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Kinetics of the Knoevenagel Condensation of Benzaldehydes with Diethyl Malonate

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The piperidine-catalyzed Knoevenagel reaction between diethyl malonate and benzaldehyde or ring-substituted benzaldehydes to yield diethyl benzylidenemalonates has been studied kinetically at 99.5° in kerosene solution. The rate of the formation of diethyl benzylidenemalonates and that of the consumption of benzaldehydes has been followed by ultraviolet spectrophotometry. It was confirmed that the reaction was accelerated by a small amount of organic acid (benzoic acid in the present case), but retarded by an excess. Both electron-attracting and releasing *p*-substituents retard the reaction. The rate was also measured in isopropyl alcohol, and the results were compared to those in kerosene.

Many synthetic studies on the Knoevenagel and related reactions, have been reported, but there seem to be little data from the kinetic or mechanistic standpoint. It is generally accepted[1] that the reaction involves a preliminary removal of proton with bases from active methylene group followed by an attack of the carbanion on a carbonyl carbon atom. However, decisive kinetic support for the mechanism has scarcely been obtained.

It is known that amines salts of organic acids are better catalysts than free amines for this reaction.[2] On the other hand, however, it will be noted that piperidine alone is more satisfactory than piperidine acetate in acetic acid for the condensation of aldehydes with ethyl cyanoacetate.[3] This mysterious role of organic acids in the condensation has often been pointed out and some studies have been made of the condensation in the presence of a large amount of acid,[4] or with free malonic acid[5] or its monoester.[6] However, no rational explanation of this mechanism has yet been postulated.

The present paper summarizes our results obtained on the kinetic study of the reaction between diethyl malonate and benzaldehydes yielding diethyl benzylidenemalonate in kerosene or isopropyl alcohol solution using both piperidine and benzoic acid as catalysts.

Experimental

Materials.—Unsubstituted and substituted benzaldehydes,[4,6] diethyl malonate, piperidine, benzoic acid and isopropyl alcohol used were of the best grade or prepared by standard methods and purified by either recrystallization or vacuum distillations, until their melting or boiling points agreed with those in the literature. All *p*-substituted diethyl benzylidenemalonates were synthesized by the condensation of the corresponding benzaldehydes with diethyl malonate using piperidine and benzoic acid as catalysts.[4] Among them, diethyl *p*-chlorobenzylidenemalonate has been reported to be an oily substance,[4] but in our hands, the compound, if maintained below 0° for three weeks, was brought to crystallization, m.p. 34–35°. Diethyl *p*-methylbenzylidenemalonate, a new compound, was obtained in colorless plates melting at 43–43.5°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.77; H, 6.86.

Commercial kerosene was treated several times with fuming sulfuric acid, washed with water and rectified. A fraction boiling between 240–280° was collected, which showed no appreciable absorption in the region 240–290 mμ in a methanolic solution of the experimental concentrations.

Typical Procedure for Rate Measurements.—As an example, the rate measurements of piperidine–benzoic acid-catalyzed condensation of benzaldehyde with diethyl malonate is described below. Definite amounts of benzaldehyde, usually containing 0.1–0.2 wt. % of benzoic acid, diethyl malonate, piperidine, benzoic acid and kerosene (20 ml.) were placed in a 100-ml. flask fitted with an outlet tube. The flask was immersed in an oil-bath thermostated at 99.5 ± 0.3°, and shaken vigorously. At appropriate time intervals aliquots (0.2 ml.) were withdrawn and diluted to 10 ml. in a volumetric flask. From the solution, 0.5 ml. was taken out and again diluted to 10 ml. with acidified methanol (5 ml. of concentrated sulfuric acid in 1 l. of methanol), the optical densities of the resulting solution being measured at appropriate wave lengths by a Beckman spectrophotometer, model DU, as shown in Table I. The percentage compositions of these solutions were determined in the same manner as previously described[7] and the initial rate V_0 was evaluated graphically[8] and listed in Tables II and III. The spectrophotometric measurements were carried out at 245, 251 and 275 mμ as shown in Table I. Two differences of the optical densities, $(E_{245}-E_{275})$ *vs.* $(E_{251}-E_{275})$, were plotted and thus the amounts of benzaldehyde and diethyl benzylidenemalonate were determined as a two-component system.[7]

TABLE I

SPECTROPHOTOMETRIC DATA FOR RATE MEASUREMENTS. OPTICAL DENSITIES OF BENZALDEHYDES AND DIETHYL BENZYLIDENEMALONATES IN ACIDIC METHANOL (5 ML. OF CONCD. SULFURIC ACID[c] IN 1 L. OF METHANOL[a])

Materials	Concentration, $M \times 10^5$	Optical density[b] at various wave lengths		
		245 mμ	251 mμ	275 mμ
C_6H_5CHO	384	0.802	0.805	0.080
$C_6H_5CH{:}C(CO_2C_2H_5)_2$	3.23	.081	.114	.294
		250 mμ	265 mμ	297.5 mμ
p-$NO_2C_6H_4CHO$	19.2	0.608	0.872	0.210
p-$NO_2C_6H_4CH{:}C(CO_2C_2H_5)_2$	2.34	.062	.098	.233
		240 mμ	245 mμ	278 mμ
p-ClC_6H_4CHO	21.3	0.107	0.0972	0.0058
p-$ClC_6H_4CH{:}C(CO_2C_2H_5)_2$	5.96	.153	.206	.810
		255 mμ	260 mμ	285 mμ
p-$CH_3C_6H_4CHO$	25.0	0.110	0.105	0.014
p-$CH_3C_6H_4CH{:}C(CO_2C_2H_5)_2$	10.3	.244	.346	.860
		240 mμ	247 mμ	312 mμ
p-$CH_3OC_6H_4CHO$	55.1	0.124	0.158	0.023
p-$CH_3OC_6H_4CH{:}C(CO_2C_2H_5)_2$	6.12	.147	.113	.728

[a] It was shown that Beer's law was obeyed in these solutions, and that these optical densities were unaltered with small variations of the acidity of the solvent. [b] $E = \log (I_0/I) = \epsilon cd = 0.5 \epsilon c$. [c] This acid considerably lowered optical densities of aldehydes.

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(1) For example, see A. R. Surrey, "Name Reactions in Organic Chemistry," Academic Press, Inc., New York, N. Y., 1954, p. 103; A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 208.

(2) A. C. Cope, THIS JOURNAL, **59**, 2327 (1937); R. Kuhn, W. Badstübner and C. Grundmann, *Ber.*, **69**, 98 (1936); R. L. Shriner and F. W. Neuman, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 377; M. J. Astle and W. C. Gergel, *J. Org. Chem.*, **21**, 493 (1956).

(3) A. C. Cope and C. M. Hofmann, THIS JOURNAL, **63**, 3456 (1941).

(4) E. F. Pratt and E. Werble, *ibid.*, **72**, 4638 (1950).

(5) S. Patai, J. Pfeffermann and Z. Rozner, *ibid.*, **76**, 3446 (1954).

(6) J. Klein and E. D. Bergmann, *ibid.*, **79**, 3452 (1957).

(7) Y. Ogata, M. Tsuchida and Y. Takagi, *ibid.*, **79**, 3397 (1957).

(8) S. L. Friess and A. Weissberger, ed., "Investigation of Rates and Mechanism of Reactions," ("Technique of Organic Chemistry," Vol. VIII), Interscience Publishers, Inc., New York, N. Y., 1953, p. 182.

TABLE II

REACTIONS IN KEROSENE AT 99.5 ± 0.3°

Initial concentration, M				Initial
Benzaldehyde B_0	Diethyl malonate M_0	Piperidine P_0	Benzoic acid Y_0	rate $V_0 \times 10^7$, mole l.$^{-1}$ sec.$^{-1}$
0.094	0.0629	0.0964	0.0014	5.90
.094	.0944	.0964	.0014	8.64
.094	.1258	.0964	.0014	11.3
.094	.1573	.0964	.0014	14.7
.094	.2516	.0964	.0014	20.7
.094	.3146	.0964	.0014	30.8
.094	.4719	.0964	.0014	33.3
.094	.0629	.0964	.0014	5.90
.141	.0629	.0964	.0014	8.30
.188	.0629	.0964	.0014	12.2
.282	.0629	.0964	.0014	15.2
.376	.0629	.0964	.0014	22.2
.094	.1573	.0964	.0014	14.7
.141	.1573	.0964	.0014	21.0
.235	.1573	.0964	.0014	33.7
.376	.1573	.0964	.0014	50.7
.235	.1573	.0482	.0014	30.0
.235	.1573	.0964	.0014	38.5
.235	.1573	.1446	.0014	44.0
.235	.1573	.1928	.0014	45.8
.188	.1258	.0964	.0010	19.0
.188	.1258	.0964	.0012	22.4
.188	.1258	.0964	.0014	24.6
.188	.1258	.0964	.0018	27.8
.188	.1258	.0964	.0022	35.2
.188	.1258	.0964	.0026	42.7
.188	.1258	.0964	.0039	44.7
.188	.1258	.0964	.0051	61.7
.188	.1258	.0964	.0092	64.0

TABLE III

REACTIONS IN ISOPROPYL ALCOHOL AT 83 ± 0.2°

Initial concentration, M				Initial
Benzaldehyde B_0	Diethyl malonate M_0	Piperidine P_0	Benzoic acid Y_0	rate $V_0 \times 10^6$, mole l.$^{-1}$ sec.$^{-1}$
0.235	0.0629	0.0964	0.0014	8.08
.235	.1258	.0964	.0014	13.7
.235	.1887	.0964	.0014	18.3
.235	.2517	.0964	.0014	21.5
.094	.1573	.0964	.0014	9.32
.188	.1573	.0964	.0014	15.9
.282	.1573	.0964	.0014	19.0
.376	.1573	.0964	.0014	20.2
.094	.1258	.0964	.0014	6.44
.094	.1258	.1928	.0014	8.92
.235	.1573	.0964	.0014	15.9
.235	.1573	.1928	.0014	22.0
.094	.1573	.0964	.0014	9.32
.094	.1573	.0964	.0022	10.1
.094	.1573	.0964	.0030	10.8
.094	.1573	.0964	.0038	10.9
.094	.1573	.0964	.0100	8.75
.094	.1573	.0964	.0500	7.32

This plot is a line and the procession of a reaction is expressed as the movement of a point along the line.[7]

The absorption of kerosene and diethyl malonate were negligible under these conditions and that of piperidine was reduced by the addition of a small amount of sulfuric acid. This sulfuric acid also served to reduce the absorption of benzaldehydes, while that of diethyl benzylidenemalonates remained almost unchanged by this acid. Thus a large absorption difference between these components permitted us to estimate the change in composition very accurately.

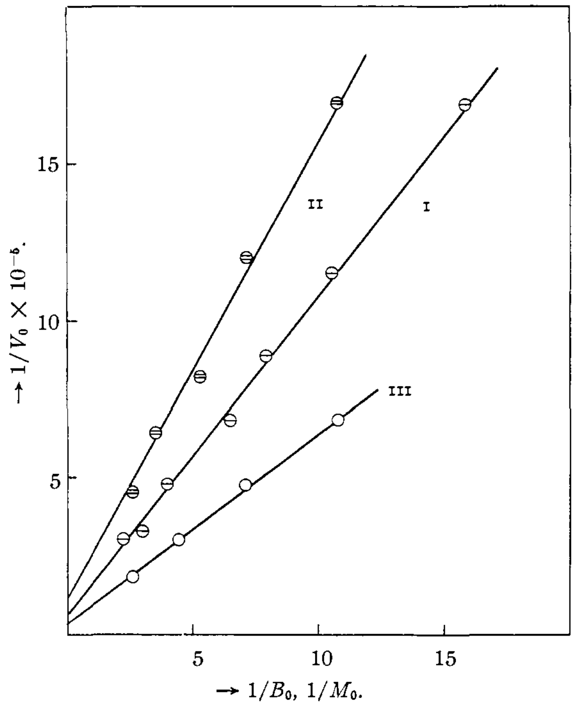

Fig. 1.—Plots of reciprocal initial rates against reciprocal concentrations of diethyl malonate (line I, ⊖) and benzaldehyde (line II, ⊜, and line III, ○).

Complementary Experiments.—Since most of the kinetic runs were not followed over 20% conversion, some complementary tests seemed necessary in order to ensure the reaction path. Diethyl benzylidenemalonate was isolated under the condition of the kinetic runs with prolonged reaction time, but the yields were low because of the loss during isolation procedure. It was confirmed preliminarily by means of a modified Vaughn's chart[7] that the reactions followed spectrophotometrically was in fact the reaction under consideration and no appreciable side reaction occurred. The chart showed that the observed lines for substituted benzaldehydes satisfactorily agreed with the calculated lines[7] at least up to 70% conversion. Only with the piperidine-catalyzed condensation between *p*-nitrobenzaldehyde and diethyl malonate in isopropyl alcohol in the absence of benzoic acid did the reaction show a drift from the expected one. The rate of disappearance of the aldehyde was considerably larger than those runs in the presence of the acid which proceeded as expected. *p*-Nitrobenzaldehyde in kerosene solvent without benzoic acid did not react with diethyl malonate under these conditions. Since the other aldehydes are very susceptible to air oxidation and the acid produced accelerates the reaction even with a small amount, the runs free from acid could not be followed. However, their rates without acid catalysts approach zero as is obvious from the extrapolation of line V in Fig. 2.

Results and Discussion

The rates were measured in both kerosene and isopropyl alcohol, the initial rates being listed in Table II and III, respectively. In Table IV are summarized the effects of *p*-substituents on benzaldehyde. Some interesting features of this reaction can be seen from these tables.

The Reaction in Kerosene as a Solvent.—The rates increase almost linearly with the amount of reactants and catalysts, if their concentrations are not large, *i.e.*, rate = k[benzaldehyde][diethyl malonate][piperidine][benzoic acid]. However, the linearity departs as the concentrations of reactants and catalysts become large, and this tendency is remarkable with piperidine. This

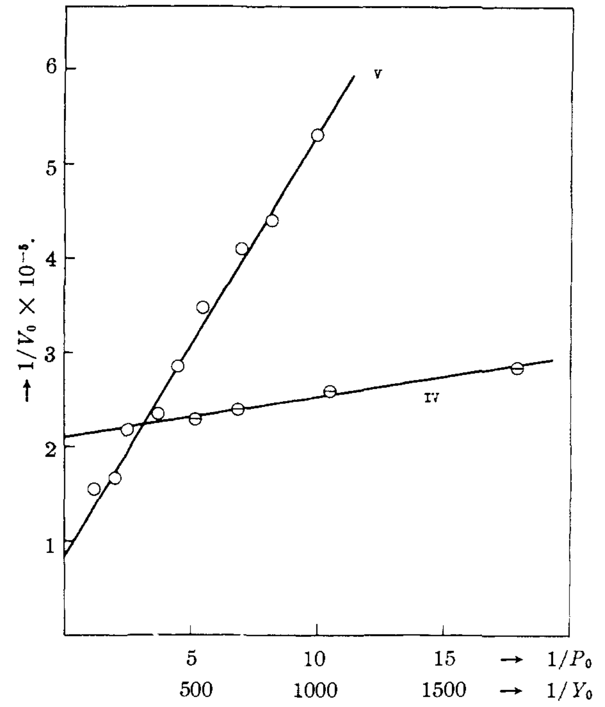

Fig. 2.—Plots of reciprocal initial rates against reciprocal concentrations of piperidine (line IV, ⊖) and benzoic acid (line V, O).

situation can well be represented graphically; the reciprocal initial rate $1/V_0$ varies linearly with reciprocal initial concentrations of diethyl malonate $1/M_0$(Fig. 1), of benzaldehyde $1/B_0$(Fig. 1), of piperidine $1/P_0$ (Fig. 2) and of benzoic acid $1/Y_0$ (Fig. 2). The reaction is accelerated by small amounts of benzoic acid, and the rates without acid catalysts approach zero.

TABLE IV

THE EFFECTS OF *p*-SUBSTITUENTS (INITIAL RATE V_0, MOLE L.$^{-1}$ SEC.$^{-1}$ × 10^6)

	Initial concentration, M				
	Benzaldehydes, B_0	Diethyl malonate, M_0	Piperidine, P_0	Benzoic acid, Y_0	
In kerosene	0.1975	0.1258	0.0964	0.0014	
In *i*-PrOH	0.1975	0.2516	0.1928	0.0014	
	Initial rate				
	CH_3O	CH_3	H	Cl	NO_2
In kerosene (99.5°)	1.63	1.65	2.56	2.19	1.52
In *i*-PrOH (83°)	11.3	11.6	19.5	15.5	9.1

Although the effect of *p*-substituents is very small, its mode of action is not simple; both electron-attracting and releasing groups retard the reaction, and a similar effect is recorded for the rate of formation of some Schiff bases.[9] With regard to this, it is of interest to note that the rates of condensation of benzaldehydes with acetic anhydride in kerosene using triethylamine as a catalyst satisfy the Hammett equation with a high positive ρ-value (+2.25).[10]

The Reaction in Isopropyl Alcohol as a Solvent.—Deviation from linearity between the initial velocities and concentrations of the reactants is more remarkable in this solvent than in kerosene. A plot of $1/V_0$ *vs.* $1/M_0$ gives satisfactory straight lines and a plot of $1/V_0$ *vs.* $1/B_0$ is almost linear. But plots of $1/V_0$ *vs.* $1/P_0$ and $1/Y_0$ tend to drift upward with increasing concentrations. In this solvent, the effect of benzoic acid on the rate is very small compared to that observed in kerosene, and the reaction is retarded by excess of the acid.

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[9] O. Bloch-Chaude, *Compt. rend.*, **239**, 804 (1954).

[10] Y. Ogata and M. Tsuchida, *J. Org. Chem.*, **24**, 78 (1959).

KYOTO, JAPAN

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The Synthesis of Citric Acid Phosphate

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Citric acid phosphate has been synthesized by phosphorylating triethyl citrate with diphenyl phosphorochloridate, followed by removal of the phenyl groups by catalytic hydrogenolysis and alkaline saponification of the resulting triethyl ester. The calcium and cyclohexylammonium salts were made.

It is well established that citric acid in some form is intimately involved in the biochemistry of bone.[1] Its exact role has yet to be defined. The present report is part of a program designed to investigate this problem and is based on the postulate that citrate *per se* may not be exclusively implicated, but possibly also a form in which the tertiary hydroxyl has reacted to give citric acid phosphate or pyrophosphate. As the calcium salts, these compounds could represent an ideal vehicle for the absorption, transport and deposition of bone salts and perhaps assume a function in other aspects of calcium, phosphorus and citrate metabolism.

The synthesis of citric acid phosphate has not been reported. From the structural standpoint it is unique among organophosphate compounds. The literature offers no other authenticated example of the phosphorylation of a tertiary hydroxyl group. The presence in the molecule of three carboxyl groups further accentuates its unique character.

The present paper describes the synthesis of citric acid phosphate effected by a modification of

[1] T. F. Dixon and H. R. Perkins in "The Biochemistry and Physiology of Bone," Academic Press, Inc., New York, N. Y., 1956, p. 309.