An Investigation of the Deuteration of Mandelic Acid

with an additional paper on

The Measurement of Acidity at Temperatures over 100°

T H E S I S

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by

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I N D E X

Part I

The Deuteration of Mandelic Acid

1. Historical Review

The availability of isotopes from 1933 onwards has given new impetus to the investigation of reaction mechanisms and to catalytic studies, since reaction between isotopic molecules has permitted the study of interaction between specific groups in the molecules. Deuterium, the most readily available isotopic species, has been widely used in tracer experiments; in the form of heavy water, it has been used to effect many exchanges at a hydrogen atom.

The exchange of a hydrogen atom in a C-H bond is more difficult than in the N-H, O-H, or Cl-H bonds, probably because of the absence of electrons not involved in bonding in the former (1). Whilst the equilibrium in the exchange between deuterium and hydrogen attached to nitrogen or oxygen is established extremely rapidly,[2] in a C-H bond only mobile hydrogen exchange directly, for example, those involved in a keto-enol tautomerism.[3] Hence it is found that the rate of exchange for acetone is very slow in neutral solution, faster in acid solution, and very fast in alkaline solution (3,4). A mechanism, similar in nature to that proposed by Pederson (5), was worked out for the reaction by Bok and Geib (6). It was based on the Brönsted theory of general acid and base catalysis, and the following schemes were postulated:

a) With bases,

$$CH_3 - \underset{\underset{O}{\|}}{C} - R \ + \ B_1^{\ominus} \ \rightleftharpoons \ \overset{\ominus}{CH_2} - \underset{\underset{O}{\|}}{C} - R \ + \ HB_1$$

$$\underset{DB_2 /\!\!/}{\rightleftharpoons} \qquad \qquad \updownarrow$$

$$B_2^{\ominus} \ + \ CH_2D - \underset{\underset{O}{\|}}{C} - R \qquad CH_2 = \underset{\underset{O^{\ominus}}{|}}{C} - R \ \underset{DB_2}{\rightleftharpoons} \ CH_2 = \underset{\underset{OD}{|}}{C} - R \ + \ B_2^{\ominus}$$

b) With acids,

$$CH_3 - \underset{\underset{O}{\|}}{C} - R \ + \ DB_1 \ \rightleftharpoons \ CH_3 - \underset{\underset{\oplus OD}{\|}}{C} - R \ + \ B_1^{\ominus} \rightleftharpoons \ \overset{\oplus}{CH_3} = \underset{\underset{OD}{|}}{C} - R$$

$$\updownarrow B_2^{\ominus}$$

$$CH_2 = \underset{\underset{OD}{|}}{C} - R$$

$$\updownarrow DB_3$$

$$DB_4 \ + \ CH_2D - \underset{\underset{O}{\|}}{C} - R \ \underset{B_4^{\ominus}}{\rightarrow} \ CH_2D - \underset{\underset{\oplus OD}{\|}}{C} - R \qquad \rightleftharpoons \qquad \overset{\oplus}{CH_2D} = \underset{\underset{OD}{|}}{C} - R$$
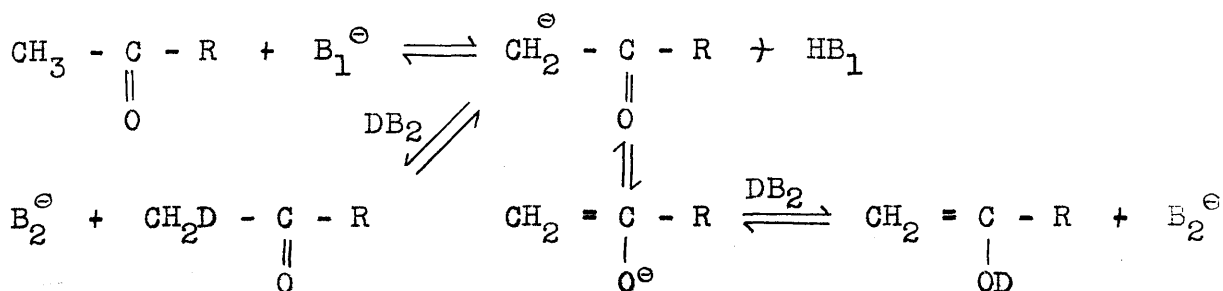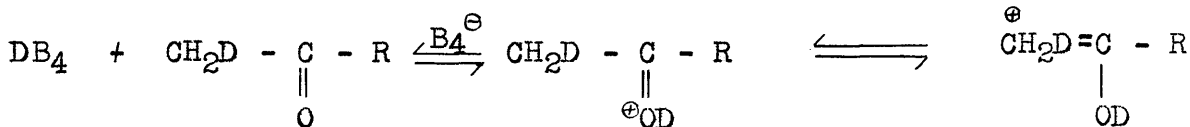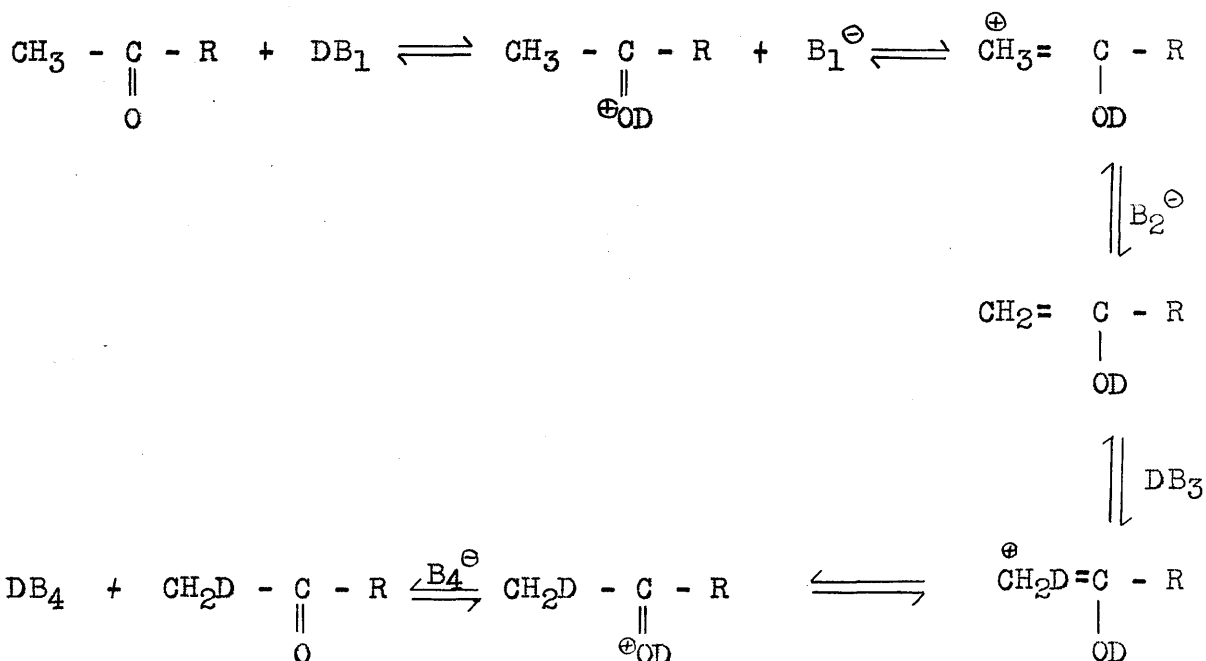
With the modifications that the intermediate ions
are probably mesomeric in form, and that five-valent
carbon atoms do not participate in the scheme, the reaction
mechanism of Bok and Geib is still widely accepted. More
recently, Swain (7) has claimed that a concerted mechanism
of the type proposed by Lowry (8), in which both nucleo-

philic and electrophilic attack are required in the rate-determining step, affords results which can be more easily reconciled with the experimental data than those obtained on the hypothesis of two competing bimolecular reactions, one acid catalysed, and the other base catalysed. Bell and Clunie (9) have, however, stated that it would be unwise to assume either a binary or a ternary mechanism for acid-base catalysed reactions in general, but that each type of reaction must be investigated separately.

On the basis of either a binary or a ternary mechanism, the rate of isotopic exchange of an optically active ketone should equal its rate of racemisation, since both are dependent on an initial ionisation. Measurements of the rates of racemisation and deuterium uptake in the alpha hydrogen position of 1-phenyl-β-n-butyl ketone, $\begin{array}{c} C_2H_5 \\ \diagdown \\ \diagup \\ C\ H_3 \end{array} CH.CO.C_6H_5$ were made by Hsü, Ingold, and Wilson (10), who found them to be equivalent. They hence concluded that racemisation and hydrogen exchange were controlled by the same fundamental process, namely, ionisation of the ketone.

Much of the early investigation on the deuterium exchange of alkyl groups of carboxylic acidsdealt with acetic acid and acetate ions; the results obtained were

conflicting. It may be noted, however, that exchange
was generally only obtained at higher temperatures. Some
clarification of the conditions and nature of the reaction
was achieved by Bok and Geib (6), who showed that the
exchange readily takes place in the methyl group of acetic
acid, the reaction being promoted by acid or base catalysis.
The mechanism suggested for the deuteration was analogous
to that proposed for the deuteration of acetone, the
reaction occurring through an intermediate enol form.

Ives (11) had previously suggested that the acetic
acid exchange resulted from a keto-enol tautomeric change,
or more probably, involved the participation of a mesomeric
ion of the form $\left[>\overset{\ominus}{C} - C = O \longleftrightarrow >C = C - O^{\ominus} \right]$. He,
however, also considered the possibility that the reaction
was termolecular, which would involve a Walden Inversion,
since the points of removal and addition of the proton are
coincident:

$$\underset{H_2O}{\overset{\displaystyle H \qquad \nearrow OH^{\ominus}}{\underset{\displaystyle \nwarrow}{\overset{\displaystyle H}{\underset{\displaystyle \nearrow}{\overset{\displaystyle |}{\underset{\displaystyle |}{\overset{\displaystyle \nwarrow}{C}}}}}}} \overset{\displaystyle H}{\nearrow}$$

. A tautomeric, termolecular
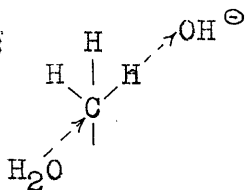
mechanism, in which the intermediate stage would not attain
kinetic independence, was envisaged also.

Ives could detect no exchange in the higher members
of the monocarboxylic acid series; subsequently Schanzer
and Clusius (12) found that an exchange occurred with
propionic and n-butyric acids in presence of added alkali.

The exchange was restricted to the hydrogen atoms attached
to the alpha carbon atom, and this has been confirmed by
Bell and his co-workers (13). The exclusive alpha substi-
tution is in accord with the ionisation mechanism of the
reaction; and the known inductive effect of alkyl groups
would tend to retard reaction by increasing the electron
density at the alpha carbon atom, thus explaining the
less ready exchange in the higher members of the series.

An investigation of the rates of racemisation and
isotope exchange of phenyl p-tolylacetic acid, $\begin{matrix} C_6H_5 \\ CH_3C_6H_4 \end{matrix} \Big\rangle CH.COOH$

was carried out by Ives and Wilks (14), who found that
the rates of racemisation and exchange were the same.
They hence concluded that both proceeded by an ionisation
mechanism.

Direct deuteration of benzene has been achieved
in the presence of catalysts; 50% sulphuric acid (D_2SO_4)
and benzene give a ready exchange on shaking together
at room temperature (15). This nuclear deuteration was
envisaged by Ingold and his co-workers as an electrophilic
substition, proceeding by attack at a single carbon atom,
as in ordinary aromatic substition.
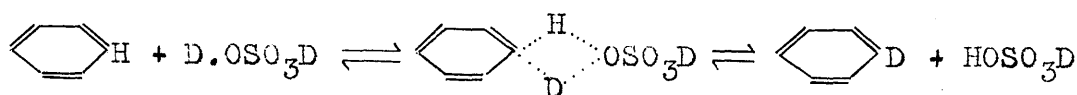
The relative velocities of nuclear exchange in various

11.

monosubstituted benzenes, such as phenol, and the relative
efficiencies of different deuterating agents, were shown
by the same workers to be in accordance with the electro-
philic substitution theory (16). Best and Wilson (17)
later demonstrated that phenol and aniline substituted in
the ortho and para positions only on heating with alkaline
D_2O, which is in accordance with the known orientating
influence of the hydroxyl and amino groups. Toluene does
not exchange hydrogen for deuterium on prolonged heating
with D_2O, even in presence of acid or alkali (1), and so
it would appear that only strongly activating groups have
a sufficient influence on the reactivity of the nucleus
to allow an exchange to occur.

The catalysing influence of platinum in hydrogen
exchange reactions was first demonstrated by Horiuti and
Polanyi (18), for the exchange between deuterium gas and
water. Several exchange reactions between simple organic
compounds and deuterium gas have since been investigated.
The applicability of transition metal catalysis to hydrogen-
deuterium exchange reactions involving D_2O rather than
deuterium gas was demonstrated by Horiuti and Polanyi (19),
who obtained an exchange on heating ethylene or benzene
with heavy water and a nickel catalyst. A platinum-
catalysed exchange was obtained by Horrex and Polanyi (20),

who found a fairly rapid exchange between D_2O and cyclo-
hexane or isopentane in presence of active platinum.
Heyningen, Rittenberg, and Schoenheimer (21) heated fatty
acids with D_2O in presence of alkali and active platinum,
thereby introducing deuterium atoms at many, and perhaps
all, of the carbon atoms. This latter observation was
confirmed by Bell et al., (13), who showed that propionic
acid, deuterated in presence of a platinum catalyst, gave
extensive exchange involving hydrogen atoms attached to
both alpha and beta carbon atoms. In general, the presence
of a platinum catalyst enhances the deuteration of those
acids which undergo exchange in the homogeneous reaction,
and promotes the deuteration of other acids with which the
homogeneous reaction does not take place, the exchange
resulting in substitution at all carbon atoms.

Deuterium exchange in the aromatic ring occurs readily
under the influence of a platinum catalyst, although not
with such facility as in D_2SO_4 solution. With a substituted
benzene, exchange would appear to occur at all available
positions, as Lauer and Errede (22) found that on heating
aniline with D_2O and Raney nickel alloy in basic solution,
whilst the exchange was predominantly in the ortho position,
the meta and para positions also contained some deuterium,
between ten and fifteen percent in each.

Investigations of the mechanism of heterogeneous catalysis, in exchange and also in other types of reaction, have been mainly carried out with gaseous reactants. As a result of work in several fields, it has been recognised that there are two distinct types of adsorption: a van der Waal's adsorption, of little significance in catalysis, and chemisorption, which might require an activation energy. The latter type of adsorption of hydrogen on transition metals is probably due to the partly empty d-band of these metals (23).

Langmuir (24) in his early papers visualised two types of bimolecular catalytic reaction:

a) The two reacting gases compete on more or less equal terms for sites in the chemisorbed monolayer, and reaction may then occur between adjacent radicals and atoms. This theory has been applied and developed by Hinshelwood (25).

b) Reaction occurs between chemisorbed A and a molecule of B colliding with it from the gas phase or van der Waal's layer. This type of treatment has been applied by Rideal (26).

Laidler (27) has stated that the Langmuir-Hinshelwood mechanism is probably the general rule, and the Rideal mechanism only applies when the reaction product is strongly adsorbed on the surface, such as when the product of reaction

is a hydrogen molecule.

In most exchanges, there is still considerable con-
troversy over the precise mechanism which is operative.
One of the most widely studied reactions is the exchange
between hydrogen and ethylene, but "the chances of agreement
on the mechanism seem remote at present."(28) The various
theories which have been proposed fall into two main groups,
the one postulating an associative mechanism, with a close
connection between exchange and hydrogenation, and the
other a dissociative mechanism.

In the former category we may place the original
mechanism of Horiuti and Polanyi (29), which postulates
that ethylene is chemisorbed by the opening of the double
bond, reaction then following with a chemisorbed hydrogen
atom,

$$CH_2=CH_2 \longrightarrow \overset{*}{C}H_2-\overset{*}{C}H_2 \xrightarrow{+D^*} \overset{*}{C}H_2-CH_2D \underset{\searrow}{\overset{+D^*\nearrow}{}} \begin{array}{l} CH_2D-CH_2D \quad (\text{hydrogenation}) \\ CH_2=CHD + H \quad (\text{exchange}) \end{array}$$
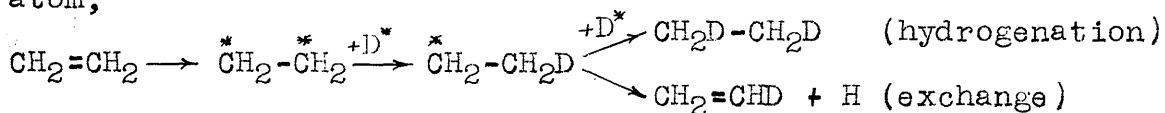
(An asterisk indicates a chemisorption bond to a metal site.)
Twigg and Rideal (30) have postulated a modified half-
hydrogenation mechanism, of the Rideal type rather than the
Langmuir-Hinshelwood one,

$$CH_2 = CH_2 \longrightarrow \overset{*}{C}H_2 - \overset{*}{C}H_2 \xrightarrow{D_2} \overset{*}{C}H_2 - CH_2D \xrightarrow{D^*} \overset{*}{C}H_2 - \overset{*}{C}HD + HD$$
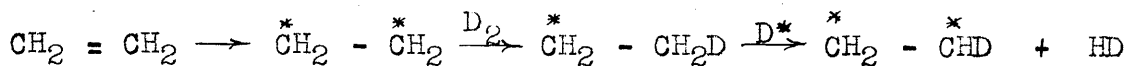
A dissociative mechanism has been suggested by
Farkas (31), reaction occurring between the chemisorbed C_2H_3
radical and an adsorbed deuterium atom. Beeck (32) has
suggested that ethylene is chemisorbed as acetylene

plus two hydrogen atoms, the latter being immediately
removed by impinging ethylene as ethane.

The exchange reactions of saturated hydrocarbons
have in general been explained assuming a dissociative
chemisorption (31,33),

$$C_nH_{2n+2} \longrightarrow C_nH_{2n+1}^* + H^*,$$
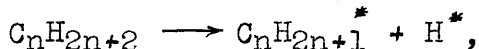
exchange following by recombination of a $C_nH_{2n+1}^*$ and a D^*.

In the case of benzene, the activation energies for
both exchange and hydrogenation are about the same, suggest-
ing a similar rate-determining process in each case (34).
It is not adsorbed so strongly, or alternatively does not
pack so well, on nickel and platinum catalysts as ethylene.
An associative mechanism was suggested by Greenhalgh and
Polanyi (35), with the step
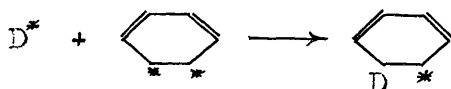
determining the rate. Because chemisorption of benzene in
this way will break the resonance energy, the benzene will
be more weakly chemisorbed than ethylene. Since the weak
adsorption will allow an ample surface concentration of
chemisorbed deuterium, the slow step will not involve D_2
molecules.

Farkas and Farkas (36) have again proposed a dissoc-
iative mechanism for the exchange, according to which the
adsorbed benzene molecules lose one hydrogen atom and take

up another (heavy) hydrogen atom. They visualise the ad-
sorption of benzene to occur as suggested by Balandin (37),
with the molecule in a flat position, and held by the co-
operation of three atoms of the catalyst arranged in an
equilateral triangle of given dimensions. Hydrogenation and
exchange are assumed to be independent reactions.

Although benzene exchanges more rapidly with hydrogen
than do the saturated hydrocarbons, the exchange of benzene
with water proceeds at about the same rate as that of the
saturated hydrocarbons (38), indicating that care must be
taken when applying the mechanisms suggested for exchange
with deuterium gas to the exchange with heavy water. It is
not certain to what extent mechanisms involving adsorption
of deuterium gas on the catalyst surface can be applied to
reactions between D_2O and organic molecules.

Bell, Macdonald, and Reed (39) have, however, invest-
igated the deuteration of optically active lactic acid in
solution, in presence of a platinum catalyst. The extent
of the exchange at the alpha and beta carbon atoms was
correlated with the stereochemical changes occurring sim-
ultaneously, and they concluded that the deuteration pro-
ceeded largely by a mechanism leading to Walden Inversion,
i.e., by a bimolecular reaction in which the entering
group attaches itself to the reactive centre on the side

opposite to the group which is expelled. A mechanism based on the Langmuir theory of surface catalysis was suggested, reaction occurring between two particles adsorbed on the catalyst, whose function was to lower the activation energy for the formation of the transition state.

In this brief review, an attempt has been made to outline the main investigations on the hydrogen-deuterium exchange which have some bearing on the present work, and to present some of the conclusions which have been derived from these investigations. No coherent, systematic account of the exchange reaction has emerged from this earlier work, and although it is unlikely that we will ever be able to explain the various exchange reactions in terms of one mechanism, some satisfactory correlation of the various theories must be achieved.

2. Aims of the Present Investigation

The conclusions reached about the mechanism of the catalytic deuteration of lactic acid (39) would seem to hold promise of their being of great importance in the building of a systematised theory of the exchange reaction. In order to find whether such a mechanism is indeed a general one, a comprehensive survey of the exchange reactions of mandelic acid was undertaken. Like lactic acid, mandelic acid has an asymmetric carbon atom, and hence it should be possible to ascertain the mechanisms of the exchange of the hydrogen atom attached to this carbon. Since mandelic acid undergoes an exchange both without and in the presence of a metal catalyst, however, a comparison of the homogeneous and heterogeneous reactions can be made, which should throw light on the mechanisms operating in different circumstances. In presence of a platinum catalyst, at least, an exchange of the hydrogen atoms attached to the benzene nucleus will occur, and a determination of the positions of entry of the deuterium should be of considerable interest. It will thus be apparent that an investigation of the mandelic acid exchange holds very attractive possibilities.

3. Summary

The deuteration of optically active mandelic acid was investigated by shaking it in a sealed, evacuated tube under various conditions of temperature, and with different catalytic agents. The effect of acid, base, and platinum catalysts was examined, and in each case the degree of exchange occurring in the alpha position of the mandelic acid was correlated with the simultaneous change in its optical activity. The results indicated that with a basic catalyst present, the reaction occurred by a racemisation mechanism, an attacked molecule having an equal chance of retaining its configuration or undergoing an inversion. The platinum-catalysed exchange in acid solution was more complex, with both racemisation and retention mechanisms playing a part. With no catalyst present, racemisation of the acid occured, but without a corresponding exchange. In presence of platinum, the benzene ring, as well as the alpha hydrogen atom, was deuterated.

These conclusions were confirmed by resolutions of the deuterated mandelic acid, when the observed deuterium contents of the resolved fractions were found to be in good agreement with the figures calculated assuming the mechanisms postulated for the first part of the experiment. The resolution also showed that alpha hydrogen exchange

and nuclear deuteration were quite independent.

Mechanisms for the various reactions have been sugg-
ested, and involve an initial ionisation of the alpha
hydrogen atom, either on the catalyst surface, or under the
influence of a basic catalyst. The racemisation without
exchange is considered to occur by a mechanism involving
an initial fission of the bond between the alpha carbon
atom and the carboxyl group.

4. Discussion

The hydrogen-deuterium exchange in mandelic acid is a complex process, which can only be accounted for by the postulation of the simultaneous occurrence of several reaction mechanisms. In some circumstances, however, one mechanism may predominate to the virtual exclusion of all others, as, for example, under the influence of a basic catalyst.

In what is superficially the simplest case, where optically active mandelic acid and heavy water are heated together in the absence of any catalyst other than the hydrogen ions obtained by ionisation of the acid, we have found that at 100° neither exchange nor racemisation proceeds at a detectable rate, but at 140° a slow exchange takes place on the hydrogen attached to the alpha carbon atom, accompanied by a relatively rapid racemisation of the acid. If, however, the racemisation occurred by a mechanism involving the alpha hydrogen atom, an appreciable amount of deuteration would be expected. The lack of correlation between alpha hydrogen exchange and racemisation in mandelic acid excludes the possibility of the reaction taking place by an enolisation mechanism in the absence of excess alkali.

The fact that the racemisation did not involve the

alpha hydrogen atom was first noted by Erlenmeyer and his
co-workers (40), who tried to determine the mechanism of
the racemisation by carrying it out in a heavy water
medium.   Heating for 51 hours at 140° resulted in complete
racemisation of the acid, although no exchange occurred,
save that of the carboxyl and hydroxyl hydrogen atoms,
whose exchange is in any case extremely rapid at much
lower temperatures.   Their failure to observe any α-deut-
eration may be due to the fact that the mandelic acid
was recrystallised from heavy water before carrying out a
deuterium estimation, a step which introduces an element
of uncertainty into the calculation, in making allowance
for the differing relative weights of acid and water in
the various experiments.   Moreover, after such recryst-
allisation, the contribution made by the small amount of
α-hydrogen exchange to the total deuterium concentration
of the acid is not great (about 5%), and hence might be
within the limits of the errors introduced by the recryst-
allisation and in the deuterium analysis.

Erlenmeyer interpreted his results as being in
favour of the Werner-Hund conception of the racemisation.
Werner (41) had considered that if the groups around the
asymmetric atom could acquire sufficient energy, the
amplitude of their vibrations might be sufficient to

overcome the potential barrier between the two stable
forms of the molecule. As a result, with the carbon tetra-
hedron it would be possible to obtain as an intermediate
a configuration in which the substituents would lie in one
plane, and from which there would be an equal probability
of the formation of either of the optical isomers. Hund
(42) considered the same question from a quantum mechanical
viewpoint, and concluded that there was always a certain
probability of a d-form changing within a certain time
into an l-form, even although the total energy were less
than the potential barrier.

Kincaid and Henriques (43), however, have denied the
feasibility of such a mechanism, claiming that computations
of the energy required show it to be entirely unreasonable.
The activation energy for it they estimated to be about
88 k.cal. per mole, compared with about 58.6 k.cal. per
mole required to break a carbon-carbon bond. The authors
concluded that "the racemisation of an asymmetric carbon
atom cannot occur except through some process which results
in the breaking of a bond attached to the central carbon
atom". The possibility of racemisationtaking place by
passing through, instead of over, the potential barrier
is not much greater, as at room temperature and above, the
effective activation energy for tunnelling is only a few

percent lower than the height of the barrier.

We must, then, postulate the dissociation of one of the bonds to the asymmetric carbon atom as a first stage in the racemisation. The C-H bond is of necessity excluded, since it has been shown in the present investigation that an H—D exchange, although accompanying the racemisation, is insufficient to account for it. If the bond breaking is a purely thermal effect, being due solely to the increasing vibrational energy of the molecule with increasing temperature, we should expect, from the table of values of bond energies, that the carbon-carbon bond would be the most readily broken. However, the actual activation energy required for the fission of a particular bond may bear very little relation to the bond energy value, since resonance stabilisation of the resulting radical may decrease the activation energy considerably. In the present case, there are five possible resonating structures for the radical, if the latter is formed by fission of the carbon-carboxyl or carbon-hydroxyl linkage, and this would be expected to facilitate the formation of the intermediate. If the bond energy of the C-C bond were taken as a measure of the activation energy of the racemisation, the reaction would not proceed at a detectable rate at 140^0, the rate constant for the reaction then being of the order of 10^{-18}. From

the results of the present series of investigations, it
would appear that the reaction occurs just as readily in
the absence of any solvent, suggesting that the racemis-
ation involves the breaking of a carbon-carbon bond in
preference to the carbon-oxygen bond, since if the reaction
involved fission of the C-OH linkage, in aqueous medium
hydroxyl ions from the solvent would be expected to have
a considerable influence on the velocity.

It is most probable that the thermal racemisation
involves an initial dissociation of the bond between the
carboxyl group and the α-carbon atom; such a mechanism
would account for the formation of benzaldehyde, the
presence of which was noted in several of the current
experiments:

$$C_6H_5CHOH-COOH \rightleftharpoons C_6H_5CHOH \cdot \underset{\longleftarrow}{\overset{H_2O}{\longrightarrow}} C_6H_5CH(OH)_2 + H \longrightarrow C_6H_5CHO + H_2O$$
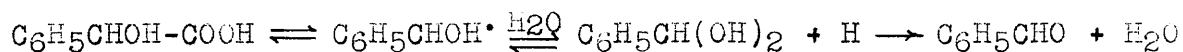
It is of significance that we could detect no benzaldehyde
when the solvent was other than water.

The occurrence of a limited amount of alpha deuter-
ation indicates that a simultaneous exchange reaction is
occurring, but the mechanism of the reaction cannot be
interpreted unequivocally from the data available. The
most likely suggestion is that it is of a type involving
racemisation of the attacked molecules, being catalysed by
hydrogen ions. Such a reaction would involve the following

intermediates:

$$Ph-\underset{\underset{OD}{|}}{\overset{\overset{H}{|}}{C}}-C\overset{O}{\underset{OD}{\diagdown}} \underset{}{\overset{D^{\oplus}}{\rightleftharpoons}} Ph-\underset{\underset{OD}{|}}{\overset{\overset{H}{|}}{C}}-C\overset{\overset{\oplus}{OD}}{\underset{OD}{\diagdown}} \overset{slow}{\longrightarrow} Ph-\underset{\underset{OD}{|}}{C}=C\overset{OD}{\underset{OD}{\diagdown}} + H^{\oplus}$$

$$\Big\Updownarrow D^{\oplus}$$

$$D^{\oplus} + Ph-\underset{\underset{OD}{|}}{\overset{\overset{D}{|}}{C}}-C\overset{O}{\underset{OD}{\diagdown}} \rightleftharpoons Ph-\underset{\underset{OD}{|}}{\overset{\overset{D}{|}}{C}}-C\overset{\overset{\ominus}{OD}}{\underset{OD}{\diagdown}}$$
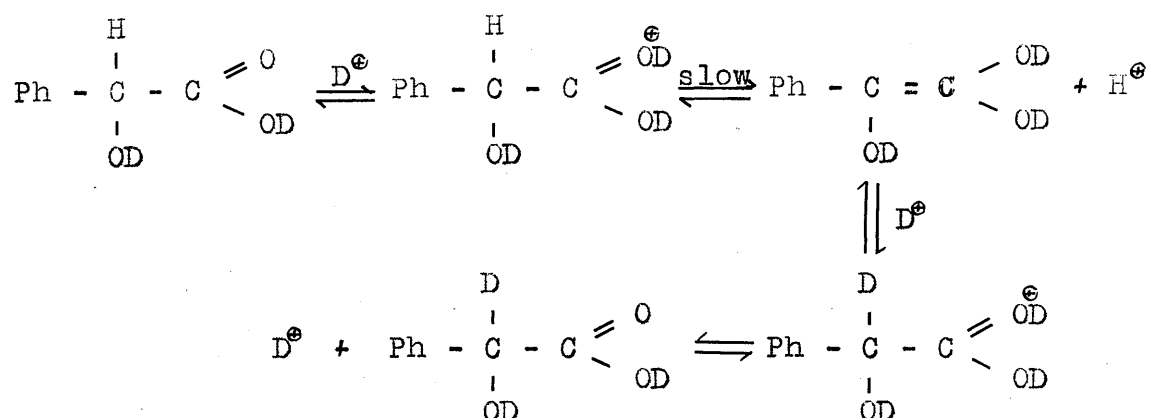
Since the rate of exchange is not increased appreciably by the addition of hydrogen ions from a mineral acid, however, the second stage in the reaction, involving the dissociation of a hydrogen ion from the addition product, must be very slow, so that the increase in the rate of formation of the addition complex in the first stage with increase of hydrogen ion concentration is counterbalanced by the suppression of the rate of the second stage.

At a temperature of 100°, we have found that the thermal racemisation occurs extremely slowly, and deuteration is negligible in solutions of mandelic acid, mandelate ions, or a mixture of the two. In presence of an excess of base, however, reaction occurs immediately and relatively quickly, the extent of exchange depending on the hydroxyl ion concentration. The α-hydrogen exchange is

accompanied by racemisation of the acid, and we have
calculated that half of the molecules substituted retain
their configuration, the other half undergoing inversion.
The initial step in the reaction must be the dissociation
of the α-hydrogen atom from the molecule; the three remain-
ing groups around the asymmetric carbon atom can then
momentarily attain a planar configuration, and addition
of a proton or deuteron to this intermediate radical will
occur with an equal probability of the formation of either
optical isomer, depending upon the direction of attack of
the deuteron. The steps in the reaction may be illustrated
schematically as follows:
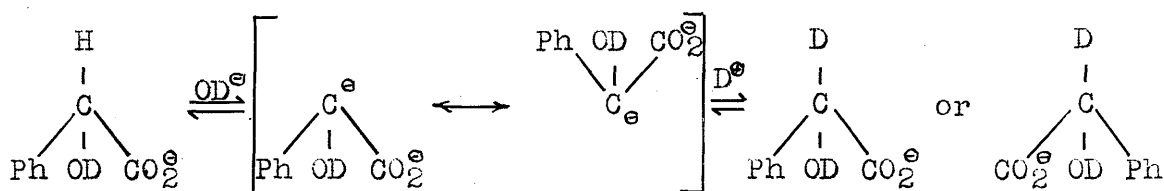
The intermediate ion will be stabilised by resonance
in which structures of the type
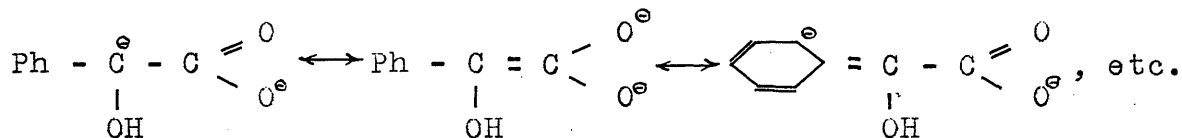
will participate. Since no nuclear deuteration occurs, the
reactivity of the nucleus cannot be increased sufficiently
to permit of an electrophilic substitution reaction result-
ing in the replacement of hydrogen by deuterium:

$$\text{ring} = C - CO_2^{\ominus} \ (OD) \ \underset{}{\overset{D^{\oplus}}{\rightleftharpoons}} \ \text{ring (H D)} = C - CO_2^{\ominus} \ (OD) \ \rightleftharpoons \ \text{ring (D} \ominus) = C - CO_2^{\ominus} \ (OD)$$
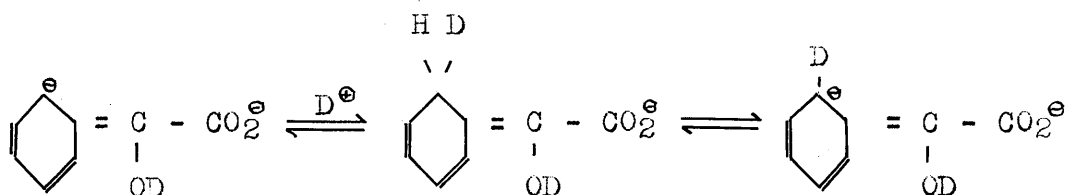
Since, in alkaline solution, the concentration of deuterons will be low, the probability of an aromatic substitution of this nature is not great, and its absence is not really surprising.

Mechanisms of the type outlined above to account for the results of the present investigation have been postulated for many years to explain the racemisation of mandelic acid (44), although it was in general considered that the reaction took place through an intermediate enol-form:

$$C_6H_5 - \underset{OH}{\overset{H}{C}} - C \overset{O}{\underset{OH}{\big<}} \ \rightleftharpoons \ C_6H_5 - \underset{OH}{C} = C \overset{OH}{\underset{OH}{\big<}}$$
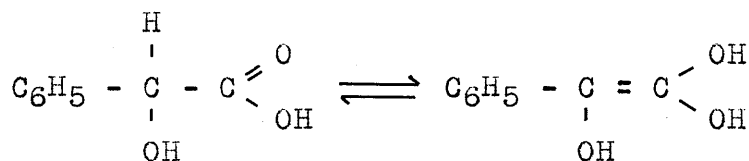
It is now considered that the formation of an enol-form is incidental to the main reaction sequence, the probability of its formation being governed by the relative stabilities of the keto and enol structures.

Only hydrogen atoms adjacent to reactive groupings are likely to be amenable to the ionisation type of mechanism ; the reactive group, by abstraction of electrons

from the neighbouring carbon atom, will facilitate removal
of the hydrogen bound to the latter, and the resultant ion
can be stabilised by resonance involving the charged
centre and the adjacent reactive group. Thus we see why
acid-base catalysed deuterations of carboxylic acids only
result in exchange at the alpha carbon atom, in general.

The establishment of the mechanism of the base-
catalysed racemisation lends support to the explanation
of the difference in stability of mandelic and atrolactic
(α-methyl mandelic) acids with excess base as being due
to the absence of an α-hydrogen atom on the latter.

The base-catalysed exchange was also investigated
by Erlenmeyer (40), who, however, came to the conclusion
that racemisation and exchange were completely independent
processes. Some of the possible sources of error in his
investigations have already been discussed (page 22).

The results of our base-catalysed experiments
would seem to indicate that some reaction is taking place
by a mechanism other than racemisation, but we are not
justified in making any quantitative deductions from this
fact, since the assumptions made in the calculation are
not strictly accurate, and an experimental error can be
considerably magnified in the calculation.

In the presence of a platinum catalyst, we have

found that exchange of all the hydrogen atoms in the
molecule takes place, those attached to the benzene ring
also being substituted by deuterium. The nuclear deut-
eration occurs quite independently of the α-hydrogen
exchange processes, however, there being no correlation
between the number of molecules deuterated in the α-pos-
ition and those undergoing nuclear exchange, and the
molecules substituted in the alpha position are not
necessarily substituted in the nucleus, or vice versa.
It is apparent that the α-hydrogen exchange has no influence
on the ring, so that inversion of a molecule does not
affect the probability of its containing nuclear deuterium,
and the proportions of the isomers which contain nuclear
deuterium are practically the same. The nuclear exchange
occurs at all five available positions, being approximately
twice as great in the meta position as in the ortho and
para. Unfortunately, no information is available on the
directive influence of the side chain in mandelic acid in
electrophilic, nuclear substitutions (see Section 8.3),
but it is unlikely that such a reaction would result in
extensive substitution at all available positions. The
evidence is thus in favour of the ring exchange being a
radical process.

However, radical processes in general show a prefer-

ential ortho-para orientation (46), which would indicate that in the present substitution there is at least a partial ionic character. If it is assumed that the attacking agent is a deuterium atom adsorbed on the catalyst by a semi-polar bond, substitution in the nucleus will result in a predominantly meta orientation if the side chain in mandelic acid withdraws electrons from the ring. Since in alkaline solution the carboxyl group will be present as an anion, the electron withdrawal from the ring will be much less marked in basic solution, and so there will be an overall enhancement of the rate of substitution in the nucleus, as is, indeed, the case. Although in alkaline solution the concentration of deuterons in the solution will be greatly reduced, and hence also the concentration of adsorbed deuterium, the latter will still be much greater than the concentration of adsorbed mandelic acid, if it is assumed that, as in the case of benzene, the adsorption of the ring is relatively weak. The rate-determining factor is thus seen to be the concentration of mandelic acid on the catalyst surface.

The platinum-catalysed exchange of the alpha hydrogen atom is more complex, and our experimental results can best be explained if reaction is assumed to take place by a dissociative mechanism, involving the adsorption of both

reacting species on the catalyst surface in acid medium, but of only one in alkaline solution. It is likely that the adsorbed particles will have at least a partial ionic character, for not only is D_2O a strongly ionising solvent, but the rate of the reaction is very markedly influenced by the pH, being several times faster in alkaline solution. The role of the base must be to influence the dissociation of the α-hydrogen atom, and if such dissociation were to produce radicals, it is difficult to see why a basic catalyst should have such a profound effect on the rate of reaction. Since it is unlikely that adsorption of the benzene nucleus and of the α-position should occur simult- aneously, and certainly not if the former is only chemi- sorbed on two adjacent positions at one time, no correlation between nuclear deuteration and α-hydrogen exchange would be expected, but both processes will occur independently.

At lower temperatures, the platinum-catalysed exchange in acid solution results in deuteration with retention of configuration. This is what would be expected if it is assumed thatreaction occurs between an adsorbed mandelic acid radical and chemisorbed deuterium. The first stage in the process, involving the dissociative chemi- sorption of the mandelic acid molecule, is assumed to be the slow, rate-determining step, the recombination with

adsorbed deuterium occurring relatively quickly.

$$C_6H_5 \quad CO_2H \qquad\qquad C_6H_5 \quad CO_2H \qquad\qquad C_6H_5 \quad CO_2H$$

$$\overset{\displaystyle OH}{\underset{\displaystyle H}{C}} \quad \xrightarrow{\text{slow}} \quad \overset{\displaystyle OH}{\underset{\displaystyle C_{\delta-}}{}} \qquad H_{\delta+} \xrightarrow{+ \; D^{\delta+}} \quad \overset{\displaystyle OH}{\underset{\displaystyle D}{C}}$$

catalyst
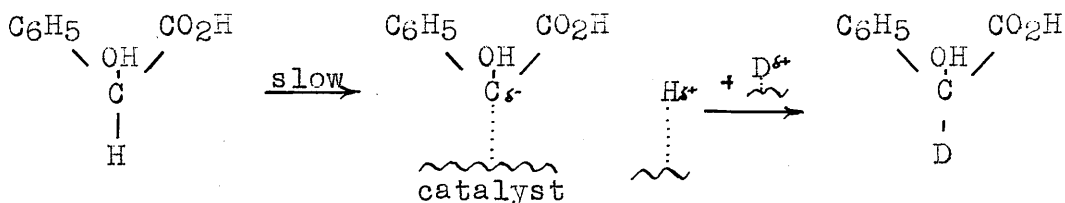
Since it has been shown that adsorbed particles may
be mobile, so that a surface migration will occur with
rise of temperature (47), reaction of the mandelic acid
radical with chemisorbed deuterium is more likely than
with deuterons from the body of the solution, which would
result in an inversion.

At higher temperatures, the platinum-catalysed
reaction does not result solely in a retention of config-
uration, but some inversion occurs by an exchange mechanism,
and the thermal racemisation effect becomes quite consider-
able. This latter type of reaction has been considered to
involve an initial breaking of the bond between the α-
carbon atom and the carboxyl group, and hence, since the rate
of the thermal racemisation is increased somewhat by the
platinum catalyst, adsorption of the molecule on the catalyst
surface must promote the dissociation of the bond. The inc-
rease in the rate is not very great, however, and the
influence of the platinum catalyst is not sufficient to
initiate the reaction at the lower temperature. This is

in agreement with the observation that on transition
metal catalysts, the ease of bond rupture is in the order
H - H > C - H > C - C, which is the reverse of their bond
energies (34). As a result, whilst the C - C bond is the
most readily broken in the normal way, it is the least
affected by a platinum catalyst.

The exchange racemisation which occurs at the higher
temperature can be accounted for if it is considered that
some of the dissociated mandelic acid molecules are de-
sorbed before they have reacted with adsorbed deuterium.
Such radicals will not then retain their original config-
uration, but will lose their stereochemical form, so that
when they do recombine with deuterium, a racemic product
will result.

In alkaline solution, the dissociation of the alpha
hydrogen atom is promoted by the basic catalyst, and since
the latter has a much greater influence on the rate of
exchange and racemisation than a platinum catalyst, it is
reasonable to suppose that the dissociation does not take
place by adsorption on the catalyst. We have shown that
the addition of a platinum catalyst to a base-catalysed
exchange reaction increases the rate of the α-hydrogen
exchange about threefold, and this can be attributed to
the increased rate of recombination of the intermediate

mandelic acid radical with deuterium, whose concentration
will be much greater on the catalyst surface than in the
solution, with a consequent higher probability of being
adjacent to a mandelic acid radical, since the latter
will probably be attracted to the catalyst surface. Thus
it is considered that the platinum-base catalysed exchange
is essentially similar to the base catalysed exchange,
the function of the platinum catalyst being to provide a
more concentrated source of deuterons. A certain amount
of reaction leading to retention of configuration might
be expected also, however, by the dissociative, adsorption
mechanism sketched previously.

In this discussion, we have concluded that several
mechanisms of exchange and racemisation must be operative,
involving two fundamentally different paths: fission of
the alpha hydrogen-carbon bond in the majority of cases,
and in the peculiar case where no exchange occurs, it has
been tentatively suggested that the racemisation takes
place by fission of the alpha carbon-carboxyl link. The
dissociation of the alpha hydrogen is promoted by basic
or metal catalysts, to a greater extent by the former,
and the racemisation and deuteration can be satisfactorily
correlated by postulating the initial dissociation of the
carbon-hydrogen bond.

It is of interest at this point to compare the exchanges of mandelic and lactic acids. Whereas mandelic acid undergoes a slow exchange in acid solution, and a rapid one in alkaline solution, optically active lactic acid heated to 120° in alkaline, neutral, or acid solution, is racemised, if at all, with extreme slowness (48). The rates of deuteration of the two acids in presence of a platinum catalyst are also vastly different; mandelic acid undergoes about 14% of α-exchange in $2\frac{1}{2}$ hours at 140°, whereas lactic acid after 46 hours at $120-130^{\circ}$ only contains 5.5% of alpha deuterium (49). The acids differ markedly in their behaviour to variation of pH. With mandelic acid, the exchange is accelerated greatly by alkali in excess of that required for complete neutralisation of the acid; the degree of deuteration of lactic acid is greatest in acid solution, decreasing to negligible amount with increasing pH. In lactic acid, under the influence of a platinum catalyst, a molecule deuterated in the alpha position is also deuterated on all three beta positions; in mandelic acid, on the other hand, alpha exchange and nuclear deuteration are completely independent, there being no connection between molecules deuterated on the one or other, or both, positions.

The much more facile alpha exchange with mandelic

acid must be attributed to the fact that the radical
formed by dissociation of an alpha hydrogen atom can be
stabilised to some degree by resonance; with lactic acid
the intermediate does not possess the same opportunities
for resonance. Hence the reason for the difference in
the mechanism of exchange: by an initial dissociation in
mandelic acid, but by a bimolecular reaction leading to
Walden Inversion with lactic acid. We are thus no further
forward in determining if the latter is a general mechanism;
it may be that the peculiar properties associated with
the phenyl group make mandelic acid an exception to the
rule where platinum catalysed exchanges are concerned. It
is likely, however, that the ionisation mechanism operative
in the acid-base catalysed exchange is a general one; the
exchange occurs so much faster than usual with mandelic
acid because of the especially favourable opportunities
for resonance.

The different conditions required for the two mech-
anisms explains the contrast in the behaviour of mandelic
and lactic acids with variation in the pH of the solution.
The α-β concomitant deuteration in lactic acid, and the
independence of the alpha and nuclear exchange in mandelic
acid, must be due in some manner to the mode of adsorption
of the molecules on the catalyst surface.

The interesting racemisation without deuteration which occurs with mandelic acid must also be attributed to the resonance stabilisation of the intermediate radical, but it is felt that this is a reaction which would justify further investigation.

5. Experimental Methods

5.1 Outline of the Investigations

Optically active mandelic acid was heated with deuterium oxide in presence of various catalytic agents, and at different temperatures. The reaction was investigated in four differing media, namely, acidic and basic solutions, both with and without the addition of a platinised asbestos catalyst. The deuterations were carried out in evacuated, sealed tubes, into which the reagents had been weighed. After the exchange had proceeded as far as was desired, the mandelic acid was separated from the other contents of the tube, and its active hydrogens (those of the hydroxyl and carboxyl groups) "normalised", i.e., their isotopic concentration reduced to the normal 0.02% D. This is achieved by dissolving the acid in a large excess of water, when the active hydrogens exchange with the hydrogen atoms of the water until their $^H/_D$ ratios are the same (50). (cf. Section 7.2). The overall deuterium content of the acid was measured; and by oxidation of a portion to benzoic acid, and measurement of its deuterium content, the deuterium concentration of the hydrogen attached to the α-carbon atom, and the average concentration per nuclear hydrogen, were calculated. The amount of racemic acid produced during deuteration was calculated from the measured optical rotations before and after reaction.

The partially racemic deutero-mandelic acid was resolved, and by deuterium analyses of samples of the resultant predominantly dextro and laevo fractions, and the benzoic acids produced from them by oxidation, the amount of exchange in the α-position and over the benzene nucleus were calculated for each fraction.

The orientation of the deuterium entering the nucleus was found by nitration of the latter, and separation of two of the mono-nitro isomers produced. Nitration is the only satisfactory substitution reaction which can be employed, as all others show an isotope effect, exchanging with hydrogen more readily than deuterium. The amount of exchange in the ortho, meta, and para positions can readily be found from deuterium analyses of the separated nitro isomers.

5.2 General Experimental Procedure

Calculated quantities of some or all of the under-mentioned reagents were weighed into "Pyrex" glass tubes or round-bottomed flasks, the choice of vessel depending on the quantities of reagents used:

> d or l mandelic acid
>
> heavy water (99.70 % D_2O)
>
> sodium or sodium hydroxide
>
> platinised asbestos (approx. 30% Pt)

Sodium metal was used in preference to sodium hydroxide in the experiments from which quantitative calculations

were made, in order to minimise dilution of the D_2O by an exchange of the deuterium with hydrogen (see Section 8.5). Since sodium reacts preferentially with hydrogen rather than deuterium (51), the net result is to increase, rather than diminish, the concentration of D_2O.

Similarly, in the experiments which yielded quantitative results, dilution of the D_2O was reduced by recrystallising the mandelic acid from heavy water before weighing it into the reaction vessel. By this means, the two readily exchangeable hydrogen atoms of the carboxyl and hydroxyl groups are replaced with deuterium until the concentration of deuterium in these two positions is the same as in the crystallising solvent.

The platinised asbestos catalyst was prepared according to the method quoted by Vogel (52), the formaldehyde reduction of a solution of a platinum compound, with purified asbestos in suspension in the liquid, which yields a product containing approximately 30% by weight of platinum. In the present investigations, the platinum compound used for reduction was platinum chloride, H_2PtCl_6. $6H_2O$, in which the platinum is present in the four-valent state, necessitating the use of a larger amount of reducing agent than that quoted in Vogel, where the initial compound is one of divalent platinum.

In the base catalysed experiments, the heavy water

was placed in the flask, and the sodium, cut into very
small pieces, added gradually, the flask being kept cool
during the addition.   After all the sodium had reacted,
the mandelic acid and platinised asbestos were added.   In
the acid-catalysed experiments, the dry reagents were
placed in the flask first, and the deuterium oxide added
last.

The contents of the tube or flask were then frozen
in liquid air or acetone/CO_2 mixture, the flask evacuated
with a Hyvac pump, and sealed.   The various reaction
vessels were heated in an automatic shaker, thermostatically
controlled at a temperature of about 100° or 140°, for
different time intervals.   Shaking is necessary in the case
of the platinum-catalysed exchanges in order to keep the
catalyst surface in contact with the whole of the liquid.

After a flask had been heated for the desired period
of time, it was opened, and platinum catalyst, if present,
filtered off.   The D_2O was then evaporated from the remain-
ing liquid by a Hyvac pump at as low a temperature as poss-
ible, and thus recovered.   Such solvent recovery is unlikely
to result in any further exchange or racemisation, since
a preliminary investigation had shown that optically active
mandelic acid, dissolved in water containing sodium hydr-
oxide, was unchanged in its specific rotation afterevap-
oration of the water, and extraction of the acid from the

resulting sodium mandelate.

The solid product left after removal of the D_2O was dissolved in water, washings from the platinum catalyst residue and vessels added, and after acidification of the solution with hydrochloric acid, the mandelic acid extracted with ether.

A portion (about $1\frac{1}{2}$g.) of the mandelic acid isolated in this way was purified as described by Erlenmeyer (40). It was shaken with a little pure benzene, the latter filtered off, and the mandelic acid dried. It was then dissolved in distilled water, the resulting solution generally being slightly cloudy, and filtered through a fine filter paper. The filtrate was evaporated to dryness under vacuum, and the mandelic acid collected. A part of it was used for measurement of its optical activity, a 4% solution in water being employed, together with a 1dm. polarimeter tube, the light source being a sodium vapour lamp. A second part was used for deuterium assay, and the remainder oxidised to benzoic acid, also for deuterium assay. Resolution of the larger portion of the acid was achieved, where necessary, with ephedrine.

5.3   Resolution of r-Mandelic Acid

The most satisfactory method of resolution is that with ephedrine (53), which is based on the greater solubility

of ephedrine d-mandelate in alcohol solution.

37.5g. r-mandelic acid, dissolved in 45 ml. absolute alcohol, were slowly added to a warm solution of ephedrine (37.5g. in 67 ml. absolute alcohol). The mixture was warmed at about 60° for two hours, and cooled at +5° over-night. The crystalline complex which separated was coll-ected, washed with fresh alcohol, and then boiled with 55 ml. alcohol. When cold, the solid ephedrine mandelate was filtered off, decomposed with dilute hydrochloric acid, and the mandelic acid extracted with ether (14.9g., $[\alpha]_D = -141°$). A further 30g. ephedrine were dissolved in the original resolution liquor, and to it added 30g. r-mandelic acid dissolved in the alcoholic washings from the previous stage. After warming at 60° for an hour, the complex which separated was treated as in the previous stage, giving 12.4g. acid, $[\alpha]_D = -128°$. Repetition of the process with a further 30g. of ephedrine and 30g. r-mandelic acid yielded another crop of active acid (17.0g., $[\alpha]_D = -119°$).

The final liquors from this series of operations were concentrated to half their volume under reduced pressure; a small amount of solid separated on cooling, which after decomposition gave 5.0g. mandelic acid, $[\alpha]_D = +62°$. The alcohol was then completely removed from the remaining liquor under reduced pressure; the syrupy residue, after

decomposition with hydrochloric acid, gave a final crop
of 41.7g. acid, $[\alpha]_D = +129.5^O$.

Recrystallisation of the first and last crops from
benzene containing a small amount of acetone gave pure
laevo and dextro mandelic acids respectively, having
specific rotations of -160.3^O and $+157.3^O$, for sodium D
light at a temperature of 20°. The active acids melted at
132°. The former specific rotation value was taken as the
rotation of pure acid, being higher than any figure
previously recorded in the literature.

5.4 Oxidation of Mandelic to Benzoic Acid

Mandelic acid may be readily oxidised to benzoic
acid; in the present investigations, the oxidising agent
selected was potassium permanganate. In spite of the fact
that benzoic acid is steam volatile, better yields were
obtained with an acid solution than with added alkali.
Some loss of material was inevitable due to formation of
benzaldehyde as a side product from the intermediately-
formed benzoylformic acid:

$$C_6H_5CHOHCOOH \longrightarrow C_6H_5CO.COOH \longrightarrow C_6H_5COOH$$
$$\downarrow$$
$$C_6H_5CHO$$
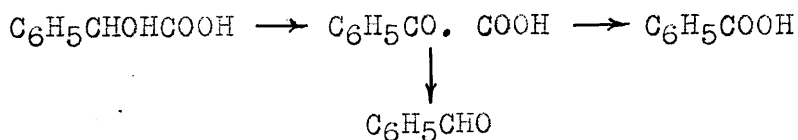
No loss of deuterium from the aromatic ring was
anticipated in the reaction, since the hydrogen-deuterium
exchange in the ring only takes place in presence of a
metal catalyst. This assumption was verified by oxidation

of a sample of deutero-mandelic acid to deutero-benzoic acid, isolation of the latter, and further treatment of part of it as in the first oxidation, using the same quantity of oxidising agent and heating for the same time. The two samples of benzoic acid were analysed for their deuterium content, which was the same, showing that the oxidation did not result in any hydrogen-deuterium exchange in the ring. Separation of the isotopic species by fractional crystallisation is unlikely, since a sample of benzoic acid obtained from the filtrate after removal of manganese dioxide had the same deuterium content as one of the acid extracted from the MnO_2 residues.

Quantities used in the oxidation were in the ratio 1 part mandelic acid, 2 parts potassium permanganate, 20 parts water. Considerable frothing and heat evolution took place on mixing; the mixture was refluxed for one to two hours, and the precipitated manganese dioxide filtered off, and washed with a little hot water. Benzoic acid was precipitated by addition of concentrated hydrochloric acid to the filtrate, a few sodium sulphite crystals being present to dissolve any colloidal manganese dioxide, or remove any unchanged potassium permanganate. Yields of up to 90% were obtained by this method.

5.5 Resolution of Partially Inactive Mandelic Acid

The separation of mandelic acid containing about 90%

of d-form into two active components of opposite rotation could not be achieved directly. To obtain a satisfactory separation of the laevo isomer, the alkaloidal reagent must be chosen so that the l-salt is the least soluble, and since it is only present in small quantity, its direct crystallisation is very difficult. On dissolving the mandelic acid in water, however, the material crystallising out is almost pure dextro acid, so that the remaining acid obtained on extraction of the mother liquors contains a higher proportion of the laevo form.

Resolution of this less active material was found to be most satisfactory using ephedrine. The procedure was the same as that outlined above for resolving mandelic acid, except that only one separation was carried out, and the amounts of alcohol used for dissolving ephedrine and mandelic acid were reduced by about 10%. The laevo form was not recrystallised after resolution; the dextro portion was combined with the acid which had earlier been removed by crystallisation, and both thoroughly mixed.

5.6 Preparation of the Nitro Derivatives

Mandelic acid is readily susceptible to oxidation, and so its direct nitration is not possible. However, the nitrobenzoic acid isomers may be readily prepared and separated, under relatively mild conditions, and so the mandelic acid was first oxidised to benzoic acid. The

simplest method of obtaining the nitrobenzoic acid isomers
was found to be by nitration of the methyl ester of ben-
zoic acid, prepared by the Fischer-Speier method of ester-
ification (54), using dry hydrogen chloride gas as catalyst.

The methyl nitrobenzoate isomers may be obtained
from methyl benzoate by treatment with nitric acid; the
separation is based on the fact that the ortho ester is a
liquid, readily soluble in methyl alcohol, whereas the
solid meta ester is much less soluble in alcohol (55).
One part of methyl benzoate was gradually added to fuming
nitric acid (5 parts), the latter having been purified by
passing a current of nitrogen through it at 60° until it
was almost colourless. By this treatment, oxides of
nitrogen, whose presence has been found to supress nitration
generally (56), are removed. During the addition of methyl
benzoate, the nitric acid was kept cool by iced water.
After all the ester had been added, the mixture was left
for about five minutes, then poured into crushed ice. The
yellowish solid which separated was filtered, and washed.
The mother liquors and washings were evaporated to about
half their volume, and saturated with sodium carbonate.
They were then extracted with ether, giving a small amount
of a yellow liquid.

The solid nitrated product was recrystallised from
methyl alcohol, yielding methyl m-nitrobenzoate, m.p. 78°.
The liquid product, consisting mainly of methyl o-nitro-

benzoate, was treated with an equal volume of methyl alcohol, cooled, and the small quantity of solid coming out of solution filtered off and discarded. The methyl alcohol was then distilled off.

Both esters were hydrolysed to the free acids with baryta water. Removal of any remaining traces of contaminating isomer can be achieved by this method, due to the large difference in the solubilities of the barium salts of ortho and meta nitrobenzoic acids (57). The hydrolysate from the solid meta ester was allowed to cool, when barium m-nitrobenzoate crystallised out. It was collected, and decomposed with hydrochloric acid, giving the free m-nitrobenzoic acid, m.p. 140-141°.

The isolation of the ortho isomer is rather more difficult, since it is present in small amount. The hydrolysis liquor was evaporated to small bulk, and the solid which separated on cooling, consisting largely of barium hydroxide, filtered off. The filtrate was again evaporated, a few drops of concentrated hydrochloric acid added, and the solution warmed for a few minutes. On allowing to cool, needles of o-nitrobenzoic acid, m.p. 143-4° crystallised out.

The melting points of both isomers remained constant in mixed melting point determinations with pure meta and ortho nitrobenzoic acids respectively.

5.7 Deuterium Assays

The mandelic and benzoic acids, after rigorous
drying, were combusted in a muffle furnace, and the water
produced collected in a U-tube immersed in acetone/CO_2
mixture. Due to the volatility of benzoic acid, special
care had to be exercised to ensure that it was fully
oxidised. The water was purified by refluxing with alk-
aline permanganate, and distilling three times, the whole
series of operations being carried out under a high
vacuum (58).

The deuterium content of the water was measured by
the gradient tube method (59), the liquids used in the
tube being xylene and bromobenzene.

6. Details of Experiments and Analysis of Results

6.1 Acid-catalysed Deuterations

The following investigations were carried out:

Table 1.

Experiment No.	1	2	3	4
Wt. of mandelic acid	0.60g.	0.517g.	0.665g.	0.50g.
Wt. of 99.70% D_2O	0.70g.	0.687g.	0.874g.	0.71g.
Temperature of heating	$100^\circ C$	$140^\circ C$	$142^\circ C$	$138^\circ C$
Time of heating	4 hrs.	$2\frac{1}{2}$hrs.	51 hrs.	117hrs.
% of dextro form present initially	3.30	99.45	3.26	3.30
% of dextro form present after reaction	3.18	92.80	44.57	50.0
Atom % D in α-position	0	0.50	9.62	13.46

It would appear that the rates of racemisation and deuteration at 100° must be very slow. At 140°, however, considerable racemisation takes place, accompanied by a small amount of α-hydrogen exchange. This result is confirmed by heating for a longer period of time at the latter temperature, when complete racemisation of the acid occurs, together with a partial exchange, in the alpha position only. No exchange of the nuclear hydrogen atoms occurred.

In view of the fact that racemisation is taking
place without a corresponding deuteration, an attempt was
made to investigate the role of the heavy water in the
reaction by substituting for it an inert solvent. Ethylene
glycol dimethyl ether, benzene, and toluene were used as
solvents in successive experiments, heating with optically
active mandelic acid at 140°. In all cases, however, the
final product proved not to be pure mandelic acid, but
contained appreciable amounts of a material which was
only soluble in a large volume of water, although it was
readily soluble in alkaline solution or acetone. Measure-
ment of the specific rotation of the isolated product, in
acetone solution, indicated that the extent of racemisation
was of the same order as when the racemisation was carried
out in an aqueous medium, but the results of these invest-
igations cannot by any means be regarded as conclusive.

In another experiment, mandelic acid was heated alone
in a sealed, evacuated tube at 140°. At this temperature,
the acid melts, and so any reaction takes place in the
liquid phase. The acid recovered after heating for $2\frac{1}{2}$ hours
was slightly sticky, but there was no evidence to suggest
the formation of side products such as benzaldehyde. (The
latter had been detected in the racemisations carried out
in a heavy water solvent, both by its smell, and by the
formation of a phenylhydrazone on adding 2:4-dinitrophenyl-

hydrazine to a sample of the recovered D_2O solvent, after removal of traces of mandelic acid from it by making alkaline and distilling.) The reaction product after heating mandelic acid alone was dissolved in water, and, after distilling off the water under vacuum, the resulting material was quite dry, and its rotation was measured in aqueous acetone solution, when it was found that a racemisation of the acid had taken place, at least as great as when the acid was heated with a solvent present (Table 2).

Table 2.

Experiment No.	Wt. of mandelic acid	Wt. of H_2O	Initial specific rotation	Final specific rotation
	g.	g.	$[\alpha]_D$	$[\alpha]_D$
1	0.45	0.54	-151.4°	-141.1°
2	0.40	..	-151.4°	-138.5°

The possibility of the exchange reaction being acid-catalysed was investigated by heating mandelic acid and D_2O with about 3% by weight of hydrochloric acid. The amount of deuterium exchanging in the α-position was no greater than that occurring in absence of the mineral acid, however, and so it would appear that the reaction is not subject to acid catalysis. In another experiment, in which heating was continued for a considerable time, the

contents of the tube became yellow, with formation of two layers, roughly equal in volume. On opening the tube, quite a considerable release of pressure occurred (probably due to carbon dioxide gas), and the reaction product had a very strong smell of benzaldehyde.

Thus, on heating mandelic acid and water, considerable racemisation of the acid occurs at 140°, but this does not appear to be dependent on the solvent in any way. A slow exchange of the α-hydrogen atom takes place simultaneously, the exchange not being subject to acid catalysis.

6.2 Base-catalysed Deuterations

An investigation of the change in the degree of deuteration with varying pH was carried out. It was found that no racemisation nor deuteration took place at 100° unless there was an excess of alkali present over that required for complete neutralisation of the mandelic acid (Table 3).

Table 3.

Experiment No.	1	2	3	4
Wt. of mandelic acid	.6045g	.6067g	.6089g	.5948g
Wt. of D_2O	.7227g	.6931g	.7004g	.7116g
Wt. of NaOH	..	.0796	.1602g	.1871g
Fraction of acid neutralised	0	$\frac{1}{2}$	1	19.5% excess base
Atom % D in α-position	0	0	0	~27
% of d-isomer present initially	1.62	1.62	1.62	1.62
% of d-isomer present finally	1.62	1.56	1.59	16.74

A fuller investigation of the base-catalysed exchange was carried out using about 20% base in excess of the amount required for complete neutralisation of the mandelic acid. 8.29g. mandelic acid, 10.19g. 99.70% D_2O, and 1.5g. sodium were heated in an evacuated, sealed tube at 100° (±5°) for 30 minutes.

Deuterium assays of the mandelic and benzoic acids after reaction, and of the mandelic acid from each of the fractions obtained by a partial resolution of the deuterated

acid were made. The results are incorporated in Table 4, along with the corresponding specific rotations of the samples.

Table 4.

	Wt. % D_2O	Atom % D	Specific rotation
Mandelic acid before reaction	..	18.76	+158.5^O
Mandelic acid after reaction	2.03	1.83	+135.5^O
Benzoic acid	0.02	normal	..
d-portion of resolved acid	1.34	1.21	+153.7^O
l-portion of resolved acid	8.65	7.85	-78.2^O

If the atom percentage deuterium in the α-position of the deuterated mandelic acid is y, and in the α-position of the dextro and laevo fractions of the resolved acid y_d and y_l respectively, then, since the other seven hydrogen atoms in the molecule have a normal deuterium content,

$$\frac{y + 7 \times .02}{8} = 1.83 \qquad y = 14.50$$

$$\frac{y_d + 7 \times .02}{8} = 1.21 \qquad y_d = 9.54$$

$$\frac{y_l + 7 \times .02}{8} = 7.85 \qquad y_l = 62.66$$

From the measured specific rotation values, the relative proportions of the optical isomers present at each stage may be calculated (see Section 7.1), and these are shown in Table 5.

Table 5.

Mandelic Acid	% d	% l
Before deuteration	99.93	0.07
After deuteration	92.30	7.70
d-portion of resolved acid	97.97	2.03
l-portion of resolved acid	25.51	74.49

The initial and final isotopic compositions of the solvent are 97.31 atom % D and 96.54 atom % D respectively (see Section 7.2), and hence the average concentration of the water during the deuteration is 96.93 atom % D.

If it is assumed that the reaction proceeds by a mechanism leading to Walden Inversion, and ignoring any back reaction, it can be calculated that we should expect 15.01% of l-form to be present at the end of the reaction (see Section 7.3). However, if the reaction involves racemisation, the percentage of l-form expected would be 7.54%. Since it has been found experimentally that the

percentage of laevo isomer is 7.70% (Table 5), it can be concluded that the reaction proceeds largely, if not entirely, by a racemisation mechanism.

From the isotopic compositions of the resolved fractions, the deuterium concentration in the α-position which would be expected on the basis of racemisation and inversion mechanisms may be calculated (see Section 7.4), and a comparison of the computed values with those realised experimentally are incorporated in Table 6.

Table 6.

	d-fraction	l-fraction
Atom % D in α-position found experimentally	9.54	62.66
Atom % D calculated on basis of Walden Inversion mechanism	1.95	71.55
Atom % D calculated on basis of a racemisation mechanism	9.81	73.64

These results confirm the suggestion that the reaction proceeds mainly by a racemisation mechanism.

The fact that the calculated value for the deuterium concentration in the laevo fraction is higher than that actually found would suggest that some of the laevo isomer is being formed by a mechanism not involving a synchronous deuteration. Such a reaction has been observed to occur in

the non-catalysed racemisations, but onlyat higher temp-
eratures than that employed here.

6.3 Platinum-catalysed deuterations

Deuteration of mandelic acid in presence of a platinum
catalyst was carried out at 100°, at which temperature
neither exchange nor racemisation proceeds at an appreciable
rate without the addition of a catalyst. The platinum
catalyst promotes deuteration, both of the α-hydrogen atom
and the hydrogen atoms of the benzene ring, without, how-
ever, any change in the specific rotation of the acid (Table
7). The reaction would thus appear to be an exchange with
retention of configuration.

Table 7.

Experiment No.	1	2	3
Wt. of mandelic acid	0.60g	0.70g	1.21g
Wt. of D_2O	0.70g	1.40g	1.40g
Wt. of platinum catalyst	-	0.12g	0.12g
Specific rotation before heating	-149.7°	-149.7°	-149.7°
Specific rotation after heating	-150.1°	-149.3°	-149.7°
Atom % D in α-position	0	~6.3	0.74
Atom % D in benzene ring	0	~8.3	0.64

The platinum catalysts used in experiments 2 and 3
were from different sources; in 3, the catalyst was an
aged sample, having been prepared about five years prev-
iously. This may account for the low degree of exchange
in the latter investigation.

The deuteration was also investigated at 140°, at
which temperature racemisation proceeds simultaneously
with deuteration. Due to the complexity of the results,
two sets of experiments were carried out, each platinum-
catalysed deuteration being accompanied by a control
experiment with no catalyst present (Table 8). In the
platinum-catalysed experiments, a resolution of the deut-
erated acid was carried out.

Table 8.

Expt. No.	Wt. of mandelic acid g.	Wt. of D_2O g.	Wt. of platinum catalyst g.	Time of heating hrs.
1	0.517	0.687	..	$2\frac{1}{2}$
2	10.29	12.43	1.02	
3	0.928	0.878	..	$2\frac{1}{4}$
4	6.336	6.440	0.66	

From the results of the deuterium assays of the

mandelic and benzoic acids, the atom % deuterium in the
α-position and the average value per hydrogen atom of the
benzene ring were calculated (Table 9). For most of the
deuterium estimations, the water obtained by combustion
of the acid was diluted with normal water before measuring
its density.

Table 9.

Expt. No.		Mandelic acid after deuteration	d-fraction of resolved acid	l-fraction of resolved acid
1	Atom % D in α-position	0.58	..	..
	Atom % D per ring posn.	0	..	..
2	Atom % D per α-position	11.83	10.18	16.93
	Atom % D per ring posn.	21.13	21.01	20.75
3	Atom % D in α-position	0.90	..	..
	Atom % D per ring posn.	0	..	..
4	Atom % D in α-position	7.94	5.48	13.14
	Atom % D per ring posn.	19.09	19.20	19.17

The specific rotations of the various fractions were as follows:

Table 10.

	$[\alpha]_D$			
	1	2	3	4
Mandelic acid before deuteration	+157.0°	+158.5°	+138.4°	+138.4°
Mandelic acid after deuteration	+137.3°	+117.4°	+126.6°	+108.3°
Dextro fraction of resolved acid	-	+151.1°	-	+141.1°
Laevo fraction of resolved acid	-	-95.0°	-	-59.0°

The amount of l-isomer present at each stage was computed (Table 11).

Table 11.

	% of laevo isomer present			
	1	2	3	4
Mandelic acid before exchange	0.55	0.07	6.41	6.41
Mandelic acid after exchange	7.20	13.10	10.50	15.99
Dextro fraction of resolved acid	-	2.51	-	5.70
Laevo fraction of resolved acid	-	79.68	-	68.54

The percentages of laevo isomer which we should finally expect to be present if the reaction were one leading to racemisation or Walden Inversion were calculated, as in Sections 7.2 and 7.3, for the platinum-catalysed exchanges 2 and 4. The results of these computations are shown in Table 12.

Table 12.

Experiment No.	2	4
Average solvent concentration Atom % D	94.11	93.49
% laevo isomer found experimentally	13.10	15.99
% laevo isomer calculated for a racemisation mechanism	6.35	10.12
% laevo isomer calculated for a Walden Inversion mechanism	12.62	13.82

It would thus appear on the basis of the simple calculation that the exchange occurs largely by a Walden Inversion mechanism. However, an analysis of the results for the resolved fractions of the deuterated acid leads to deuterium concentration values showing a very marked discrepancy from the experimentally realised ones, the figures for the laevo fractions, in particular, being some four times greater than the actual ones. An explanation of this lack of correlation between calculated and experimental

values is to be found when it is remembered that mandelic
acid may be racemised in absence of a catalyst at 140°,
and that at lower temperatures deuteration with retention
of configuration occurs. If it is assumed that the rate of
the thermal racemisation reaction is independent of the
platinum catalyst, so that the amount of racemisation tak-
ing place in the control experiments 1 and 3 is the same
as that occurring by a thermal racemisation mechanism in
the platinum-catalysed exchanges 2 and 4 respectively, a
modified series of results for the percentage of 1-form,
and the amount of deuterium in the α-positions of the
resolved fractions, calculated on the basis of a Walden
Inversion or a racemisation mechanism, may be obtained.
(Table 13). In the derivation of the figures it has been
assumed that no molecule undergoes a reaction more than
once, which is equivalent to ignoring the occurrence of a
"back reaction".

Table 13.

Experiment No.	2	4
% laevo isomer found experimentally	13.10	15.99
% laevo isomer calculated for a racemisation mechanism	13.06	14.20
% laevo isomer calculated for a Walden Inversion mechanism	19.34	17.90

Table 13 (continued).

Experiment No.	2.		4.	
	dextro fraction	laevo fraction	dextro fraction	laevo fraction
Atom % D in α-posn. found experimentally	10.18	16.93	5.48	13.14
Atom % D calculated for a racemisation mechanism	7.81	37.58	8.71	27.44
Atom % D calculated for an inversion mechanism	1.14	36.16	2.39	23.75

These values obtained for Walden Inversion or racemisation mechanisms do not bear a sufficiently close relation to the experimental ones to justify the acceptance of either as the predominating mechanism.

It would appear that the reaction is complex, mechanisms involving racemisation without deuteration, deuteration with retention of configuration, and either (or both) deuteration by racemisation or Walden Inversion, all playing a part.

In presence of a platinum catalyst, exchange occurs in the benzene nucleus as well as on the α-carbon atom (Table 9), and the relative amounts of deuterium in the different ring positions was determined (cf. Section 5.6). 8.11g. mandelic acid, 9.07g. heavy water and 0.82g.

platinised asbestos were heated in a sealed tube at 140°,
and deuterium analyses of the products carried out (Table
14).

Table 14.

	Wt. % D_2O	Atom % D
Benzoic acid	4.80	4.34
m-Nitrobenzoic acid	4.11	3.71
o-Nitrobenzoic acid	1.39*	4.49

*Deuterated acid diluted with normal o-nitrobenzoic acid
before combustion.

If the atom percentage of deuterium in the ortho,
meta, and para positions of the ring are o, m, and p resp-
ectively, then

$$\frac{2o + 2m + p + .02}{6} = 4.34$$

$$\frac{2o + m + p + .02}{5} = 3.71$$

$$\frac{o + 2m + p + .02}{5} = 4.49$$

Hence   o = 3.59 ; m = 7.49 ; p = 3.86 (by difference)

The deuterium is thus distributed between the ring
positions as follows:

ortho position   13.80%

meta   position   28.78%

para   position   14.84%

The degree of accuracy of these results is not very high, since a small error in the deuterium estimation will result in a greatly magnified error in the final result. The significance of the isomeric proportions is qualitative rather than quantitative, and we are probably not justified in drawing any conclusions from them beyond the fact that exchange occurs in all three positions, greatest in amount in the meta position.

6.4 Platinum-base catalysed Deuterations

8.96g. mandelic acid, 11.02g. 99.70% D_2O, 1.6g. sodium, and 0.90g. platinised asbestos were heated in an evacuated, sealed tube at 100° ($\pm5°$) for 17 minutes. Addition of this amount of sodium results in about 18.5% excess basic catalyst in the solution.

The atom % D on the α-carbon atom, and the average value per hydrogen atom of the benzene ring were calculated from the deuterium assays of the mandelic and benzoic acid samples, and are shown in Table 15.

Table 15.

	Atom % D in α-position	Atom % D per ring posn.
Mandelic acid after deuteration	21.14	9.63
Dextro fraction of resolved acid	13.50	9.65
Laevo fraction of resolved acid	71.74	9.60

From the specific rotations of the various samples, the relative proportions of the optical isomers present at each stage were calculated (Table 16).

Table 16.

	Specific rotation $[\alpha]_D$	% dextro isomer	% laevo isomer
Mandelic acid before deuteration	$+157.7^{O}$	99.67	0.33
Mandelic acid after deuteration	$+122.5^{O}$	88.39	11.61
Dextro fraction of resolved acid	$+152.7^{O}$	97.82	2.18
Laevo fraction of resolved acid	-121.8^{O}	11.71	88.29

The average solvent concentration during the exchange was 95.50 atom % D (see Section 7.2), and if the reaction is assumed to occur solely by a mechanism leading to inversion, the percentage of laevo isomer expected at the end

of the reaction would be 22.33%, ignoring any back reaction. A racemisation mechanism would lead to there being present 11.33% laevo form, and since it is found that 11.61% of l-isomer are present finally, the reaction would appear to be largely a racemisation exchange.

From a consideration of the amounts of isomers in the deuterated acid and in the resolved fractions, the amount of deuterium to be expected in the latter can be calculated:

Table 17.

	d-fraction	l-fraction
Atom % D in α-position found experimentally	13.50	71.74
Atom % D calculated for a racemisation mechanism	14.03	83.87
Atom % D calculated for a Walden Inversion mechanism	2.07	82.24

These results indicate that the greater part of the reaction occurs by a racemisation mechanism. The discrepancy between calculated and experimental values for the atom percentage deuterium in the laevo fraction is of the same order as that in the base-catalysed experiment (Table 6).

In an investigation of the ring deuteration, 8.10g.

mandelic acid, 9.02g. D$_2$O, 1.4g. sodium, and 0.81g. plat-
inised asbestos were heated in a sealed tube for 30 minutes
at 100°. The deuterium analyses gave the following
results (Table 18):

Table 18.

	Wt. % D$_2$O	Atom % D
Benzoic acid	7.98	7.24
m-Nitrobenzoic acid	7.02	6.36

These results indicate that the meta position of
the ring contains 26.81% of deuterium, which figure is
in good agreement with that obtained in the platinum-
catalysed exchange.

6.5 Amount of reaction occuring by the various mechanisms

The exchange and racemisation reactions can be
accounted for on the basis of the following degrees of
reaction by the various mechanisms (see Section 7.5).

Table 19.

	Acid-catalysed	Base-catalysed	Platinum-catalysed	Pt/base catalysed
Conditions of reaction	$2\frac{1}{2}$ hrs. at 140°	30 min. at 100°	$2\frac{1}{2}$ hrs. at 140°	17 min. at 100°
% of molecules reacting by a racemisation mechanism	0.51	13.49	5.70	20.72
% of molecules reacting with retention of configuration	-	1.20	6.61	1.32
% of molecules undergoing racemisation without deut[n].	12.94	1.79	20.39	1.99

7. Explanatory Notes on the Calculations

7.1 Calculation of the Proportions of Isomers Present

The relative amounts of dextro and laevo forms present in any given sample of deutero-mandelic acid may be readily calculated if it is assumed that the normal and deutero mandelic acids both have the same molecular rotation (see Section 8.5).

If the specific rotation of a sample of deutero-mandelic acid is α, and its atom percentage of deuterium is x, then the deutero-mandelic acid has a molecular weight of $(152 + \frac{8x}{100})$.

Hence its molecular rotation, β, is $(152 + \frac{8x}{100}).\alpha$

Now, the molecular rotation of normal d-mandelic acid is $152 \times 160.3 = 24365^{\circ}$ (cf. Section 5.3).

Hence, if it is assumed that optically pure, normal and deutero mandelic acids do not differ significantly in their molecular rotations,
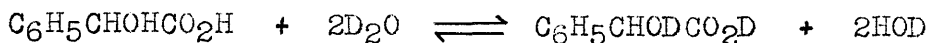
$$\% \text{ of laevo form present} = \frac{1 - \frac{\beta}{24365}}{2} \times 100$$

$$\% \text{ of dextro form present} = \frac{1 + \frac{\beta}{24365}}{2} \times 100$$

7.2 Average Concentration of Solvent during the Experiment

Mixing the mandelic acid and D_2O results in the

equilibrium

$$C_6H_5CHOHCO_2H \ + \ 2D_2O \ \rightleftharpoons \ C_6H_5CHODCO_2D \ + \ 2HOD$$

being set up. If it is assumed that $(\frac{D}{H})$ in water $= (\frac{D}{H})$ in solute[*] when equilibrium has been reached, which is the case for most molecules where no great change in configuration is induced (50), then after mixing,

atom % D in water $=$ atom % D in mandelic acid[*] $= c_0$.

Now, the heavy water used has a concentration of 99.70%, which is equivalent to a deuterium content of 99.68 atom % D.

The mandelic acid, previously recrystallised from heavy water, has an initial deuterium concentration of A atom % D, and from this the average deuterium content of the two exchangeable atoms, z, may readily be found.

Hence on mixing 1 mole of mandelic acid with m moles D_2O,

Decrease in deuterium content of the solvent $= \left[\dfrac{(99.68 - c_0)}{100}\right] \times m \times 2$ g-atom D

Increase in deuterium of the acid $= \left[\dfrac{(c_0 - z)}{100}\right] \times 1 \times 2$ g-atom D

Hence the concentration of solvent at the beginning of the experiment, $c_0 = \left(\dfrac{99.68m + z}{1 + m}\right)$ atom % D.

---

[*] Only the two exchangeable hydrogen atoms of the mandelic acid are considered, i.e., those of the hydroxyl and carboxyl groups.

In the calculation of the molar quantity of mandelic acid present, the molecular weight of the acid is taken to be ($152 + \frac{8A}{100}$).

Before the deuteration, the solvent contains c_0 atom % D, and the mandelic acid z_0 atom % D. z_0 may be found from the concentration of deuterium in the exchangeable positions (C_0), and in the others (normal).

$$z_0 = \frac{2c_0 + 6 \times .02}{8} = \frac{c_0 + .06}{4}$$

After reaction, the mandelic acid has a deuterium content of z_t atom % D, and the solvent of c_t atom % D. z_t may be found from the concentration of deuterium in the two active positions (c_t, which, since it does not differ greatly from c_0, may, as a first approximation, be put equal to c_0), and in the others (z', which is readily obtained from the deuterium assay of the deuterated mandelic acid, for which estimation, the two active hydrogens have been "normalised" with respect to their deuterium content).

$$z_t = \frac{2c_0 + 6z'}{8} = \frac{c_0 + 3z'}{4}$$

Then,

The increase in deuterium content of the acid $= \left[\frac{(z_t - z_0)}{100} \times 1 \times 8 \right]$ g-atom D

The decrease in deuterium content of the solvent $= \left[\frac{(c_0 - c_t)}{100} \times m \times 2 \right]$ g-atom D

Hence the concentration of solvent at the end of
the experiment, $c_t = (\dfrac{c_0 \cdot m - 4z_t + 4z_0}{m})$ atom % D.

Over small sections, the graph of concentration
D_2O - time will approximate to a straight line. Hence if
c_t and c_0 do not differ by too great an amount, the mean
of them will give a value for the average concentration
of D_2O, c_a, in the solution during the experiment.

$$c_a = \frac{c_t + c_0}{2}$$

7.3   Calculation of % isomers present finally

If the concentration of deuterium in the α-position
is finally Q atom % D, the total number of molecules sub-
stituted in the α-position, n, is ($Q \times \dfrac{100}{c_a}$), taking
account of the exchanges which result in the substitution
of a hydrogen, instead of a deuterium, atom. The assumption
is made here that H and D atoms react with the acid at the
same rate, which is not strictly true, protons being trans-
ferred more quickly than deuterons (see Section 8.5).
However, since the protons only constitute between three
and six percent of the whole, the error introduced in this
way will not be too large.

There are three courses, differing in their effect
on the stereochemical configuration of the molecule, by

which an exchange of the α-hydrogen atom may take place:

a) every reaction leads to a change of configuration at the alpha carbon atom (Walden Inversion),

b) an attacked molecule has an equal chance of retaining its configuration or undergoing an inversion (racemisation),

c) reaction leads to no configurational change (retention of configuration).

With the latter type of mechanism, the proportion of isomers present finally will be identical with the original.

If the reaction occurs by a Walden Inversion mechanism, each substitution resulting in an inversion of configuration at that molecule, we should finally expect

$$d_0 \times \frac{n}{100} + (l_0 - l_0 \times \frac{n}{100}) \text{ \% l-form,}$$

where d_0 and l_0 are the percentages of dextro and laevo isomers present before deuteration. It is assumed that there is no preferential deuteration of either optical isomer on configurational grounds, but that each behaves in an identical manner in exchange phenomena.

In this first instance, the "back reaction", resulting in a molecule being substituted more than once, has been neglected. However, the l (or d) molecules formed by inversion will be subject to further attack, and may undergo

a second inversion. Thus the amount of laevo isomer
formed will not be equal to the number of d-molecules
attacked, but only those attacked an odd number of times,
and so the actual proportion of molecules which are in-
verted is less than the proportion which are deuterated.
In consequence, the simple calculation of the percentage
of l-isomer formed gives a value which is too high, the
discrepancy increasing with the extent of reaction.

A racemisation mechanism, with an equal probability
of an attacked molecule either retaining or inverting its
configuration, would result in their being finally present

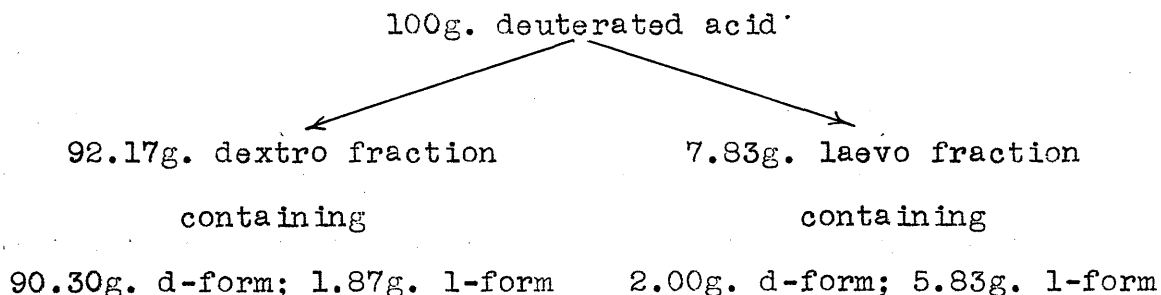$$d_0 \times \frac{n}{200} + (l_0 - l_0 \times \frac{n}{200}) \% \text{ of l-form.}$$

. In this case, the occurrence of a "back reaction"
will lead to some of the molecules already deuterated in
the α-position undergoing an inversion. However, since
equal amounts of d and l isomers are formed by the first
substitutions, equal amounts of them will undergo a second
inversion, and there will be no change in the extent of
racemisation.

7.4 Correlation of Deuterium Contents and Isotopic

Proportions of the Resolved Fractions

The computation of the deuterium contents of the
resolved fractions from the data for the deuterated acid,

and the percentage of laevo form in the resolved fractions, will be demonstrated for a particular case, that of the base-catalysed experiment (cf. Section 6.2).

The deuterated acid, containing 7.70% of laevo form, was resolved into two fractions containing 2.03% and 74.49% of l-form. From this data, it can be readily deduced that every 100g. of deuterated acid will be resolved into the two fractions as follows:

<div align="center">100g. deuterated acid·</div>

<div align="center">92.17g. dextro fraction   7.83g. laevo fraction</div>
<div align="center">containing   containing</div>

90.30g. d-form; 1.87g. l-form   2.00g. d-form; 5.83g. l-form

If it is assumed that a fraction x of the acid is substituted once, and that no further substitutions occur, then, if the reaction is one leading solely to Walden Inversion,

99.93% of d-acid present originally give rise to

99.93x % l-form; 99.93(1 - x) % d-form.

0.07% of l-acid present originally give rise to

0.07x % d-form ; 0.07(1 - x) % l-form.

Hence there are finally present

99.93x + 0.07(1 - x) % of l-form.

i.e., 99.86x + 0.07 = 7.70

so that $x = 0.0764$

Hence

% of l-form obtained by exchange $= 99.93 \times 0.0764 = 7.635$

% of d-form obtained by exchange $= 0.07 \times 0.0764 = 0.005$

Since the average solvent concentration is 96.93 atom % D , if we assume that H and D react at the same rate in substitution, we should expect that 96.93% of the molecules substituted will be deuterated in the α-position, so that

% of deuterated l-acid finally present $= 7.635 \times \dfrac{96.93}{100} = 7.399$

% of deuterated d-acid finally present $= 0.005 \times \dfrac{96.93}{100} = 0.005$

Hence the dextro and laevo fractions will contain respectively

$\dfrac{7.399}{7.70} \times 1.87 = 1.797$g. deuterated l-form

$\dfrac{0.005}{92.30} \times 90.30 = 0.005$g. deuterated d-form

Total $= 1.802$g. deuterated acid

and $\dfrac{7.399}{7.70} \times 5.83 = 5.603$g. deuterated l-form

$\dfrac{0.005}{92.30} \times 2.00 = 0$ g. deuterated d-form

Total $= 5.603$g. deuterated acid

In this step, the assumption has been made that in the resolution, the normal and deutero acids show the same behaviour to the resolving agent as regards the solubilities

of their enantiomorphic salts (see Section 8.2).

The two resolved fractions will therefore contain

$$\frac{1.802}{92.17} = \underline{1.95 \text{ atom } \% \text{ D}} \text{ in the dextro form, and}$$

$$\frac{5.603}{7.83} = \underline{71.55 \text{ atom } \% \text{ D}} \text{ in the laevo form.}$$

If, however, the mechanism is one leading solely to racemisation, and a fraction 2x of the acid is substituted,

$$x = 0.0764.$$

For every molecule substituted with inversion, one is substituted with retention of configuration, so that

% of l (or d) form obtained by exchange =

$$99.93 \times 0.0764 + 0.07 \times 0.0764 = 7.64.$$

and % of deuterated l (or d) acid finally present =

$$7.64 \times \frac{96.93}{100} = 7.404.$$

Hence the dextro and laevo fractions will contain respectively

$$\frac{7.404}{7.70} \times 1.87 = 1.798g. \text{ deuterated l-form}$$

$$\frac{7.404}{92.30} \times 90.30 = \underline{7.243g. \text{ deuterated d-form}}$$

$$\text{Total} = 9.041g. \text{ deuterated acid.}$$

and $\quad \dfrac{7.404}{7.70} \times 5.83 = 5.606g. \text{ deuterated l-form}$

$$\frac{7.404}{92.30} \times 2.00 = \underline{0.160g. \text{ deuterated d-form}}$$

$$\text{Total} = 5.766g. \text{ deuterated acid.}$$

The two resolved fractions will therefore contain

$$\frac{9.041}{92.17} \times 100 = \underline{9.81 \text{ atom } \% \text{ D}} \text{ in the dextro fraction,}$$

and $\frac{5.766}{7.83} \times 100 = \underline{73.64 \text{ atom } \% \text{ D}}$ in the laevo fraction.

7.5   Amount of Reaction by the various Mechanisms

Mechanisms involving racemisation, retention of configuration, and racemisation without accompanying α-exchange have all been shown to take part in the overall reaction. The proportion of molecules undergoing attack by each of these processes can be readily calculated if it is assumed that any one molecule only reacts by one mechanism. If a% of the molecules react by a retention of configuration mechanism, b% by a racemisation process, and c% undergo racemisation without substitution,

$$d_o.\left(\frac{b}{200} + \frac{c}{200}\right) + l_o.\left(1 - \frac{b}{200} - \frac{c}{200}\right) = \begin{array}{l} \% \text{ of laevo isomer} \\ \text{finally present} \end{array}$$

$$\frac{d_o.\frac{b}{2} + l_o.(a + \frac{b}{2})}{l} \times \frac{c_a}{100} \quad = \begin{array}{l} \text{atom } \% \text{ D} \\ \text{in laevo form} \end{array}$$

$$\frac{l_o.\frac{b}{2} + d_o.(a + \frac{b}{2})}{d} \times \frac{c_a}{100} \quad = \begin{array}{l} \text{atom } \% \text{ D} \\ \text{in dextro form} \end{array}$$

$$(a + b) \times \frac{c_a}{100} \quad = \begin{array}{l} \text{atom } \% \text{ D in } \alpha\text{-posn.} \\ \text{of unresolved acid} \end{array}$$

c_a is the average solvent concentration during the experiment; d_o and l_o the percentages of dextro and laevo isomers present beforehand, and d and l after. The atom

percentages deuterium in the pure dextro and laevo forms
may be readily found from the measured deuterium concen-
trations in the resolved fractions, by solution of sim-
ultaneous equations.

The latter three equations should give a mutually
agreeable set of results for a and b, since they only
involve the two variables. However, due to experimental
errors, they rarely do so; solution of the equations, as
three sets of simultaneous equations, gives values of a
and b from which medial values may be computed.

The assumption has been made that hydrogen and
deuterium react at the same rate in substitution, but this
is not really justifiable (see Section 8.5). As a result,
use of the average solvent concentration during deuteration,
in determining the fraction of molecules which exchange
with deuteration, does not give accurate values for the
latter, and the net result will be to afford values of a
and b which are lower than the true values, and a value of
c which is higher than the actual one.

8. Appendix

8.1 Resolution of r-Mandelic Acid using Cinchonine

r-Mandelic acid may be resolved into the optically active acids by crystallisation of a variety of alkaloidal salts.

The first resolution was achieved by Lewkowitsch (60), using cinchonine; he isolated the d-acid as cinchonine d-mandelate. The method was later modified by Rimbach (61), who observed that, although it was extremely difficult to obtain crystals of the active mandelate without the use of seeding material, the cinchonine hydrochloride formed by addition of a little concentrated salt solution to the cinchonine mandelate could in some cases induce the separation of the active form from the solution. This method was tried several times in the present investigation, but without success; in no case could more than a very small amount of material be induced to crystallise from the solution, even on standing several weeks. This solid which separated was shown by analysis to be impure cinchonine d-mandelate; crystallisation of it was of no avail, and it had no effect when used as a seeding agent. The same difficulty was found by Mackenzie (62), who stated that "on repetition of his (Lewkowitsch') method under varying conditions, an oil usually separated on cooling the solution, and I

invariably obtained a mixture of alkaloidal salts."

The use of cinchonine to effect a resolution of mandelic acid has thus been found thoroughly unsatisfactory in the present investigations, and it cannot be recommended for this purpose.

8.2   Sources of Error in the Resolution of Deuteromandelic Acid

There are two possible sources of error which would lead to the deuterium contents of the dextro and laevo isomers, calculated from the resolved fractions, being different from the corresponding values in the deuterated acid. If the solubilities of the ephedrine salts of mandelic and deuteromandelic acids were not the same, a preferential crystallisation of the laevo form of either the normal or the heavy acid would occur. Attempts to resolve alkaloidal salts of organic acids with an asymmetry caused by the replacement of hydrogen by deuterium have proved unsuccessful, however (63), and if there is any error introduced into the separation by this effect, it is likely to be within the experimental error of the measurements.

The possibility of the occurrence of an asymmetric transformation of the first or second order (64), although very unlikely, since the optical stability of the acid is quite high, in the normal temperature range, must also be considered. Such transformations involve the conversion

of one isomer to the other, either by the attainment of
an equilibrium, d-Base l-Acid ⇌ d-Base d-Acid, in solution
only (first order), or by the separation of one diastereo-
isomeride in preponderating quantity (second order). If
such a transformation were shown to occur, the effect would
be to invalidate the results of the resolutions. A sample
of mandelic acid containing deuterium in the alpha position
was resolved, and the dextro fraction then treated with
more ephedrine, and a further partial resolution carried out.
The specific rotation values and deuterium contents of the
various fractions were mutually consistent, within the
experimental error, indicating that transformation and
solubility effects do not have a determining influence
in the resolution.

8.3 Electrophilic substitution in Mandelic Acid

The orientating influences of the side chain in
mandelic acid are difficult to predict on the basis of the
electronic theory, and no evidence is available in the
literature to give any indication of the direction of
substitution, all derivatives of mandelic acid being pre-
pared from the nitrile or from benzaldehyde. The possibility
of a slow exchange occurring in the nucleus on heating
mandelic acid with heavy water was investigated; such an
exchange would be likely to be electrophilic in nature,

but no deuteration was observed after heating for ten
days at 100°. Accordingly, attempts were made to carry
out a direct substitution in mandelic acid derivatives
to obtain some information on the direction of reaction.
Nitration was selected as the reaction most likely to
lead to conclusive results, and, since mandelic acid
undergoes oxidation very readily in presence of nitric
acid, the O-methyl ether derivative was prepared (65).
Nitration of this compound was attempted under various
conditions, with fuming and concentrated acids, but in no
instance could a satisfactory yield be obtained. In view
of the fact that the interpretation of any results obtained
in such a substitution would be highly arbitrary, it was
decided not to investigate the reaction further.

8.4 Validity of the Nitration Procedure

Esterification does not affect the deuterium con-
centration in the ring, since after esterification of a
sample of deuterobenzoic acid, and hydrolysis of the
resulting methyl benzoate, the deuterium content of the
recovered benzoic acid was unchanged.
Comparison of the deuterium contents of methyl m-nitro-
benzoate and of the m-nitrobenzoic acid obtained from it
by hydrolysis showed that the hydrolysis was not respons-
ible for any loss of deuterium from the ring, the value

for the hydrolysed product being in fact the higher, the difference between the two being, however, within the experimental error.

For methyl m-nitrobenzoate, atom % D = 2.62,

i.e., $\dfrac{2o + m + p + 3\times.02}{7} = 2.62$; $2o + m + p = 18.28$

For m-nitrobenzoic acid, atom % D = 3.71,

i.e., $\dfrac{2o + m + p + .02}{5} = 3.71$; $2o + m + p = 18.53$

There is no direct evidence that the actual nitration does not result in a hydrogen-deuterium exchange, but the conditions of the reaction are very mild, the temperature being controlled at about 0°, and the reaction not continued for longer than about five minutes. As the substitution of a nitro group in the ring would be expected to deactivate the ester, deuterium exchange of the nitrated products is made less likely, and hence, since the nitration occurs rapidly, the amount of exchange to be anticipated in the ring, if any, will be small.

8.5 Discussion of Assumptions made in the Calculation

It has been assumed that normal and deuteromandelic acids have the same molecular rotations (see Section 7.1). Since optical activity is a property of the molecules, and equal weights of normal and deutero-mandelic acids will not contain equal numbers of molecules, an identity between

specific rotation values, which are given in terms of concentration, is not to be expected. If the concentrations are expressed as molarities, however, this objection will be overcome, but even after making this correction, it is probably true to say that the substitution of deuterium for hydrogen will cause slight changes in the rotation.

Recently, several optically active compounds of the type R_1R_2CHD have been prepared (66), and the optical rotations, while small, appear to be well established experimentally. $[\alpha]_D$ lies in the range 0.1 to 0.5°, and is of the order of magnitude to be expected from the isotopic mass dissymmetry (67). Small changes in rotation caused by the introduction of deuterium atoms into highly polar positions in the molecule, more particularly OH and NH_2 groups, have also been reported (68). How far the substitution of D for H in other positions, such as the benzene ring, will affect the rotation is not clear, but, on the strength of the results obtained for the other types of exchange, the discrepancy should not be greater than about one per cent.

The assumption has also been made that the rates of exchange of hydrogen and deuterium with a given hydrogen atom are the same. This is, in fact, not the case; it has been established that protons and deuterons are trans-

ferred at different rates in one and the same reaction.
At the outset, the ratio of these rates is not known, but
estimates of the ratio of the rate of proton transfer to
deuteron transfer in different cases vary from three to
more than ten (10). We wish to determine the rate at
which original protons are removed from the acid, but, if
in a mixed H-D solvent, the places vacated by these protons
are going to be filled by protons and deuterons in a ratio
bearing no known relation to the isotopic composition of
the solvent, we are no further forward. The simplest way
round the difficulty is to employ an excess of deuterium
solvent, as nearly hydrogen-free as possible, so that
almost every proton has its place taken by a deuteron. The
net effect of the difference in rates is that the calcul-
ated percentage of laevo isomer formed will be rather
lower than the true value, and that the atom percentages
of deuterium in the resolved fractions will be rather
higher than the actual values. The calculated results
for a racemisation mechanism in the base-catalysed exper-
iments do,in fact, show such a relation to the experimental
ones.

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Part II

Measurement of Acidity

at Temperatures over 100°.

Contents

1. Introduction.

The exchange of deuterium with carbon-bound hydrogen atoms in carboxylic acids has been surveyed by Bell and his co-workers (1), and the effect of various factors on the rate and extent of deuteration has been investigated. A correlation between the acid strength and the amount of exchange in the alpha position has been considered, but since most of the deuterations were carried out at fairly high temperatures, no reliable estimate of the acidity of the various acids at the temperature of deuteration can be obtained from the data available in the literature, which mostly refers to temperatures below 50°. The present research was hence carried out to discover if the acid strengths of the carboxylic acids do indeed show any marked variation at higher temperatures from the values at room temperature.

The determination of hydrogen ion concentration at relatively high temperatures cannot be satisfactorily achieved by extrapolation of the values obtained in the normal range of measurement, i.e., from about 20° to 50°, since some of the factors involved, e.g., degree of assoc- iation, do not vary in a regular manner with change of temperature.

The measurement of acidity at temperatures above 100°

introduces several difficulties not encountered at lower temperatures. The use of sealed vessels is imperative if water is used as solvent; temperature control is more difficult; and variations in the concentration of solutions with temperature have to be considered.

Noyes and several co-workers (2, 3) undertook a comprehensive survey of equivalent conductivities and ionisations of selected acids, bases, and salts at temperatures up to 360°. Noyes' method was not suitable in the present case, however, as the solutions under examination were too concentrated for conductivity measurements; and the apparatus used by Noyes was too complicated to be of general application.

The method of measurement chosen in the present investigation was hydrolysis of a disaccharide, the velocity of which is known to be directly proportional to the hydrogen ion concentration (general acid-base catalysis does not appear to apply to the reaction). Of the four principal disaccharides, sucrose was rejected on account of the high velocity of its hydrolysis; maltose decomposes at 110°, which is lower than the temperature at which hydrolyses were carried out; and cellubiose, althoughit would appear most suitable from the kinetic viewpoint, is relatively inaccessible. Lactose was therefore chosen for the measurements.

2. Experimental Methods

2.1 Preparation and Purification of Materials

It was found that when the lactose was recrystallised from water, the resulting sugar had an appreciable acidity when dissolved in water, its pH being about four. By dissolving lactose in a small amount of boiling water, and then adding absolute alcohol to the hot solution until a slight turbidity was evident, the sugar crystallising out was completely neutral in water, however.

Acetic, propionic, n-butyric and iso-butyric acids were dried over magnesium sulphate, and then distilled twice at atmospheric pressure. Purification of lactic acid is more difficult, since the pure acid is very hygroscopic, although it readily loses water to form the anhydride. By distilling at a pressure of less than 1 mm. from a flask loosely packed with glass wool, lactic acid came over extremely slowly after all the water vapour had been driven off.

α-Methoxy-propionic acid was synthesised by the method of Levene and Marker (4). 20g. ethyl lactate were dissolved in 100cc. methyl iodide, and 120g. silver oxide added slowly, the temperature being controlled at about 50°. The silver salts were filtered off and extracted with ether. The combined filtrate and extract were distilled, yielding

the ethyl ester of methoxy-propionic acid, b.p. 140-142°.
The latter was hydrolysed by refluxing for one hour with
an equal weight of potassium hydroxide in 80% alcohol.
After removal of the alcohol, and acidification of the
salt, the organic acid was extracted in a continuous
extractor.

2.2 Preliminary Investigations

A 5.5% lactose solution was prepared and its muta-
rotation followed with a polarimeter. It was found that
24 to 30 hours were necessary for complete mutarotation.
All sugar solutions were hence set aside for this time
before use.

Under the same conditions as were used in the later
experiments, a 0.04 N hydrochloric acid solution of lactose
was prepared. It was found that no hydrolysis of the
lactose occurred in 48 hours at 20°.

With water in place of acid, a lactose solution was
maintained at the experimental temperature of 140° for 10
minutes, but no change in the rotation of the solution
could be observed. Hence any change in the rotation of
acid-sugar solutions on heating is due to the catalytic
effect of the hydrogen ions.

The lactic and methoxy-propionic acids were completely
inactive, and a sample of lactic acid and water after

heating for 30 minutes was still inactive.

2.3 Kinetic measurements

Standard solutions of acetic, propionic, n-butyric and iso-butyric acids were prepared, of such concentration as to afford a final mixture of unit molarity with respect to the acid, measured at 20°, when 2 ml. of the acid solution were added to 3 ml. of 5.5% lactose solution. With lactic and methoxypropionic acids, the final mixture was $\frac{M}{10}$ with respect to the acid.

The 2 ml. of acid solution were placed in a test-tube, frozen in $MeOH/CO_2$, and 3 ml. of lactose solution added and treated similarly. The tube was then sealed, the contents allowed to melt, and the tube placed in a thermostat at 140°. The temperature control consisted of a flask of boiling xylene, in the vapour of which the solutions under examination were suspended for various intervals, ranging from 0 to 40 minutes. At the end of the specified time, each tube was removed, and the reaction halted by immersing the tube in ice. Before reading the optical rotation of the solution, it was allowed to attain the temperature of the polarimeter. As noted earlier (Section 2.2), no hydrolysis occurs at room temperature. The average of ten readings was taken for each solution.

A standard curve was first drawn up by measuring

the velocity of hydrolysis of lactose by hydrochloric
acid solutions, ranging in concentration from .02 to
.0018 N. The velocity constant with each of the six
carboxylic acids was then measured at the concentrations
specified above, and at one-half of these concentration
values. In the case of acetic acid, measurements were
made at M, $M/_2$, and $M/_4$ concentrations.

2.4   Correction for Concentration Changes

Owing to the expansion of liquids on heating, con-
centration changes will occur when the temperature of
the solutions are raised to 140°. Measurement of the
expansion of pure water, and acetic acid-lactose solution,
was made over a range of temperature, using a dilatometer,
consisting of a long capillary tube with a bulb blown at
one end. The heights of the liquid in the tube at various
temperatures were measured with a cathetometer, after
allowing a suitable interval of time for the tube to come
to equilibrium at each temperature. The results are shown
in the graph below, from which it may be seen that the
expansion of the sugar solution is slightly greater than
that of the water. It should be noted, however, that the
accuracy of the method falls off considerably with increase
of temperature. Although the effect of the difference in
the coefficient of expansion has been taken into consider-

ation (see Section 3.1), its influence on the final

result is negligible.

Graph 1: Comparison of the Expansion of Water and Lactose
Solutions.

Height

of

meniscus

sugar
solution

water
solution

25   40   80   100   140

Temperature
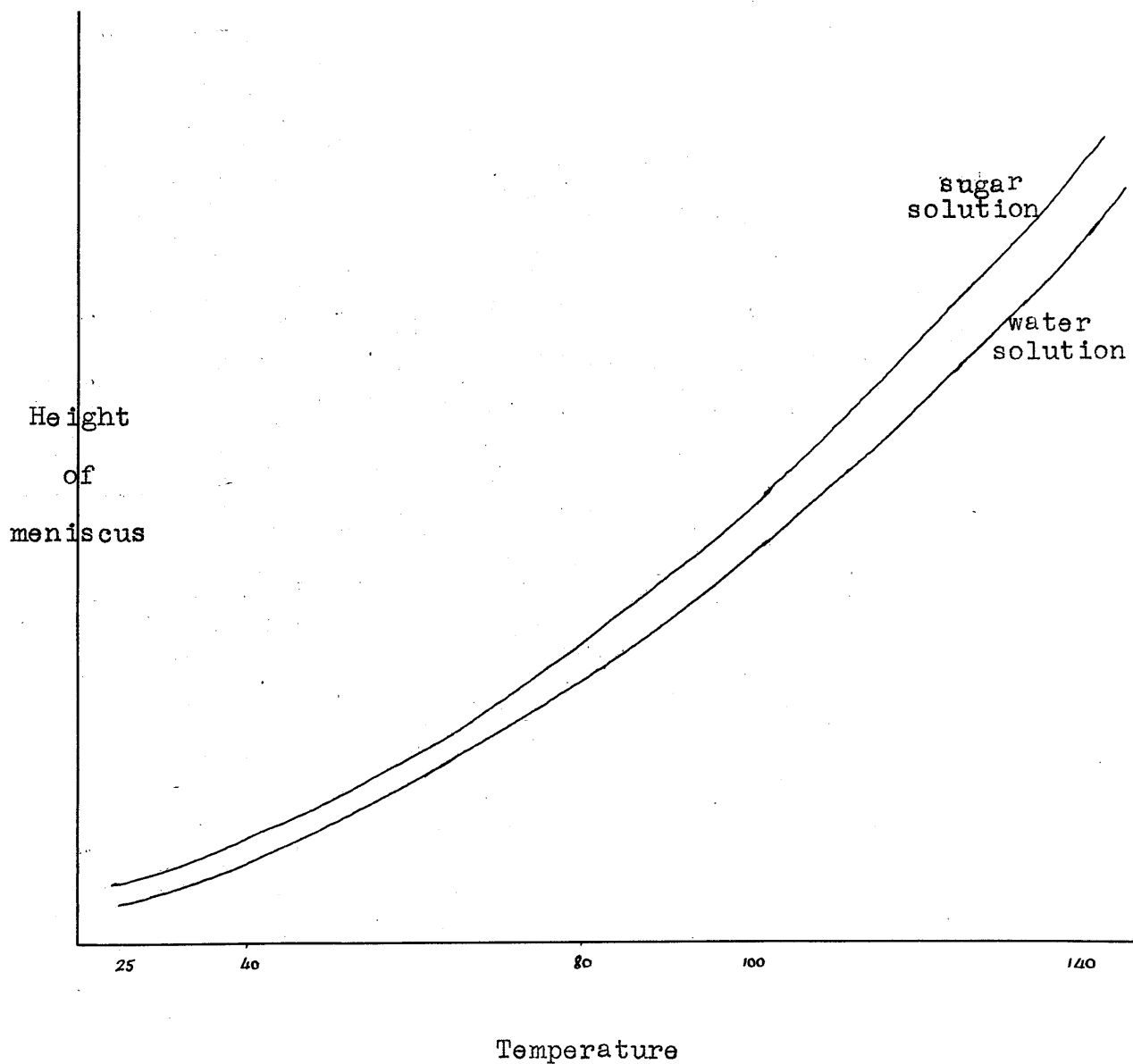
3. Theoretical Considerations

3.1 Specific Volume Change

Several factors have an influence on the specific volume change. The most important of these are discussed below.

(i) Vaporisation of solvent.

The volume of the vapour space above the solution in the tubes varied somewhat, depending on the exact location of the seal. However, at a maximum, the vapour space did not exceed 3 ml., whilst the solution occupied 5 ml. at room temperature.

The saturated specific volumes of liquid water and water vapour at 140° are 1.0776 cc./g. and 508 cc./g. respectively.(5). Hence the relative amount of solvent in the vapour is $\frac{^3/508.0}{^5/1.0776}$, i.e., about 0.127 per cent. This would result in there being about .006 ml. less of solvent.

Since addition of solute lowers the vapour pressure of the solvent, this latter figure will be too high, and the fact that the volume of liquid at 140° is rather greater than 5 ml., and the volume of vapour rather less than 3 ml., will have the same influence.

(ii) Volatilisation of solute.

Noyes (2) found that at 218° the amount of hydro-
chloric or acetic acid which volatilised is not appreciable.
It is hence improbable that any serious error will be
introduced by ignoring volatilisation of the acids con-
cerned in the present investigation, since the temperature
of operation is considerably lower.

(iii) Effect of air pressure above the solution.

The air pressure in the tubes will be increased
above atmospheric, but since liquids are virtually in-
compressible, the effect on the solution will be slight.
The only consequence of the increased air pressure would
be to reduce the errors introduced under (i) and (ii).

The effect of all these factors is that there will
be about .005 ml. less of solvent in the liquid phase.

Since the densities of water at 20° and 140° are
0.9982 and 0.9264 respectively (6), 5 ml. of water will
expand to 5.388 ml.. In the dilatometer investigations,
x cc. of water expanded to (x + 43.75a) cc. at 140°, and
xcc. of solution to (x + 48.5a) cc., where a is the cross-
section of the bore of the dilatometer. From this data,
it may readily be calculated that 5 ml. of solution will
expand to 5.422 ml. at 140°. It is assumed that the
expansion of the various acid solutions will be the same,

within the experimental error of measurement.

Taking account of the systematic errors discussed above leads to an average expansion of 0.417 ml. per 5 ml. of solution.

3.2 Hydrochloric Acid Standard

Since the solutions are not too concentrated, hydrochloric acid, being a strong acid, may be regarded as completely ionised in aqueous solution; its hydrogen ion concentration can then be taken as equal to the total acid concentration, if it is assumed that the addition of lactose does not affect the ionic concentration. From the acid concentrations at 20°, the hydrogen ion concentrations at 140° can hence be calculated, and the values are shown in Table 1.

3.3 Kinetic Measurements

The hydrolysis of lactose is a first order reaction, and conforms to the usual first order equation

$$- \ln c = k.t + K ,$$

c being the concentration of lactose at time t; k the first order rate constant; and K the integration constant.

The measurement of the rotation of the solution gives an estimate of the concentration of lactose present at any time, since c is proportional to $(\alpha_\infty - \alpha_t)$, where α_∞ and α_t are the rotations after an "infinite" time, and

time t, respectively. The first order equation may therefore be modified to

$$\log \frac{\alpha_\infty - \alpha_o}{\alpha_\infty - \alpha_t} = \frac{k}{2.3} \cdot t$$

In practice, a graph of $\log (\alpha_\infty - \alpha_t)$ against time was drawn, and a quantity K $(= k/2.3.t)$, proportional to the first order constant k, calculated for each hydrolysis experiment for t = 20 minutes.

To test the reproducibility of results, two hydro-lyses were carried out with .005 N hydrochloric acid. These gave values of K of .265 and .270, which agreement is well within the experimental error.

4. Results

4.1 Hydrochloric Acid

Hydrolysis experiments were carried out with hydrochloric acid present in the solution in the concentrations shown in Table 1. From the graphs of log $(\alpha_\infty - \alpha_t)$ against time, values of K were obtained. The hydrogen ion concentration corresponding to each acid concentration is also incorporated in the table.

Table 1.

Concentration of HCl at 20°	Concentration of H⁺ at 140°	K
.02008	.01853	0.61
.01004	.00927	0.445 0.425 } 0.435
.00502	.00463	0.265 0.270 } 0.267
.00251	.00232	0.123
.0018	.00166	0.085

A standard reference graph of concentration of hydrogen ions against K was drawn. The graph approximated to a straight line for concentrations lower than .005 g. mol. H⁺/l., although considerable curvature was

evident at the higher concentrations. Although it did
not pass through the origin, the deviation from the
latter was within the experimental error of the results
(Graph 2).

4.2   Other Acids

Graphs of log $(\alpha_\infty - \alpha_t)$ against time were drawn for
acetic, propionic, n-butyric, iso-butyric, lactic, and
methoxypropionic acids, for the concentrations of acid
specified earlier (Section 2.3). The values of K deduced
from the graphs are shown below (Table 2).

Table 2.

Acid	Concentration of acid at 20°. M	K
Acetic	1	0.26
	0.5	0.13
	0.25	0.07
Propionic	1	0.16
	0.5	0.08
n-Butyric	1	0.185
	0.5	0.105
iso-Butyric	1	0.17
	0.5	0.08

Table 2 (continued).

Acid	Concentration of acid at 20°. M	K
Lactic	0.1	0.20
Methoxypropionic	0.1	0.115
	0.05	0.06

The lactic acid graph displayed a marked curvature, probably due to the decrease in the catalysing power of the acid by the reduction in its hydrogen ion concentration caused by formation of lactide. It is known that lactide formation occurs rapidly at 140°.

Using the various values of K obtained for the different acids, the corresponding values of the hydrogen ion concentration were derived from the standard reference graph, and the values are shown in Table 3. The final column shows, for comparison, the hydrogen ion concentrations at 25° of solutions of a concentration equal to that attained by $M/2$ solutions at 140° ($M/10$, $M/20$ respectively for lactic and methoxypropionic acids). The values were obtained from the dissociation constants of the acids at 25° for concentrations of 0.12 downwards.

Table 3.

Acid	Hydrogen ion concentration values:			
	for concentration of acid at 20° of			Theoretical for $M/2$ soln. at 25°
	M	$M/2$	$M/4$	
Acetic	0.00455	0.0024	0.0014	0.00288
Propionic	0.0029	0.00155	..	0.00246
n-Butyric	0.0033	0.0020	..	0.00262
iso-Butyric	0.0031	0.00155	..	0.00255

Acid	Hydrogen ion concentration values:		
	for concentration of acid at 20° of		Theoretical for $M/10$, $M/20$ solns at 25°
	$M/10$	$M/20$	
Lactic	0.00355	..	0.00347
-Methoxy-propionic	0.00215	0.00125	0.00375

4.3 Buffered Solutions

Attempts were made to measure the velocity of hydrolysis of lactose by lactic acid/potassium lactate buffer solutions, in order to determine the acid strength of such buffered solutions. The result of all such

experiments was that the solutions turned a deep yellow in a short time - ten to fifteen minutes - and it was hence not possible to measure their rotations. When the solution was only heated for a very short time, so that it was sufficiently clear to allow a polarimeter reading to be obtained, the result was invariably a large fall in the rotation. It is probable that the lactose is being decomposed by the alkali, as it is known that dl-lactic acid may be readily obtained by the action of alkali on a wide range of carbohydrates, including lactose.

5. Discussion and Significance of Results

At 140°, the acid strengths of the first four acids
listed bear the same relation to one another as they do
at 25°, although in every case a decrease in the strength
occurs with rise in temperature, the fall being less
marked with acetic acid than with the other acids, however.
The values of acid strength of ∝-methoxy-propionic acid
are considerably lower than at 25°. There is a degree of
uncertainty in the result obtained for lactic acid, since,
as noted earlier, its hydrogen ion concentration progress-
ively decreases with formation of lactide, with a con-
sequent curvature in the kinetic graph. The value quoted
was obtained by extrapolation of the first, relatively
straight, portion of the graph.

It may be remarked that the graph of hydrogen ion
concentration against acid concentration for acetic acid
would appear to be almost linear, whereas, in general,
concentration varies as the square root of hydrogen ion
concentration (Graph 3). The latter relation is only
valid at fairly low concentrations, however, when it is
permissible to assume that the activity coefficients are
all unity, and no fundamental significance can be attached
to the result in the present case. The results obtained
are of the same order as those found by Noyes (2), who

quotes a value of 0.92% for the extent of ionisation of a 0.08 N solution of acetic acid.

It should be emphasised that the hydrogen ion concentration values are only approximate, and have no precise significance, since, at the high concentrations used, the solutions behave far from ideally. It can be concluded, however, that for the acids investigated, the acidities are rather lower than in the normal range of temperature measurement, although α-methoxypropionic acid would appear to show a considerable fall in its acid strength.

It follows that any qualitative conclusions about the mechanisms of deuteration of carboxylic acids at higher temperatures, based on the acid strengths at 25°, will not be greatly in error with regard to the hydrogen ion concentration values taken.

6. Bibliography

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Graph 2 : Standard Reference Graph
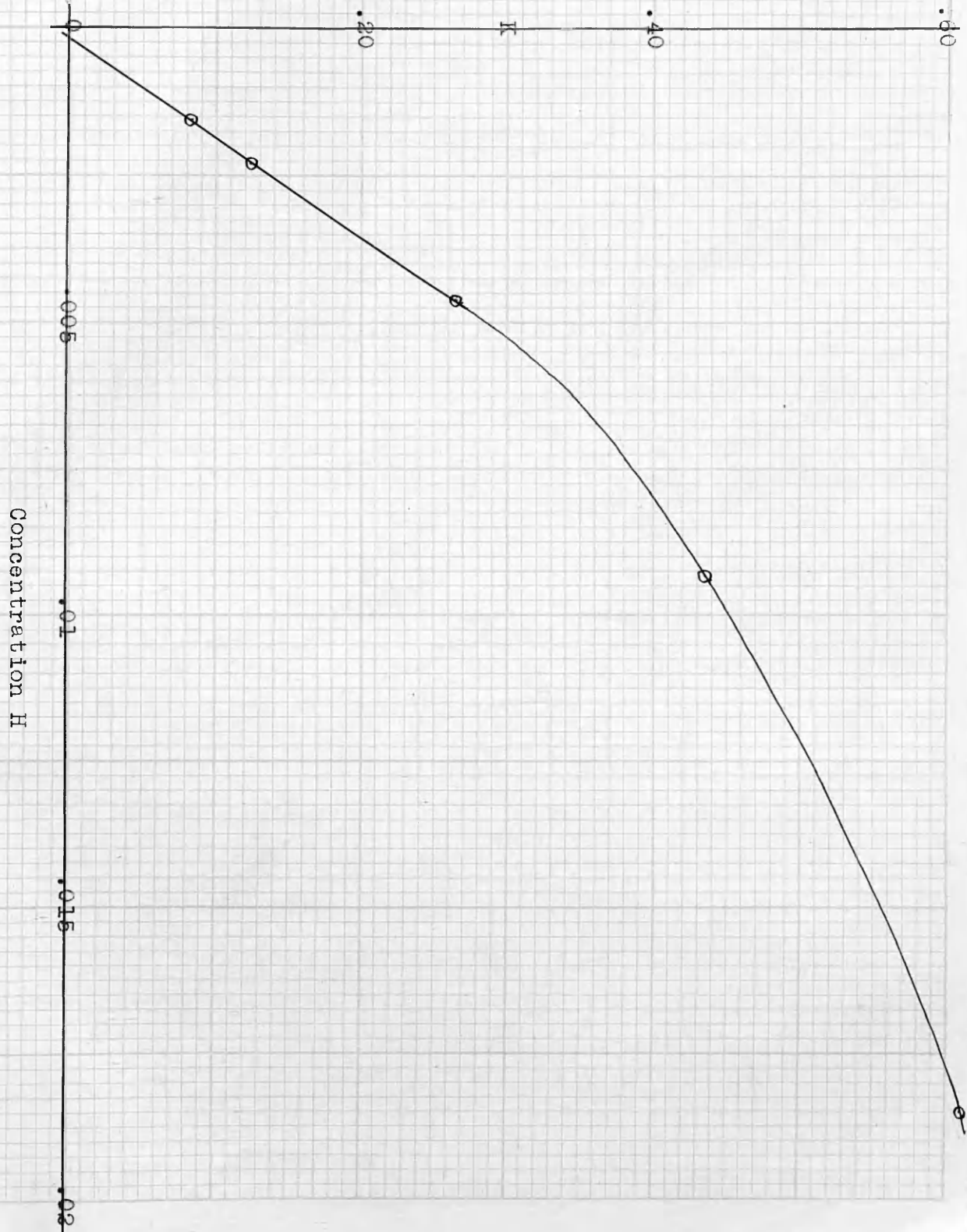
Graph 3 : Acetic Acid.

Concentration - Hydrogen Ion Concentration Graph
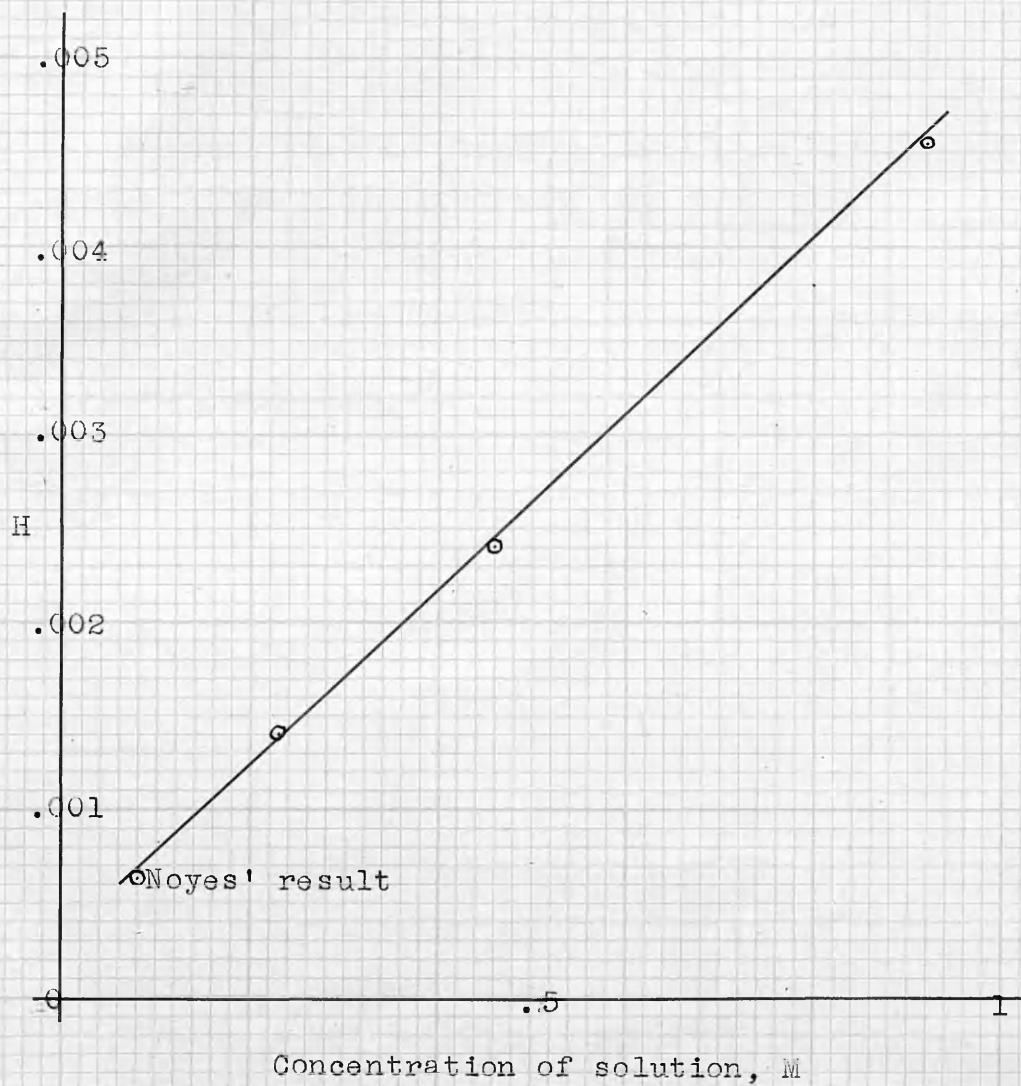
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