[Contribution from the Institute for Chemical Research, Kyoto University]

STUDIES ON THE MICHAEL REACTION

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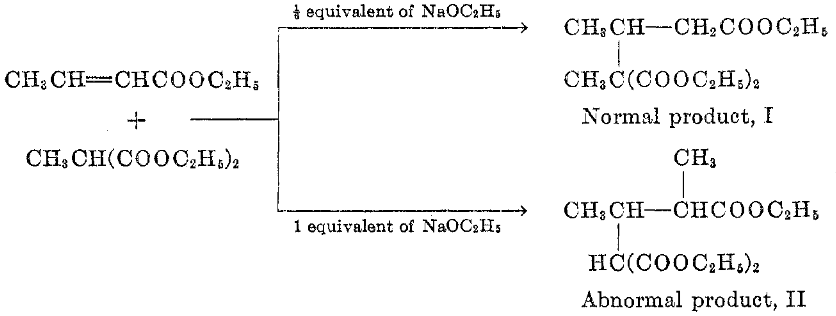
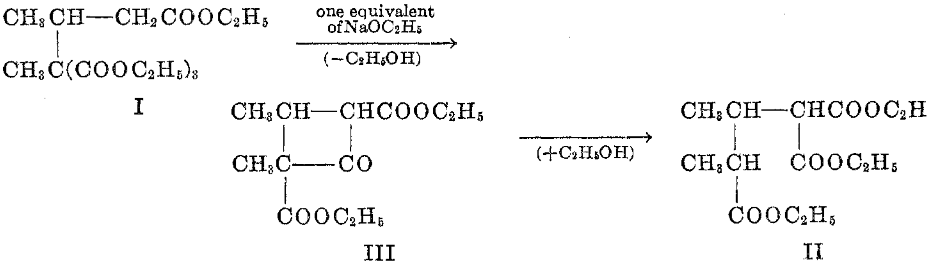
Received November 5, 1952

Michael and Ross (1) reported that the course of the addition of methylmalonic ester to crotonic and cinnamic esters varies in response to the amount of condensing agent (sodium ethoxide) used.



As a mechanism of the abnormal product formation, Michael and Ross proposed that the methyl group of dimethyl methylmalonate migrates directly to the α-carbon atom of crotonic ester. Holden and Lapworth (2) criticized the Michael's mechanism and suggested that the primary addition product (I) might undergo the Dieckmann type condensation followed by decomposition of the cyclobutanone (III).



Michael and Ross replied to this criticism, but they could not present any direct experimental evidence (3).

Gardner and Rydon (4), who examined both of the suggested mechanisms, suggested that the course of the addition reaction is affected markedly not only by the amount of condensing agent but also by the structures of the reactants.

Up to the present no data have been published which clarify the quantitative relationship between the amount of sodium ethoxide used and the ratio of the normal to the abnormal addition products. This situation is no doubt related to the difficulties involved in analyzing the addition products. Gardner and Rydon (4b), upon examining the addition products from diethyl benzylmalonate and

TABLE I

Normal Product Content *versus* Specific Gravity

NORMAL PRODUCT, %	SPECIFIC GRAVITY, d_{25}^{25}
0	1.0956
14.17	1.0967
23.97	1.0981
40.85	1.1008
66.91	1.1037
80.82	1.1061
100.00	1.1088

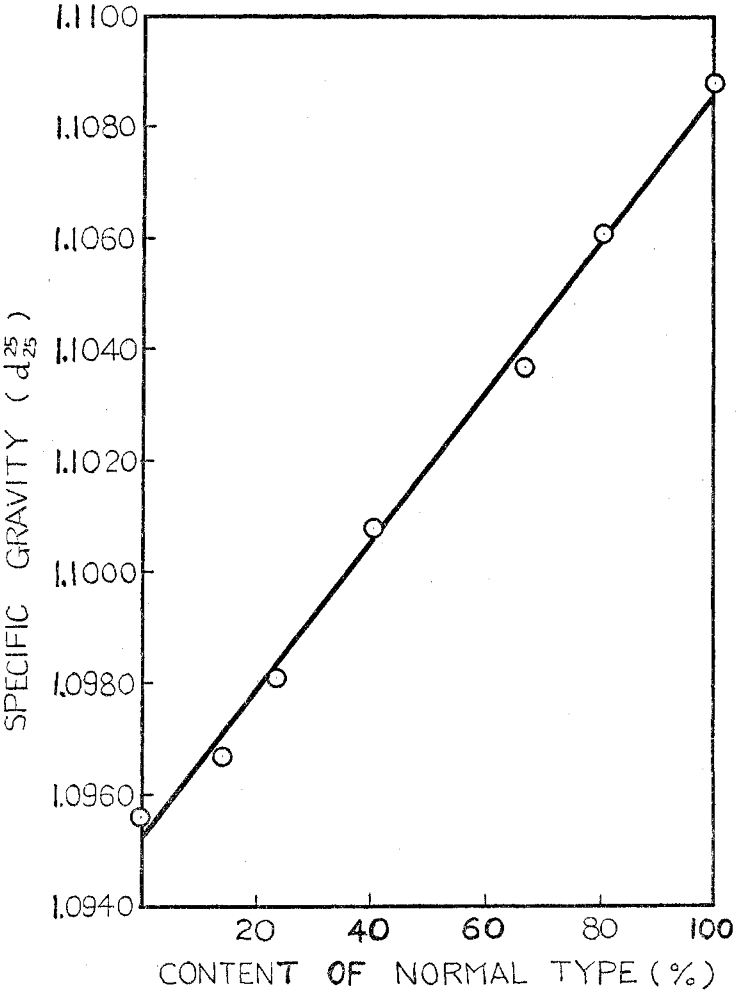


Fig. 1. Normal Product Content *versus* Specific Gravity

diethyl fumarate, reported that the two isomers differ slightly in their densities. This situation has also been observed in the present experiment in which the addition reaction between diethyl ethylmalonate and diethyl fumarate has been studied. Detailed examination has revealed a linearity between the ratio of the isomers and the density of their mixtures (Table I and Figure 1). In this paper the ratio of formation of the two isomers under various experimental conditions has been determined.

TABLE II

THE MICHAEL REACTION; EXPERIMENTAL DETAILS

EXPERIMENT	AMOUNT OF SODIUM ETHOXIDE[a]	REACTION		SPECIFIC GRAVITY, d^{25}_{25}	NORMAL PRODUCT, %	TOTAL ADDUCTS, Yield, %
		Time, Minutes	Temp., °C.			
SERIES I. Influence of the amount of sodium ethoxide	0.11	180	70	1.1054	77.4	55.5
	.29	180	70	1.1040	67.0	57.5
	.47	180	70	1.1020	52.2	65.7
	.62	180	70	1.1007	42.5	75.0
	.72	180	70	1.0993	32.0	56.0
	.91	180	70	1.0967	13.0	66.6
SERIES II. Effect of the reaction period	.62	1⅓	70	1.1022	53.7	69
	.62	3⅔	70	1.1030	59.6	67
	.62	10	70	1.1000	37.4	71
	.62	60	70	1.1001	38.0	72
SERIES III. Temperature dependence of the reaction	.62	10	0	1.1061	82.0	76
	.62	10	30	1.1024	55.0	78
	.62	10	70	1.1000	37.4	71

[a] Mole ratio of sodium ethoxide *versus* diethyl ethylmalonate.

EXPERIMENTAL

1. *Materials.* (a) *Diethyl fumurate,* b.p. 100.5° at 19 mm., was prepared by the esterification of fumaric acid; *p*-toluenesulfonic acid was used as the catalyst.

(b) *Diethyl ethylmalonate.* Commercial diethyl malonate (250 g.) was purified by treating with a mixture of absolute alcohol (125 ml.) and concentrated sulfuric acid (75 ml.) in a steam-bath for 36 hours. The purified diethyl malonate was ascertained to be nitrogen-free; b.p. 194–195°, d^{25}_{25} 1.0507. Diethyl malonate thus purified was ethylated according to the usual procedure (5); b.p. 203–206°, d^{25}_{25} 1.0059.

(c) *Ethyl pentane-α,β,γ,γ-tetracarboxylate* (IV) was prepared by treating diethyl bromosuccinate with diethyl ethylmalonate according to Rydon's method (4b); b.p. 189–192° at 15 mm., d^{25}_{25} 1.1087.

(d) *Ethyl pentane-α,α,β,γ-tetracarboxylate* (V) was prepared according to Michael's method (6); b.p. 199–200° at 15 mm., d^{25}_{25} 1.0956.

2. *General procedure of the Michael Reaction.* (a) *Ethyl alcohol as the solvent.* To a solution of metallic sodium in 70 ml. of absolute alcohol was added 22.6 g. (0.12 mole) of diethyl ethylmalonate, followed by 17.2 g. (0.1 mole) of diethyl fumarate in 20 ml. of absolute alcohol. After the mixture was stirred for a finite period, it was acidified with glacial acetic acid and the solvent was evaporated *in vacuo.* Some water was added to the residue and the adducts were extracted five times with carbon tetrachloride. The carbon tetrachloride ex-

tract was washed with water and dried with sodium sulfate; the solvent was evaporated and the residue was distilled at reduced pressure.

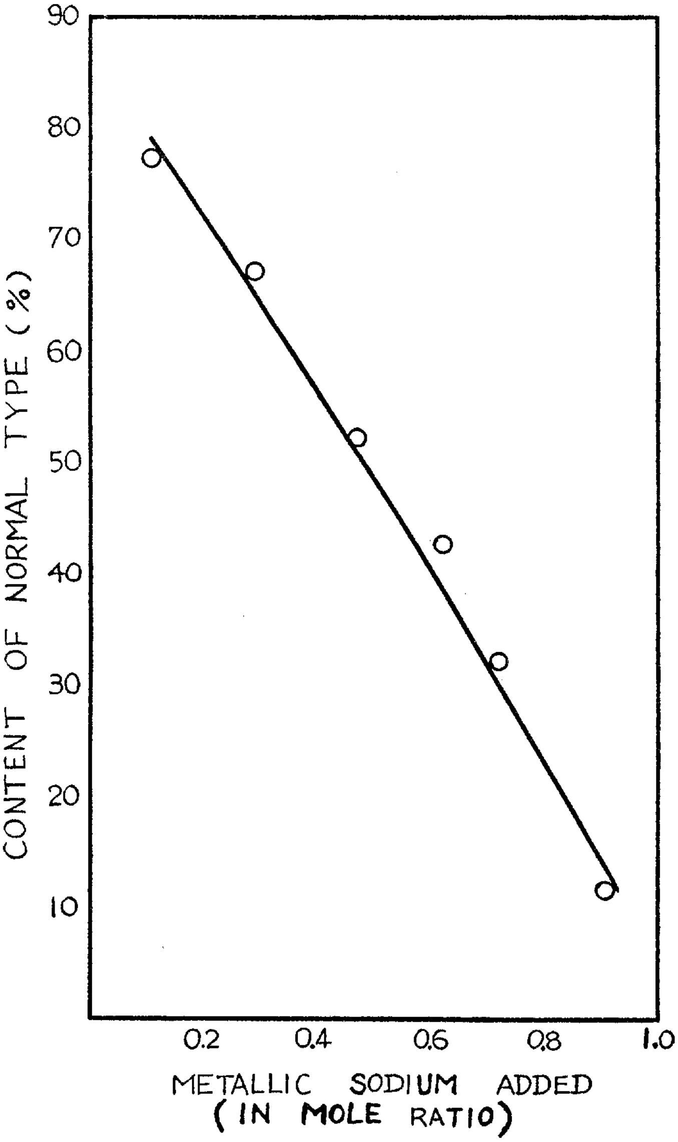


FIG. 2. NORMAL PRODUCT CONTENT *versus* SODIUM ADDED

(b) *Benzene as the solvent.* Metallic sodium (1.7 g.) was powdered under 150 ml. of xylene, and the latter was replaced by 70 ml. of benzene. To this mixture 22.6 g. of diethyl ethylmalonate was added. By stirring for a while the metallic sodium was completely dissolved in the solution with the evolution of hydrogen gas. To this solution 17.2 g. of diethyl fumarate in 20 ml. of dry benzene was added. Further treatment was the same as that in (*a*).

RESULTS

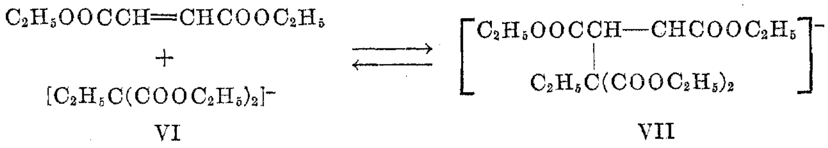
The results obtained are shown in Tables I and II, and Figures 1 and 2.

DISCUSSION

From the results obtained, it is obvious that Michael's mechanism for the abnormal formation, which assumed the separation of the ethyl group prior to the addition of the malonate residue to the fumarate, is quite implausible. According to Michael's mechanism, since the normal and the abnormal adducts should be former independently and the rate of formation of the former is much larger, the total yield of the adducts should be smaller if the reaction is interrupted at an early period. However, as is shown in Series II or III of Table II, the total yield was much the same while the content of the normal varied by a factor of 1.5–2. This will rule out the Michael mechanism.

Another mechanism, which assumes the normal adduct (IV) is formed rapidly and IV then undergoes a slower isomerization, seems also less likely. For, in the benzene solution,[1] as is seen from the experimental part, only 40% of the ethylmalonic ester has hydrogen available to form the normal product, whereas the yield of the total adducts was much larger than 40%. Any reasonable mechanism cannot account for this fact, so far as the formation of (IV) is regarded as a necessary condition for the abnormal adduct formation.[2]

In the present paper it is proposed that it must be an adduct anion (VII), but not the normal adduct (IV) itself, that is formed at the first stage of the reaction.



$$\underset{\text{VI}}{\begin{matrix} C_2H_5OOCCH{=}CHCOOC_2H_5 \\ + \\ [C_2H_5C(COOC_2H_5)_2]^- \end{matrix}} \rightleftarrows \underset{\text{VII}}{\begin{bmatrix} C_2H_5OOCCH{-}CHCOOC_2H_5 \\ | \\ C_2H_5C(COOC_2H_5)_2 \end{bmatrix}^-} \qquad 1.$$

Two courses for the stabilization of the energetic adduct anion (VII) are possible.

1. Interaction with free ethylmalonic ester to form the normal adduct (IV), together with the malonic ester anion (VI):

$$\text{VII} + C_2H_5CH(COOC_2H_5)_2 \xrightarrow{v_1} \text{IV} + \text{VI} \qquad 2.$$

The rate (v_1) of formation of the normal adduct (IV) can be expressed as follows:

$$v_1 = k_1 \text{ [adduct anion (VII)] [free ethylmalonic ester]} \qquad 3.$$

where K_1 is a rate constant.

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[1] In our experiment, any appreciable variations in the yields both of the total and of the normal adducts could not be observed even when benzene instead of alcohol was used as the solvent. This means that the concentration of alcohol in the reaction system does hardly affect the course of the reaction and that the mechanism is presumably the same in both solvents.

[2] The normal product indeed can undergo the isomerization to the abnormal under the effect of sodium ethoxide, but this does not mean the preliminary formation of the normal is necessary for the abnormal adduct formation.

2. An isomerization to the abnormal type:

$$\text{VII} \xrightarrow{v_2} \text{V} \qquad 4.$$

The rate (v_2) of the isomerization will be:

$$v_2 = k_2 \text{ [adduct anion (VII)]} \qquad 5.$$

where K_2 is a rate constant.

From equations 3 and 5, equation 6 is obtained:

$$\frac{v_1}{v_2} = \frac{k_1}{k_2} \text{ [free ethylmalonic ester]} \qquad 6.$$

As will be seen later, since K_1 is much larger than K_2, the rate v_2 will be able to predominate over v_1 only when the concentration of free ethylmalonic ester becomes very small (in actuality, nearly zero).

If equation 2 above represented a rapidly attained equilibrium, then the concentration of the adduct anion (VII), will still be similarly dependent on the concentration of free ethylmalonic ester, since the equilibrium constant, K_1, is given by the expression:

$$K_1 = \frac{\text{[normal adduct IV] [ethylmalonic ester anion VI]}}{\text{[adduct anion VII] [ethylmalonic ester]}}$$

These considerations will make it possible to expect the yield of the adduct to be proportional to the free ethylmalonic ester initially present. From Table II (Series I) or Figure 2, it can be seen that the yield of the normal adduct is inversely proportional to the amount of sodium ethoxide used. Most of the malonic ester added to the alchoholic solution of sodium ethoxide will be converted to the conjugated base (VI) because the malonate is more acidic than alcohol:

$$C_2H_5CH(COOC_2H_5)_2 + C_2H_5O^- \rightleftarrows \text{VI} + C_2H_5OH \qquad 7.$$

Thus it can be concluded that Series I or Figure 2 shows that the expected proportionality between the yield of the normal adduct and the free ethylmalonic ester is actually present. According to this view, if there is present free ester in an effective concentration, the isomerization to the abnormal adduct should not take place. As a matter of fact, when fumaric ester was treated with 2 equivalents of ethylmalonic ester, the adduct isolated has been proven to be the pure normal product even though the larger quantity (1 equivalent) of sodium ethoxide was used.[3] It seems, in this case, that the excess free ethylmalonic ester thoroughly suppressed the abnormal adduct formation.

As can be seen from Table II, Series II, the yields of the total addition products were much the same over the range of these reaction times, but those of the normal product were larger in the earlier stage of the reaction.

These results indicate that the adduct anion (VII) is formed rapidly, but the isomerization of (VII) to the abnormal product (V) can proceed only slowly. If

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[3] Diethyl fumarate (0.1 mole, 17.2 g.) was dropped into an alcoholic solution of ethylmalonic ester (0.24 mole, 45.4 g.) and metallic sodium (0.12 atom, 2.8 g.). The adduct of this reaction was the pure normal product (d_{25}^{25} 1.1084).

the reaction is interrupted by acidifying with acetic acid before the isomerization has not been completed, the acetic acid will interact with the anion (VII) to give rise to the normal product as follows:

$$\text{VII} + CH_3COOH \rightarrow \text{IV} + CH_3COO^- \qquad 8.$$

Thus the content of the normal product becomes larger. From an analogous consideration, the higher content of the normal product at the lower reaction temperature can be ascribed to the slower rate of the isomerization (Table II, Series III).

Stabilization of the anion (VII) might take place in the following manner:

$$\text{VII} + C_2H_5OH \rightarrow \text{IV} + C_2H_5O^- \qquad 9.$$

But such a reaction seems very unlikely.[1]

From the present study, some information about the Michael reaction has been obtained. But the nature of the isomerization is still obscure. The authors believe a four-membered cyclic intermediate, as Holden proposed, is less likely on account of the highly distorted valency bond. The use of isotopic carbon should afford clear evidence for the reaction mechanism.

Acknowledgement. The authors are grateful to the suggestive discussions and the encouragement made by Professor Ryohei Oda, Kyoto University, in this work. (Takatsuki, Osaka-Fu, Japan).

SUMMARY

1. In the reaction between diethyl ethylmalonate and diethyl fumarate, the ratio of formation of the two isomers under various conditions has been determined by measuring the specific gravity of the mixtures of these adducts.

2. It was concluded that the reaction probably proceeds in two stages, *i.e.*, rapid formation of an adduct anion (VII) at the first step and the successive interaction with free ethylmalonic ester or the slower isomerization to the abnormal product at the second step.

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