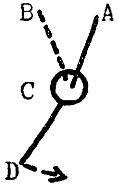


$$\begin{array}{l}a\\b{>}C{-}X\\c\end{array} + B{-}Y \longrightarrow \begin{array}{l}a\\b{>}C{-}X\\Y\cdots\;\vert B\\c\end{array} \longrightarrow \begin{array}{l}a\\Y{>}C{-}b\\c\end{array} + BX.$$

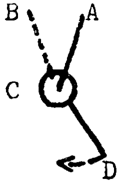
If the distance B—Y is greater than the distance C—X, then inversion must take place, but if the latter distance is the greater, no inversion will occur. Since, however, the ratio of these two distances must be the same so long as we are considering the same reaction, this hypothesis (unless additional assumptions are made) is inconsistent with the influence exercised upon the inversion by the various factors mentioned above.

By means of the following conception, it is possible to explain the phenomenon and to calculate the fraction n of the reaction product which has a steric configuration agreeing with that of the initial active substance. Let C represent an asymmetric carbon





(I.)



(II.)

atom, and A, B, D, and E the atoms or radicals linked to it. C, D, and E are supposed to lie in the plane of the paper, with A above and B below this plane. If now the atom E is split off, the configuration (I) is formed, and the remaining radicals are assumed to oscillate as the result of this disturbance. For simplicity, I shall consider the oscillation of only one radical, say D, between the positions occupied in (I) and (II). Whether inversion takes place or not will now depend upon whether the atom, ion, or radical X which enters the molecule instead of E is able to do so while D is still upon its original side of the plane ACB, as in (I), or has passed it, as in (II). (The above representation is purely diagrammatic and makes no assumption as to the actual distribution of the four directed valency sources, but merely postulates a disturbance among them when one is temporarily out of action.)

From these conceptions we can derive a quantitative theory of the Walden inversion based upon the time of oscillation θ of the molecule, the concentrations, and the activity conditions in the solution. Of these factors, at present we know nothing of the time of oscillation and very little about the activity coefficients in such high concentrations as are usually employed in researches on the subject. Moreover, most of the experiments bearing on this inversion were carried out under conditions in which temperature and concentration were varied during the experiment in such a way as to preclude any calculation of the result, but Holmberg's experiments upon the reaction between xanthogenates and active halogenosuccinic acids (*loc. cit.*) are so precise that it is possible to apply to them the equation deduced below.

We assume that the fraction n of the reaction product which retains its original configuration is proportional to the probability that the oscillating molecule reacts with the entering ion X while still in configuration (I); this probability will evidently increase with the length of the time of oscillation and with the speed of the reaction between the single oscillating molecule and X.

Introducing the kinetic activity factor of Brönsted (*Z. physikal. Chem.*, 1922, **102**, 169) in the expression for the reaction velocity, we get the equation $n = kc_{\mathrm{X}}f_1f_2\theta/f_{1,2}$ where c_{X} denotes the mean concentration of X at the beginning and end of the reaction, and f_1, f_2, and $f_{1,2}$ respectively denote the activity coefficients of the oscillating molecule, of X, and of the compound resulting from the union of these two. We can obtain the same equation from Brönsted's formula for the velocity of a bimolecular reaction, *viz.*, $-dc_1/dt = k'c_1c_2f_1f_2/f_{1,2}$; for if we replace dt by $\theta/4$ and let subscripts 1 and X refer to the oscillating molecule and to X respectively, we have

$$n = dc_1/c_1 = k'c_{\mathrm{X}}(f_1f_{\mathrm{X}}/f_{1,\mathrm{X}})(\theta/4) \quad . \quad . \quad . \quad . \quad (a)$$

If, moreover, for lack of knowledge, we assume that θ depends only upon the nature of the oscillating molecule and is independent of the potential in the solution, θ can be included in the constant and the equation takes the form

$$n = kc_{\mathrm{X}}f_1f_{\mathrm{X}}/f_{1,\mathrm{X}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (b)$$

We shall now test the application of equation (*b*) to Holmberg's experiments, but quantitative agreement with his results cannot be expected, owing to the nature of our approximations and to our lack of precise data relating to activity coefficients.

The first reaction to be considered is that between potassium, sodium, calcium, barium, and strontium salts of *l*-bromosuccinic acid and alkali xanthogenates $\bar{\mathrm{O}}\cdot\mathrm{CO}\cdot\mathrm{CH_2}\cdot\mathrm{CHBr}\cdot\mathrm{CO}\cdot\bar{\mathrm{O}} + \mathrm{CS(OEt)}\cdot\bar{\mathrm{S}} \longrightarrow \bar{\mathrm{O}}\cdot\mathrm{CO}\cdot\mathrm{CH_2}\cdot\mathrm{CH[S\cdot CS(OEt)]}\cdot\mathrm{CO}\cdot\bar{\mathrm{O}} + \bar{\mathrm{Br}}$, which is assumed to take place in two steps, *viz.*, (1) a spontaneous splitting off of the bromine atom : $\bar{\mathrm{O}}\cdot\mathrm{CO}\cdot\mathrm{CH_2}\cdot\mathrm{CHBr}\cdot\mathrm{CO}\cdot\bar{\mathrm{O}} \longrightarrow \bar{\mathrm{O}}\cdot\mathrm{CO}\cdot\mathrm{CH_2}\cdot\overset{+}{\mathrm{C}}\mathrm{H}\cdot\mathrm{CO}\cdot\bar{\mathrm{O}} + \bar{\mathrm{Br}}$, and (2) an addition of the xanthogenate ion (denoted by X) :

$$\bar{\mathrm{O}}\cdot\mathrm{CO}\cdot\mathrm{CH_2}\cdot\overset{+}{\mathrm{C}}\mathrm{H}\cdot\mathrm{CO}\cdot\bar{\mathrm{O}} + \bar{\mathrm{X}} \longrightarrow \bar{\mathrm{O}}\cdot\mathrm{CO}\cdot\mathrm{CH_2}\cdot\mathrm{CHX}\cdot\mathrm{CO}\cdot\bar{\mathrm{O}}$$

The activity coefficient f_1 for the amphoteric ion $\bar{\mathrm{O}}\cdot\mathrm{CO}\cdot\mathrm{CH_2}\cdot\overset{+}{\mathrm{C}}\mathrm{H}\cdot\mathrm{CO}\cdot\bar{\mathrm{O}}$, with an excess of one negative electric charge, is assumed to be approximately equal to that of an ordinary univalent ion; and for both f_1 and f_X we shall use the values of a commoner uni-univalent salt, silver nitrate being chosen for this purpose since its values are known for high ionic strengths (Lewis and Randall, "Thermodynamics," p. 363), and its structure is not so simple as that of the alkali chlorides, which are therefore less comparable with the larger ions involved here.

For the activity coefficient $f_{1,X}$ of the bivalent ion

$$\bar{\mathrm{O}}\cdot\mathrm{CO}\cdot\mathrm{CH_2}\cdot\mathrm{CHX}\cdot\mathrm{CO}\cdot\bar{\mathrm{O}},$$

I have chosen the values for magnesium sulphate in pure solutions of the same ionic strength (see Rørdam, "Studies on Activity," Copenhagen, 1925) up to $0{\cdot}5M$-solutions, and values for higher concentrations have been calculated from the freezing-point data of Loomis (Landolt–Börnstein, "Tabellen," 5th edition, 3070) by use of the equation $\log f = -0{\cdot}4343\left[(1-\phi)+\int_0^c \frac{1-\phi}{c}dc\right]$, f being the activity coefficient, c the concentration, and $\phi = i/2$ ($i =$ van 't Hoff's factor). The data thus used are collected in Table I, where the ionic strength μ is added. The assumption that the activity coefficient of a given electrolyte is the same in all

TABLE I.

$MgSO_4$ (mol./l.).	f.	μ.	$MgSO_4$ (mol./l.).	f.	μ.
0·1	0·212	0·4	1·2	0·077	4·8
0·2	0·152	0·8	1·4	0·073	5·6
0·4	0·114	1·6	1·6	0·071	6·4
0·6	0·102	2·4	1·8	0·071	7·2
0·8	0·092	3·2	2·0	0·073	8·0
1·0	0·084	4·0			

solutions of the same ionic strength (Lewis and Randall, *J. Amer. Chem. Soc.*, 1921, **43**, 1112) is well known to be strictly valid only in dilute solutions, but of necessity we apply it here up to greater concentrations.

In Table II all Holmberg's data relevant to these experiments are collected. For the calculation of *n* from equation (*b*), the empirical value $k = 200$ has been employed. (For experiments where the ionic strength exceeds 6, no calculations have been made, the basis for the calculation of the activity coefficients here seeming too uncertain.) The third column of the table contains the percentage of dextrorotatory xanthogeno-succinic acid found by Holmberg in the partly active acid resulting from the experiments. If the theory now propounded is valid, it affords a means whereby to decide which of the two possible optical isomerides that may be formed possesses the same steric configuration as the initial active component in a reaction leading to a Walden inversion. Hence we may conclude from the calculations that *d*-xanthogenosuccinic acid and *l*-bromosuccinic acid have corresponding configurations.

TABLE II.

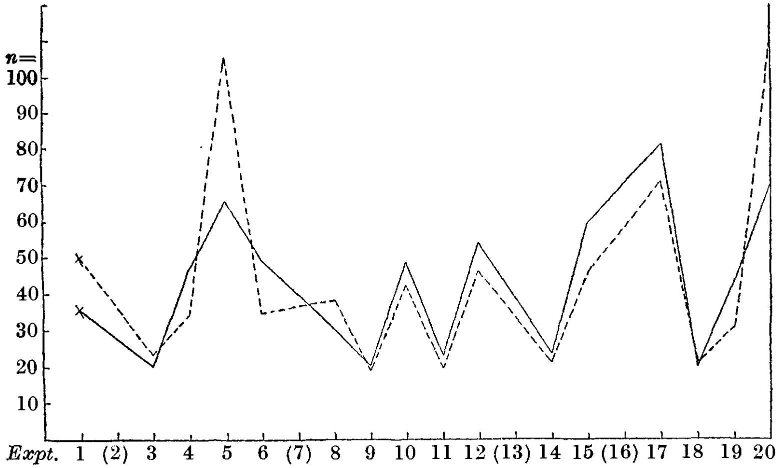
(Bs = Bromosuccinate radical; X = Xanthogenate radical.)

No.	Composition of mixture.	% *d*-Acid, found.	μ.	$f_1 = f_X$.	$f_{1,X}$.	*n*, calc.
1.	0·51 Na_2Bs; 0·61 NaX	35·5	2·14	0·273	0·103	51
2.	,, ,, ,, ,, ; 5·0 NaBr	44·2	7·14	0·080	0·072	—
3.	0·12 ,, 0·14 ,,	20·1	0·50	0·526	0·190	23
4.	0·8 ,, 0·75 KX	46·5	3·15	0·202	0·090	34
5.	0·5 ,, 1·1 ,,	67·1	2·60	0·245	0·100	106
6.	0·75 K_2Bs; 0·96 ,, ; 1·6 KBr	49·2	4·80	0·150	0·077	35
7.	,, ,, ,, ,, ; 4·0 ,,	50·0	7·21	0·080	0·072	—
8.	0·11 ,, 0·18 ,,	30·3	0·51	0·526	0·190	38
9.	0·08 CaBs; 0·10 NaX	20·1	0·42	0·552	0·205	19
10.	0·4 ,, 0·5 KX	48·4	2·10	0·273	0·103	42
11.	0·08 ,, 0·10 ,,	22·8	0·42	0·552	0·205	19
12.	0·8 BaBs; 1·0 ,,	53·8	4·20	0·175	0·080	46
13.	,, ,, ,, ,, ; 0·8 $BaBr_2$	63·8	6·60	0·100	0·071	—
14.	0·10 ,, 0·12 ,,	23·3	0·52	0·526	0·190	21
15.	0·8 SrBs; 1·0 ,,	59·3	4·20	0·175	0·080	46
16.	,, ,, ,, ,, ; 0·8 $SrBr_2$	69·4	6·60	0·100	0·071	—
17.	,, ,, 1·7 ,,	81·7	4·90	0·145	0·077	71
18.	0·10 ,, 0·12 ,,	20·1	0·52	0·526	0·190	21
19.	0·27 ,, 0·29 ,,	44·2	1·37	0·340	0·120	31
20.	,, ,, 0·87 ,,	70·4	1·95	0·280	0·105	110

The results shown in Table II are represented graphically in Fig. 1, the calculated (broken line) and experimental (full line) values of *n* being given in connexion with the series number of the experiment. These curves show that variation in experimental values is closely related to that in the calculated values. In view of the fact that the individual peculiarities of the activity coefficients and the deviations in the "rule of ionic strength" are both very marked at the high concentrations used, the agreement seems fairly good.

In spite of the accuracy of Holmberg's experiments, it is possible that the percentages found by him do not agree exactly with the total amount formed in the reaction, for the product was obtained by spontaneous crystallisation from the more or less concentrated salt solutions, and in most cases the solubilities of racemic and corresponding active substances are different in, and perhaps also unequally influenced by, different salt concentrations.

FIG. 1.



In future experimental researches in this field, it would be of interest to avoid uncertainty of this sort by determining the composition optically, without isolation of the reaction product; and in order to test the validity of the present theory it will be necessary to use reaction conditions such that the activity coefficients can be accurately calculated. The theory suggests possibilities for planning experiments which may throw more light upon the Walden inversion. If valid, it will account for the influence of the concentrations of reagents and of salts present in the solution, as well as of the nature of the solvent.

The literature affords only one other series of experiments suitable for testing the present theory, *viz.*, those of Holmberg (*Arkiv. Kemi, Min. Geol.*, 1915, **6**, 1) on the reaction between hydrosulphides and salts of *l*-bromosuccinic acid, which is assumed to occur in two stages exactly like the foregoing reaction. As the SH′ ion is considerably less complicated in structure than the xanthogenate ion, its activity coefficient is more appropriately represented by that of sodium nitrate than that of silver nitrate; the necessary values are only available up to 0·5*M* (Rørdam, *op. cit.*), and values for higher concentrations are therefore obtained by plotting these values by the side of those already used for silver nitrate and extrapolating the curve so that it remains parallel to the curve for silver nitrate.

The value used for *k* is 200 as before. The agreement between calculated and observed values is not so good in this case, perhaps owing to the less definite composition of hydrosulphide solutions and to their instability. The data appear in Table III and are represented in Fig. 2 as for the former reaction. The displacement of the curve when foreign salts are present cannot yet be explained.

FIG. 2.

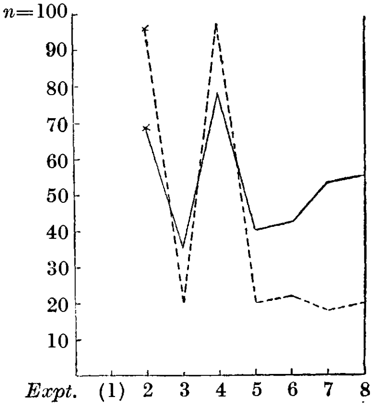


TABLE III.

No.	Composition of mixture.	% d-Acid found.	μ.	$f_1 = f_{SH}$.	$f_{1.SH}$.	n, calc.
1.	1·0 K_2Bs; 1·0 KSH	95·9	4·0	0·33	0·084	—
2.	0·5 ,, 0·5 ,,	68·6	2·0	0·45	0·105	96
3.	0·1 ,, 0·1 ,,	35·2	0·4	0·65	0·212	20
4.	0·1 ,, 0·3 ,,	77·7	0·6	0·59	0·180	97
5.	,, ,, 0·1 ,, ; 0·5 K_2SO_4	40·3	1·9	0·46	0·107	20
6.	,, ,, ,, ,, ; 1·0 KBr	42·5	1·4	0·50	0·115	22
7.	,, ,, ,, ,, ; 2·0 KBr	53·2	2·4	0·43	0·102	18
8.	,, ,, ,, ,, ; 0·5 $SrBr_2$	55·4	1·9	0·46	0·107	20

Finally, it may be remarked that a complete theoretical calculation should perhaps take into consideration the possibility that some of the oscillating molecules can escape reaction both while in configuration (I) and in configuration (II) for the first time, and only react during a subsequent oscillation. It is also possible that very accurate experiments would show that the time of oscillation of the molecule is influenced by the potential in the solution. The conception of the Walden inversion now put forward seems to have the advantage that it is capable of experimental verification.

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