# LXXXIX.—*The Reactions of Malonic Esters with Formaldehyde. Part II.*

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IN Part I (J., 1930, 257) it was shown that the action of formaldehyde on malonic ester in the presence of dilute alkali led first to the formation of mono- and di-(hydroxymethyl)malonic ester, and that these could be further condensed with malonic ester to give ethyl pentane-$\alpha\alpha\gamma\gamma\epsilon\epsilon$-hexacarboxylate and ethyl methylenedimalonate, also in the presence of inorganic alkalis (see also this vol., p. 673). This seemed to support the original theory of Lapworth and his collaborators (J., 1904, **85**, 46; 1922, **121**, 2741, 2824) * that the secondary bases in Knoevenagel's reaction might be functioning simply as bases (see, *e.g.*, Kohler and Corson, *J. Amer. Chem. Soc.*, 1923, **45**, 1975). However, other authors have obtained evidence for a specific action of the organic base (see Knoevenagel *Ber.*, 1898, **31**, 730; Mannich and Ganz, *Ber.*, 1922, **55**, 3486; Dilthey, *Ber.*, 1929, **62**, 1609; Rodionow and Postovskaja, *J. Amer. Chem. Soc.*, 1929, **51**, 841).

Few, if any, measurements of reaction velocity have been carried out on this and similar reactions, doubtless owing to the difficulty in analysis of the reaction products. Formaldehyde, however, is readily estimated, and a series of kinetic studies of the reaction $CH_2(CO_2Et)_2 + CH_2O \longrightarrow CH_2(OH)\cdot CH(CO_2Et)_2$ under various conditions has been undertaken.

Previous work had shown (*loc. cit.*) that a further combination of the product with formaldehyde took place, and, moreover, both reactions are probably reversible, thus :

$$CH_2(CO_2Et)_2 \underset{\longleftarrow}{\overset{CH_2O}{\longrightarrow}} CH_2(OH)\cdot CH(CO_2Et)_2 \underset{\longleftarrow}{\overset{CH_2O}{\longrightarrow}} (HO\cdot CH_2)_2C(CO_2Et)_2.$$
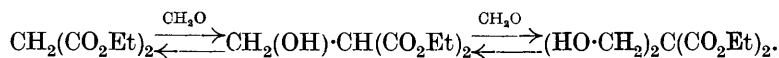
This would make any mathematical analysis of the total reaction curve difficult or impossible, but the method of integration of frac-

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* Lapworth seems to have seen reason later to ascribe a more complex function to secondary bases (compare J., 1911, **99**, 2117).

tional parts may be applied to the early stages of the reaction to obtain its order, n, from the equation

$$n = 1 + (\log t_1 - \log t_2)/(\log c_2 - \log c_1)$$

(Noyes, $Z.\ physikal.\ Chem.$, 1896, **19**, 599 ; see also Mellor, " Chemical Statics and Dynamics," p. 63). The time, $t_{0.2}$, taken for one-fifth of the formaldehyde to react was obtained by interpolation from the graph of the first part of the reaction, a slight initial period of disturbance being neglected. The following are the results obtained, the concentrations being expressed as normalities.

Temp. 21° ; $p_H = 4.9$.

Expt.	[CH$_2$O].	[Ester].	$t_{0.2}$ (hours).	n.
1	1.11	1.15	59	2.07
2	0.555	0.575	124	—
3	0.277	0.287	244	1.92

The reaction is obviously of the second order; moreover, the following results show that the initial speed of reaction, v, is approximately proportional to the first power of the concentration of each reactant separately.

Temp. $= 21°$; $p_H = 4.9$.

[CH$_2$O].	[Ester].	$v = \Delta[CH_2O]/\Delta t$.*
1.11	1.15	0.0034
1.11	0.575	0.00185
0.555	1.15	0.00157†

* $\Delta[CH_2O] = 0.1N$; Δt is expressed in hours.

† This reaction showed a greater period of initial disturbance than the others.

The effect of varying hydrogen-ion concentration on the reaction velocity was next measured. Since it is impossible to obtain an accurate value of the velocity coefficient by integration, the following method was adopted. The equation for a reaction of any order may be written $kt = f(a, x)$, where $f(a, x)$ is some function of the initial concentrations and of those after time t. Experiments were therefore made in which a and x had identical values, but k varied; if it be assumed that consecutive reactions are negligible in the first stages of the reaction, it is clear that $k \propto 1/t_{0.2}$. The following are the results :

[CH$_2$O] $= 1.11N$; [Ester] $= 1.15N$; Temp. $= 21°$.

p_H.	[H$\cdot$] $\times 10^8$.	$t_{0.2}$ (hours).
4.9	1260	59
6.0	100	4.2
7.1	8	0.32

It will be seen that within the limits that could be conveniently investigated, k is inversely proportional to the hydrogen-ion concentration.

In order to see whether organic bases owed their activity to the repression of hydrogen-ion concentration that they produce, a small quantity of the appropriate base was added to the reaction mixture, the p_H being then readjusted to 4·9 in each case.

The results are illustrated by the accompanying figure, from which it will be seen that piperidine has a profound effect on the reaction velocity, whilst triethylamine and ammonia are without action within the limits of experimental error.   The action of

FIG. 1.
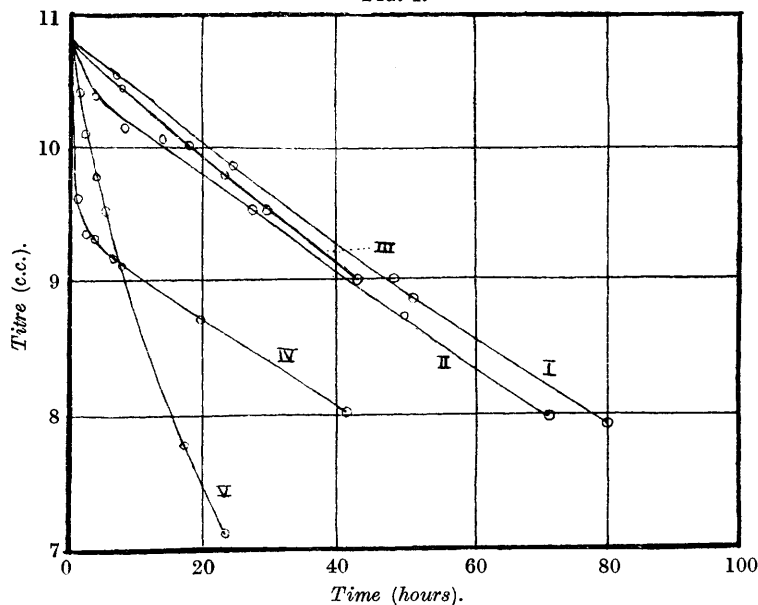
I. *No catalyst.*   II. 0·01N-*Ammonia.*   III. 0·01N-*Triethylamine.*
IV. 0·003N-*Methylamine.*   V. 0·0011N-*Piperidine.*
p_H 4·9;   Temp. $= 21°$.   Concentrations as in Expt. 1, p. 654.

methylamine appears to be temporary (possibly due to destruction of the catalyst).*

These results receive a simple explanation by the theories of Lapworth and others (see Cocker, Walton, and Lapworth, J., 1930, 440, for the historical development of these ideas), *viz.*, that the reaction takes place between the ion of the malonic ester and the formaldehyde, although less simple explanations cannot, of course, be excluded.   It is obvious, however, that the reaction takes a different course in the presence of piperidine, and under the normal conditions

* The lack of permanent effect of ammonia and methylamine may be due to their almost complete removal as hexamine and its analogue.

of Knoevenagel's reaction both reactions must proceed simultaneously. This investigation is being continued.

EXPERIMENTAL.

Materials.—Malonic ester. A good commercial sample was fractionated by distillation in a vacuum, the fraction boiling within 0·5° being taken.

Formaldehyde. Commercial formalin was distilled, the first half and last sixth being rejected.

Piperidine. Merck's purest.

Methylamine. All available specimens were contaminated with secondary base, and a pure specimen was prepared from acetamide.

Triethylamine. A commercially pure product found to be practically free from secondary base.

Buffer. An $M/300$-phosphate buffer or a very dilute universal buffer mixture was used, experience having shown that variations in the very weak buffer had in general no detectable effect on the reaction velocity.

Method. The required quantities of ester, formaldehyde solution, buffer, and an appropriate indicator were diluted to 100 or 200 c.c. with 66% alcohol, any catalyst being added and the p_H adjusted before final adjustment of the volume. The rate of disappearance of formaldehyde was measured, the analytical method of Brochet and Cambier (*Compt. rend.*, 1895, **120**, 449) being used, since this had the advantage that the acid produced stopped the reaction. It was necessary to standardise the conditions very exactly to obtain reproducible results (addition of a measured excess of hydroxylamine hydrochloride, and the allowance of 10 mins. before titration). Also the use of bromophenol-blue with a comparison flask was found to be more satisfactory than the methyl-orange recommended by those authors.

The chief difficulty encountered was in keeping the p_H constant during the reaction, as slight hydrolysis of the ester took place; to compensate for this, concentrated sodium hydroxide solution was introduced on a platinum wire from time to time into the reaction mixture containing a suitable indicator which was matched against a 66% alcoholic colorimetric standard, and this in turn was checked by electrometric p_H measurements. In this way, no appreciable change in volume took place and the p_H could be maintained constant within 0·1 unit. This method of control is not ideal but was adopted for lack of a better. However, it is thought that no serious error exists, for the results were reproducible within a limit of about 10% in the value of k, an error which would not invalidate the con-

clusions drawn as to the order of reaction or to the relationship of k to the first power of the hydrogen-ion concentration.

In conclusion, the author desires to express his thanks to Mr. G. W. Leeper, M.Sc., for carrying out many of the p_H determinations.