Elucidation of the Mechanism of the Michael Condensation with Oxygen-18 as Tracer. Part I. The "Abnormal" Reaction.

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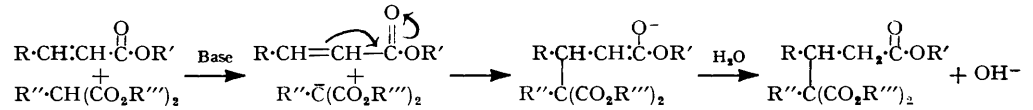
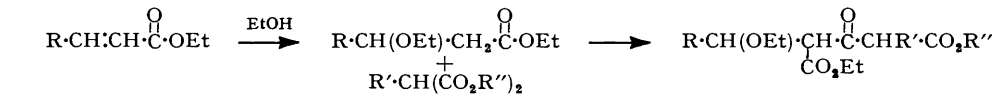
In the Michael condensations of dialkyl methylmalonates with ethyl crotonate or ethyl cinnamate, it has been shown, by using ^{18}O as tracer, that the "abnormal" reaction occurs with migration of the carboxyl group only. The isotopic results are consistent with the mechanism proposed by Lapworth for this reaction.

THE Michael condensation is the base-catalysed reaction between an "acceptor" compound containing an activated double or triple bond and a "donor" compound containing an active α-hydrogen atom, which results in the apparent addition of the component parts of the "donor" (proton and carbanion) to the multiple bond of the "acceptor." It is believed at present that the carbanion formed from the "donor" in alkaline solution attacks the more positive end of the polarised system of the "acceptor," yielding an anion which after treatment with water yields the ultimate adduct. (For a fuller discussion, see Bergmann, Ginsburg, and Pappo, "The Michael Condensation," in "Organic Reactions," Wiley, New York, in the press).

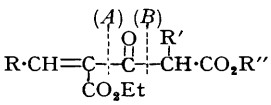
The Michael condensation may be exemplified by the following reaction scheme:



It has been suggested, however, that the first stage of the process may not necessarily be the formation of the new carbon–carbon bond, but rather a condensation of the Claisen type between the "acceptor" which has been modified for this purpose through the addition of ethanol across the double bond and the carboxylate group of the "donor" (Shafer, Loeb, and Johnson, *J. Amer. Chem. Soc.*, 1953, **75**, 5963; personal discussion with Professor Johnson in New Hampshire, August, 1954):



Subsequently, by concerted alcoholysis at either (*A*) or (*B*) and addition of the remaining fragment to the regenerated double bond, the reaction product is obtained.

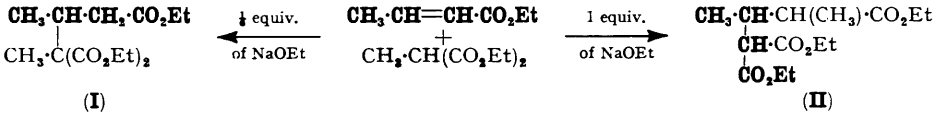


In order to elucidate the mechanism of the Michael condensation, it was felt, therefore, that the use of ^{18}O as tracer would furnish much information as to the intimate course of the reaction, since the functional groups of the "donor," "acceptor," solvent, and catalyst, all contain oxygen.

Since debate has been raging for some decades regarding the mechanism of the Michael condensation (see, *e.g.*, Thorpe, *J.*, 1900, **77**, 923; Michael and Ross, *J. Amer. Chem. Soc.*, 1930, **52**, 4598; Farmer, Ghosal, and Kon, *J.*, 1936, 1804; Holden and Lapworth, *J.*, 1931, 2368; Michael, *J. Org. Chem.*, 1938, **2**, 303), it was decided to select as the subject of this investigation those reactions chiefly involved in these polemics (Michael, *Ber.*, 1900, **33**, 3731; Michael and Ross, *loc. cit.*; Holden and Lapworth, *loc. cit.*).

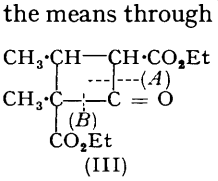
When ethyl crotonate is treated with diethyl methylmalonate in the presence of one-sixth of an equivalent of sodium ethoxide, the so-called "normal" product (I) is obtained.

When, however, a full equivalent of sodium ethoxide is used, the so-called " abnormal " product (II) results. It is this reaction which has caused much of the confusion in the literature. In this communication we report our isotopic results for the " abnormal " reactions of esters of methylmalonic acid with ethyl crotonate and with ethyl cinnamate.



The formulation proposed by Michael and Ross (*loc. cit.*; cf. Thorpe, *J.*, 1900, **77**, 932) to account for the structures of the products when different quantities of sodium are used is that, when one-sixth of an equivalent of sodium is used, the " donor " adds to the double bond of the " acceptor " in form of the components H · · · $CMe(CO_2Et)_2$, whilst when a full equivalent of sodium is used, the " donor " breaks up into the components Me · · · $CH(CO_2Et)_2$. Such a formulation, proposed for the splitting of sodiomethyl cyanoacetate in 1900, is inconsistent with present-day knowledge of base-catalysed ionic or free-radical mechanisms in organic chemistry. The portion of the Michael condensation adducts resulting from the crotonate precursor is indicated by the heavy type in the above formulæ (I and II) : thus, if a rearrangement is involved in this base-catalysed reaction, it is more plausible to assume that the ethoxycarbonyl group migrates and not the methyl group.

Holden and Lapworth (*loc. cit.*) have, indeed, presented a formulation which explains the means through which migration of an ethoxycarbonyl group can occur. They assumed that an intermediate *cyclo*butanone (III) is obtained. If alcoholysis of this postulated but unisolated intermediate of intramolecular Dieckmann condensation occurs at (*A*), the " normal " adduct is obtained. If, on the other hand, alcoholysis occurs at (*B*), the " abnormal " product results. Johnson's suggestion avoids the necessity for assuming even the transient existence of this strained intermediate and explains the results obtained in certain other " abnormal " Michael condensations (Shafer, Loeb, and Johnson, *loc. cit.*).



(III)

Using ^{18}O as tracer in the carboxyl group, we have shown, labelling each component separately, that, both for crotonate and for cinnamate, " abnormal " reaction occurs with migration of the carboxyl group only. Dimethyl [$^{18}O_4$]methylmalonate (all four oxygen atoms isotopically enriched) was condensed with unlabelled ethyl crotonate in the presence of one equivalent of sodium, under the exact conditions described by Michael and Ross (*loc. cit.*). The resulting triester was hydrolysed with aqueous sodium hydroxide; the free acid was extracted but had to be purified by recrystallisation as, in analogy to the work of Tsuruta, Yasuhara, and Furukawa (*J. Org. Chem.*, 1953, **18**, 1246), here also mixtures of " normal " and " abnormal " esters were obtained. However, there is no doubt that the " abnormal " product predominated.

Since *n*-alkyl esters of carboxylic acids are hydrolysed by acyl–oxygen fission (Polanyi and Szabo, *Trans. Faraday Soc.*, 1934, **30**, 508; Datta, Day, and Ingold, *J.*, 1939, 838; Samuel, unpublished results) the ethoxyl oxygen atoms of the ethoxycarbonyl groups are lost on hydrolysis. Separate experiments showed that no exchange between the oxygen of the carbonyl group and the solvent occurred on hydrolysis or working up (cf. Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1626). The tricarboxylic acid was then decarboxylated at 200° and the resulting carbon dioxide was introduced directly into the mass spectrometer. The ratio of mass 46 to mass 44 was determined and the atom % excess of ^{18}O calculated.

The results are tabulated together with the atom % excess of ^{18}O calculated by assuming migration of an ethoxycarbonyl group, and, for comparison, with the atom % excess of ^{18}O calculated by assuming the Thorpe–Michael methyl migration. It should be noted that no isotope effects in the decarboxylation were evident.

Similarly, the results for the " abnormal " reaction of ethyl [^{18}O]crotonate and unlabelled diethyl methylmalonate and for dimethyl [$^{18}O_4$]methylmalonate and unlabelled ethyl cinnamate, are given in the Table.

Atom % excess ^{18}O in " abnormal " Michael condensation.

Reactants	^{18}O in labelled reactants	Found	Calc. for CO_2H migration	Calc. for Me migration
$Me{\cdot}CH(C^{18}O_2Me)_2 + Me{\cdot}CH{:}CH{\cdot}CO_2Et$ ...	1·68	0·52	0·42	1·68
$Me{\cdot}CH(CO_2Et)_2 + Me{\cdot}CH{:}CH{\cdot}C^{18}O^{16}OEt$ ...	0·43	0·10	0·10	0·00
$Me{\cdot}CH(C^{18}O_2Me)_2 + Ph{\cdot}CH{:}CH{\cdot}CO_2Et$ ...	0·88	0·22	0·22	0·88

All of these results are in accord with the postulated Lapworth *cyclo*butanone formulation or its mechanistic variant.

After completion of this work, the paper by Simamura, Inamoto, and Suehiro (*Bull. Chem. Soc. Japan*, 1954, **27**, 221) came to our attention. These workers concluded that in the " abnormal " reaction between ethyl [*carboxy*-^{14}C]-crotonate and diethyl methylmalonate, it is the ethoxycarbonyl group that migrates. Our conclusions are in full accord with these results, but as stated above, the use of ^{18}O in this case appears to afford a tool for the investigation of the various other aspects of the Michael condensation. Our further conclusions regarding the mechanism of the " normal " reaction will be reported in a subsequent publication.

Experimental

Preparation of Unlabelled Materials.—Diethyl methylmalonate was prepared (81% yield) according to *Org. Synth.*, Coll. Vol. II, p. 279, procedure B, Wiley, New York; it had b. p. 197°.

Ethyl crotonate was prepared by keeping crotonic acid (50 g.) in absolute ethanol (200 ml.) and concentrated sulphuric acid (2 ml.) for 24 hr. at room temperature. The mixture was then worked up as described by Michael (*Ber.*, 1900, **33**, 3766); the ester had b. p. 143° (yield, 60 g., 75%).

Ethyl cinnamate was redistilled Eastman Kodak " white label " material, b. p. 158°/25 mm.

Preparation of Labelled Materials.—A 5N-$Na^{18}OH$ stock solution was prepared from the required amount of 3% sodium amalgam and water enriched in ^{18}O. This was diluted with enriched water as required.

N-Sulphuric acid was prepared from the required amount of concentrated sulphuric acid and water enriched in ^{18}O.

Dimethyl [^{18}O]*Methylmalonate.*—[$^{18}O_4$]Methylmalonic acid was prepared by two methods. (*a*) Methylmalononitrile (2·4 g.), prepared from α-bromopropionic acid according to the method of Strack and Schwaneberg (*Ber.*, 1934, **67**, 41), was refluxed with 5N-$Na^{18}OH$ (13 ml.) until there was no further evolution of ammonia. Calcium chloride (4 g.) was then added to the hot solution, and the precipitate of calcium methylmalonate was removed by filtration and then washed alternately with hot water and cold water and finally with ether. The dry salt (4·7 g.) was then suspended in dry ice-cold ether (about 10 ml.), and concentrated hydrochloric acid (5 ml.) was added with cooling and stirring. The ether solution was separated, washed once with saturated aqueous sodium sulphate (2 ml.), and dried (Na_2SO_4). On removal of the ether, colourless [$^{18}O_4$]methylmalonic acid, m. p. 139°, was obtained (3·5 g.). Owing to the low yields of methylmalononitrile obtained by us according to the somewhat ambiguous directions of Strack and Schwaneberg, further quantities of labelled methylmalonic acid were obtained by method (*b*).

(*b*) Diethyl methylmalonate was refluxed with a slight excess of N-$Na^{18}OH$ until a homogeneous solution was obtained. The aqueous solution was extracted once with ether, then brought to the b. p. and the calculated amount of calcium chloride was added to precipitate the calcium methylmalonate. The salt was worked up as described above. The methylmalonic acid obtained in this manner was also labelled in all four oxygen atoms but with an atom % excess of ^{18}O one-half of that of the water used.

An ether solution of methylmalonic acid obtained by either method was then esterified with diazomethane. On distillation, dimethyl [$^{18}O_4$]methylmalonate, b. p. 75°/11 mm., was obtained.

Ethyl [^{18}O]*Crotonate.*—Ethyl crotonate (30 g.) was refluxed in 1N-sulphuric acid enriched in ^{18}O (30 ml.) for 7 days. The aqueous suspension was extracted with ether (3 times), and the extract was washed with water and dried (Na_2SO_4). On removal of the ether, colourless crystals of [$^{18}O_2$]crotonic acid, m. p. 74°, were obtained. In addition to the labelled oxygen atom introduced by hydrolysis, slow exchange between the free carboxyl group and the ^{18}O-enriched acid medium also increases the enrichment of the crotonic acid. Esterification was

accomplished as describedabove for the unlabelled acid. Distillation afforded ethyl [*carbonyl*-^{18}O]-crotonate, b. p. 143° (35 g.).

Michael Condensations.—The reactions between unlabelled diethyl methylmalonate and labelled ethyl crotonate, and between labelled dimethyl methylmalonate and unlabelled ethyl crotonate, were carried out precisely under the conditions described by Michael and Ross (*loc. cit.*, p. 4605), using 0·05 molar quantities. The yields reported were duplicated.

Similarly, the reaction between labelled dimethyl methylmalonate and unlabelled ethyl cinnamate was carried out according to Michael and Ross (*loc. cit.*, p. 4609) but a lower yield was obtained.

The triesters in each case were hydrolysed by refluxing with N-sodium hydroxide. The mixtures were then chilled, covered with ether, and carefully acidified by dropwise addition of hydrochloric acid with stirring and ice-cooling. The ether was removed and the acids were recrystallised to constant m. p. and isotopic content from a mixture of light petroleum, chloroform, and ether. α-Carboxy-βγ-dimethylglutaric acid formed crystals, m. p. 145°. α-Carboxy-γ-methyl-β-phenylglutaric acid formed crystals, m. p. 145°. Michael and Ross (*loc. cit.*) report m. p. 145° for both acids.

Mass-spectrometric Analyses of Reactants and Products.—Ethyl crotonate was hydrolysed with excess of N-sodium hydroxide, the solution was made exactly neutral with N-nitric acid, excess of silver nitrate was added, and N-sodium hydroxide was added dropwise until the white precipitate retained a brownish tinge. The silver crotonate was removed by filtration, washed with water, and dried in a vacuum. A sample (0·1 g.) was decarboxylated at 400° in the gas-inlet system of the mass spectrometer.

Dimethyl methylmalonate was hydrolysed with a slight excess of N-sodium hydroxide, the calcium salt was isolated, and the free acid obtained as described above. The acid was decarboxylated at 160° in the gas-inlet system of the mass spectrometer.

α-Carboxy-βγ-dimethylglutaric acid and α-carboxy-γ-methyl-β-phenylglutaric acid were decarboxylated in sealed tubes with break-off tips. Samples of approx. 0·01 g. were heated in evacuated sealed tubes to 200°. The sealed tubes were then opened by a magnet-operated iron breaker in the gas-inlet system of the mass spectrometer.

In each case the ratio of mass 46 to mass 44 was determined and the atom % excess of ^{18}O given in the Table was calculated.

Tests of Exchange and Working Up.—The following experiments were performed in order to determine whether any change in ^{18}O content occurred on isolation of the products or in preparation and decarboxylation of the samples: (*a*) Unlabelled methylmalonic acid was decarboxylated in sealed tubes. The results showed that no significant isotope effect occurs on decarboxylation and that no other products of masses 44 or 46 are produced. (*b*) Glutaric acid was heated to 200° with carbon dioxide enriched in ^{18}O in a sealed tube. No decrease in atom % excess of ^{18}O in the carbon dioxide occurred. This indicates that no direct exchange, or decarboxylation or dehydration of the glutaric acid, occurred. (*c*) Unlabelled methylmalonic acid was refluxed with N-Na^{18}OH for 48 hr. The acid was then isolated and analysed as described above. No exchange between the methylmalonate ion and the solvent was detected. (*d*) Methylmalonic acid enriched in ^{18}O was esterified with diazomethane. The ester was hydrolysed with N-sodium hydroxide solution, and worked-up as described above. The enrichment of the carbonyl-^{18}O before esterification and after working up remained unchanged.

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