695. *The Catalytic Deuteration of Organic Compounds. Part IV.* The Deuteration of Optically Active Lactic Acid.*

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The deuteration, at 120—130°, of optically active lactic acid by deuterium oxide in presence of a platinum catalyst has been examined and the extent of deuteration at the α- and the β-carbon atom correlated with the stereochemical changes which occurred simultaneously. The results indicate that the α-substitution of hydrogen by deuterium is, in general, accompanied by inversion. This is supported by a resolution of a partially racemised salt. The substitutions at the α- and the β-carbon atom are shown to be concurrent processes. A mechanism consistent with these observations is discussed.

In Part III * it was reported that, whereas lactic acid could be deuterated by shaking it with deuterium oxide at 130° in the presence of platinised asbestos, no detectable reaction occurred in the absence of the catalyst. Lactic acid can be readily resolved, and thus this reaction can be used to investigate the stereochemical changes associated with deuteration at a catalytic surface. In two such catalytic deuterations of lactic acid consisting substantially of the lævorotatory form the following results have been obtained.

Table 1. *Deuteration of (—)lactic acid.*

	Experiment	
	1	2
(+)-Form present initially (%)	1·48	2·94
,, ,, after deuteration (%) [a]	7·08	8·23
Initial concn. of D in water (atom %) [b]	82·9	82·05
Overall D content of silver lactate (atom %) [c]	4·89	4·51
Concn. of D at α-carbon atom (atom %)	5·52	5·39
,, ,, β-carbon atom (atom %)	6·30	5·71
(+)-Form reqd. for occurrence of Walden inversion (calc.) [d]	7·95	9·12
,, ,, ,, Walden inversion (corr.) [e]	7·30	8·44
,, ,, ,, racemisation (calc.) [f]	4·71	6·03

[a] The assumption is made here that the molecular rotations of $CH_3O{\cdot}CH(CH_3){\cdot}CO_2CH_3$ and $CH_3O{\cdot}CD(CD_3){\cdot}CO_2CH_3$ are not significantly different. [b] Deduced from that of the 99·75% deuterium oxide used by the instantaneous equilibrium, $CH_3{\cdot}CH(OH){\cdot}CO_2H + 2D_2O \rightleftharpoons CH_3{\cdot}CH(OD){\cdot}CO_2D + 2HOD$. [c] Includes the hydroxyl-hydrogen which has been "normalised." [d] Calc. on the assumption that every substitution at the α-carbon atom leads to an inversion of the sign of rotation; β-substitutions are assumed to be without effect on the optical activity. An isotope effect between hydrogen and deuterium has been neglected in the calculation since this would be very small at the relatively high temperature of the reaction. [e] The uncorrected values neglect the small but finite possibility of any molecules undergoing two substitution reactions in the course of the experiment. [f] Based on the symmetrical transition state's having an equal probability of giving D- or L-deuterated forms, no allowance being made for systems where this condition is not met; the present system, however, approximates closely to this condition.

It is apparent from Table 1 that the deuteration reaction proceeds to a substantial extent by a mechanism leading to Walden inversion. Reaction mechanisms of this type

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* Part III, preceding paper.

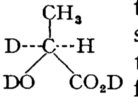
have been extensively studied by Hughes, Ingold, and their co-workers (*J.*, 1937, 1252; 1946, 173) and evidence has been accumulated in the study of homogeneous reaction systems that such inversions occur by a bimolecular reaction mechanism in which the entering group attaches itself to the reactive centre on the side opposite to the group which is expelled. It has also been shown that in general cases of bimolecular substitution of this kind the molecule in the transition state is planar with respect to the active centre and the unreacting groups are distributed around the centre in positions in the plane consistent with the lowest energy configuration. The entering group and that being expelled are coaxial with the reactive centre, the axis so formed being normal to the plane of the rest of the molecule. It is possible, however, that these requirements may not be rigidly met in the case of a molecule reacting on a catalytic surface.

The existence of an inversion in the process excludes from consideration mechanisms involving reversible dehydration and reversible dehydrogenation reactions. The former type clearly cannot effect any deuteration in the α-position unless it is associated with some other concurrent process. Reversible dehydrogenations, involving either αβ-elimination or elimination from the α-hydrogen and the hydroxyl-hydrogen atom, can also be excluded, since the elimination-and-addition reactions could not result in an inversion in the second of these processes and could do so in the first only under certain specified conditions of reaction such as *trans*-elimination followed by *cis*-addition, or the reverse sequence, involving a bimolecular type of reaction at some stage. In either case the presence of deuterium for re-saturation is a condition not fulfilled in these experiments where the bulk of the deuterium was present as the oxide. Under the experimental conditions employed no evidence was found for the presence of acrylic acid or pyruvic acid, although some indication of the latter was obtained at higher temperatures.

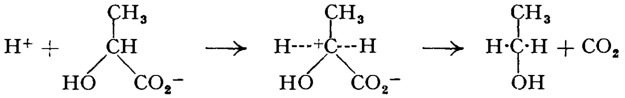
Alternative theories which involve the replacement of only one of the hydrogen atoms by the dissociation of a C–H bond as the initial step in the reaction may also be excluded since, if the hydrogen atom is removed and the rest of the molecule attached to the catalyst by the bonding electron or electrons, it is difficult to see why the substitution does not occur with retention of configuration. On the other hand, if the residue becomes detached from the catalyst as a radical which eventually abstracts a deuterium atom either from the catalyst or from the solvent, the reaction should lead to racemisation, as evidence has accumulated that, in general, radicals do not retain their stereochemical configuration even if of very short life (Hey, *Ann. Reports*, 1944, **41**, 189).

The remaining type of substitution is that requiring synchronous addition and expulsion of the groups and as this appears to be consistent with the experimental evidence available, a general reaction process based on such a mechanism can be described.

According to Laidler (*Discuss. Faraday Soc.*, 1950, 47) the theory of bimolecular surface reactions formulated by Langmuir (*Trans. Faraday Soc.*, 1921, **17**, 621) is more generally applicable than that suggested by Rideal (*Proc. Camb. Phil. Soc.*, 1939, **35**, 130) and a mechanism based on the former theory is considered to be operative in this case, such a mechanism being favoured by the polar nature of the reactants. The high heat of desorption usually associated with this type of mechanism is consistent with the observed rapid sintering of the catalyst in the present experiments. It is suggested, therefore, that this reaction occurs between two particles adsorbed on the catalyst, an equilibrium being set up between deuterium ions in solution and chemisorbed deuterium which may be regarded as bonded to the platinum, the bond being substantially covalent in character so that there is an electron density around the deuterium atom. The lactic acid molecule is also adsorbed on the catalyst, whose function is to lower the activation energy for the formation of the transition state; this will be assisted by the covalent character of the chemisorbed deuterium. The transition state formed between the deuterium and the lactic acid molecule (or the anion) will be essentially of the annexed form and it is clear that expulsion of the hydrogen will lead to inversion. No evidence is available to decide whether the breaking of the D–Pt bond will result in the formation of deuterium ions or atoms and hence no decision as to the nature of the ejected particle can be made.



The presence, among the by-products of the reaction, of a very small amount of ethyl alcohol is in agreement with the view that the reaction is one between a lactic acid molecule (or anion) and a deuterium atom or ion with considerable covalent character. Ethyl alcohol may arise from a reaction of the type



$$H^+ + CH_3CH(OH)CO_2^- \longrightarrow H\cdots{}^{+}C(CH_3)(OH)(CO_2^-)\cdots H \longrightarrow H{\cdot}C(CH_3)(OH){\cdot}H + CO_2$$

in which the loss of carbon dioxide is occasioned by charge neutralisation (Brown, *Quart. Reviews*, **1951**, 5, 131). The amount of alcohol found, corresponding to not more than 0·8% of the reaction, indicates that this process is of almost negligible occurrence.

That the reaction process is not exclusively one of Walden inversion is clear from the extent of inversion and substitution shown in Table 1, from which it has been calculated that the number of substitutions occurring with inversion is approximately six times the number occurring with retention of configuration. Further evidence to this effect has been obtained by a partial resolution, through the morphine salt, of the deuterated lactic acid from Experiment 2, and the assay of the deuterium content in the α- and the β-position. The weight of each fraction being known, in addition to the rotation and the extent of deuteration, the amounts of substitution accompanied by inversion and by retention of configuration have been calculated and are included in Table 2. Little evidence is available to decide whether the second mechanism operating is one leading to racemisation or retention of configuration; it is, however, probable that the alternative reaction occurs by a mechanism similar to that of the main process but with the entering group approaching from the same side of the molecule as that to which the group being expelled is attached. This view is not inconsistent with the adsorption of the lactic acid molecule, which could undergo slight distortion, and replacement of the hydrogen by deuterium chemisorbed deep into the platinum.

TABLE 2.

(−)-Lactic acid (%)	95·49	91·77	46·55
Deuterium in α-position (atom %)	3·30	5·39	30·33
,, β-positions (atom %)	3·40	5·71	36·25
Molecules reacting with inversion (%)	90	85·6	90

The simultaneous deuteration of the α- and the three β-positions is shown clearly in Table 2, but the fact that α- and β-substitutions occur together is not considered as evidence that they are interdependent except in so far as the chemisorption of the molecule brings all four hydrogen atoms into the proximity of the catalyst. For results consistent with the optical rotation and the deuterium content at the two carbon atoms, the substitution processes must occur at least three times for β-substitution, and, for the stereochemical requirements, an odd number of times for each molecule. Little significance can be attached to the observation that three β-substitutions occur for one α-substitution, at least with regard to the relative rates of the two reactions, since a consequence of the Langmuir mechanism is the high energy associated with desorption which is often the rate-controlling process. The fact that the main process in the reaction is that of inversion indicates that, once an inversion has occurred as the result of one substitution at the α-carbon atom, no further reaction takes place at this centre even though this step may be over before desorption occurs. This implies that, once inverted, the molecule is unsuitably placed on the catalyst surface for further reaction, which would appear to be more consistent with the geometry of chemisorbed reacting systems rather than those in which one reacting species is held by long-range van der Waals forces.

The observation that, although the deuteration takes place readily with lactic acid, a similar reaction fails to occur to any significant extent with methoxypropionic acid is explained if such a mechanism involves covalently bonded deuterium by reason of a steric effect in the transition state of the latter acid. Calculations of the steric effects in the molecules of lactic and methoxypropionic acids have been made for the initial state and the transition state and will be discussed in a subsequent communication.

EXPERIMENTAL

Resolution of Optically Inactive Lactic Acid.—The optical enantiomer for use in the exchange reactions was prepared by Purdie and Walker's method (*J.*, 1895, **67**, 617), the criterion of optical purity being the number of molecules of water of crystallisation in the zinc salt (Purdie, *J.*, 1893, **63**, 1143). The zinc lactate was converted into lactic acid by passing hydrogen sulphide into an aqueous solution of the salt and filtering off the zinc sulphide repeatedly until no further precipitate was obtained. The filtered solution was evaporated to small bulk and extracted with ether in a continuous extractor for 16 hr. The ethereal layer was dried (Na_2SO_4), the ether removed, and the lactic acid distilled, the fraction, b. p. 79—81/0·1 mm., being collected. On shaking, the distillate, subsequently found to contain 98·5% of the lævorotatory form, set to a white crystalline mass, m. p. 49·5°. A second sample, prepared by the same method (97·1% of the lævorotatory form), had m. p. 54° (Found: C, 39·8; H, 6·7. Calc. for $C_3H_6O_3$: C, 40·0; H, 6·7%).

The deuterated lactic acid was resolved by means of the morphine salt. Lactic acid (20 g.) in solution from the deuteration reaction was diluted to 200 ml. with water and refluxed for 3 hr. to hydrolyse any lactide. Morphine (63·5 g.) was added, and, on cooling, a copious precipitate of morphine lactate settled out and was filtered off. Four further crops were obtained by concentration. The residue (6 g.) set to a syrup. Lactic acid was recovered by addition of ammonia, in excess, to aqueous solutions of the morphine lactate, removal of the morphine by filtration, boiling to remove the excess of ammonia, decomposition of the ammonium lactate with dilute sulphuric acid, and extraction with ether.

Silver Lactate.—Active lactic acid was refluxed with water for 3 hr. to hydrolyse lactide. The calculated quantity of silver oxide was gradually added to the boiling solution which was boiled for a further 5 min. after all the silver oxide had been added, and then evaporated to small bulk. After filtration from small quantities of silver oxide, the solution was cooled in ice and the precipitated silver lactate filtered off. This process was repeated until the final volume of the solution was about 2 ml., from which the remaining silver lactate was precipitated by the addition of alcohol (yield 83—84%). Although the later fractions contained some silver oxide it was considered advisable to include these in order to assay a representative sample.

Methyl Lactate.—Lactic acid was converted into methyl lactate by Walker's method (*J.*, 1895, **67**, 916), the fraction, b. p. 58—60°, being collected.

Methyl Methoxypropionate.—This was prepared from methyl lactate by Purdie and Irvine's method (*J.*, 1899, **75**, 485), the crude product being fractionated at atmospheric pressure, b. p. 130—131°.

Methoxypropionic Acid.—The acid, prepared from the methyl ester as described by Freudenberg (*Ber.*, 1927, **60**, 2452), had b. p. 85—90°/9 mm.

Rotations.—These were measured at 20° in a 1-dm. tube, for the sodium *D* line. Lactic acid specimens were converted into methyl methoxypropionate, and the activity of the acid determined by measurement of the rotation of this ester, the value for the pure ester, taken as standard, being $[\alpha]_D^{20}$ +95·53° (Purdie and Irvine, *loc. cit.*).

Oxidations.—Several methods were used for converting the lactic acid and its derived esters into acetic acid for deuterium assay. (*a*) *Lactic acid to acetic acid.* The lactic acid was oxidised by refluxing it with excess of potassium permanganate in 2N-sulphuric acid for $\frac{1}{2}$—1 hr. The manganese dioxide was filtered off and the filtrate steam-distilled, the distillate being treated with silver oxide by the method described above for the preparation of silver lactate. The silver acetate so obtained was dried *in vacuo* over sulphuric acid before assay. By using information previously obtained (Part I, *J.*, 1952, 572) it was possible to show that under these conditions the loss of deuterium from the acetic acid was less than 0·5% of the amount estimated.

(b) *Methyl methoxypropionate to acetic acid.* (i) *Direct.* Refluxing the ester with the calculated quantity of potassium permanganate in 2N-sulphuric acid, removal of the manganese dioxide by filtration, and steam-distillation yielded acetic acid which was converted into silver acetate and assayed for deuterium. This method was discarded since a check showed that the deuterium content of the derived acetic acid was 10% below that of the methyl group of the methoxypropionic acid. (ii) *Indirect.* This method gave satisfactory results and was adopted. The ester (4 g.) was refluxed with constant-boiling hydriodic acid (30 g.) for 1 hr. at 140°, the cooled mixture being then diluted to 100 ml. with water and extracted with ether. Free iodine was removed by shaking with sodium metabisulphite, and the ethereal extract dried (Na_2SO_4). Part of the residue after removal of the ether was converted into the silver salt and analysed

(Found : C, 21·9; H, 3·3; Ag, 51·4. Calc. for $C_4H_7O_3Ag$: C, 22·8; H, 3·3; Ag, 51·2%). The silver methoxypropionate, or the free acid, was converted into acetic acid by permanganate oxidation, followed by steam-distillation, and silver acetate prepared by the standard procedure (Found : C, 14·1; H, 1·7; Ag, 64·7. Calc. for $C_2H_3O_2Ag$: C, 14·4; H, 1·8; Ag, 64·7%).

Deuterations.—The active lactic acid, heavy water, and platinum black catalyst on an asbestos support, were weighed into Pyrex tubes in quantities shown in the following Table.

Experiment	1	2
Lactic acid (g.)	16·80	20·08
D_2O (99·78%) (g.)	18·37	20·07
Pt catalyst * (g.)	1·50	1·80
Duration of heating (hr.)	46	44

* Pt (30%) on asbestos; figures give wt. of catalyst plus support.

The tubes were cooled in liquid air, evacuated, sealed, and shaken at 120—130°. The resultant mixture was filtered from the catalyst, and the heavy water recovered by vacuum-distillation at 40° For deuterium assay, one small portion of the lactic acid was converted into silver lactate and another into silver acetate by the methods outlined above. Further amounts were converted into methyl methoxpropionate for measurement of the optical rotation, and in Experiment 2 a portion of the deuterated lactic acid was partially resolved by means of morphine. All samples of lactic acid were treated with a large excess of ordinary water at some stage in the treatment to normalise the hydrogen atoms of the hydroxyl and the carboxyl group.

By-products.—The aqueous (D_2O) solution obtained by vacuum-distillation was made alkaline with sodium hydroxide and fractionally distilled, only a few ml. of distillate being collected. A portion of this distillate was dried (Na_2SO_4), re-distilled at the temperature of an acetone–carbon dioxide freezing mixture, and examined in a mass spectrometer. The highest peak recorded was one at mass 46, with which were associated peaks at masses 29, 17, and 15, the last two being less prominent. In addition, a small peak at mass 44 and a fairly large peak at mass 28 were obtained. Some of these mass numbers could be derived from ethyl alcohol (46) giving rise, by breakdown, to ethyl (29), hydroxyl (17), and methyl (15) radicals.

The distillate gave a positive iodoform reaction, and on the assumption that this was due solely to ethyl alcohol, the amount of the latter formed was 4·5 mg., corresponding to about 0·8% of the total reaction. A further portion gave a slight precipitate of a 2 : 4-dinitrophenylhydrazone indicating the presence of an aldehyde or ketone, probably acetaldehyde, since the absence of a peak above mass 46, in the mass spectrometer examination, excludes acetone (58). The presence of acetaldehyde could account for the peak at mass 28 as carbon monoxide produced by the breaking up of the molecule.

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