Gas Chromatographic Rate Study of the Methanolysis of Diethyl Malonates

David O. Johnston, A. B. Cottingham, and W. Paul Roland

Contribution from David Lipscomb College, Nashville, Tennessee.
Received August 11, 1967

Abstract: The kinetics of the methoxide-catalyzed methanolysis of diethyl malonate and ethyl-substituted diethyl malonates have been investigated by gas chromatography at 20, 30, and 40°. Each transesterification of a methoxy group for an ethoxy group is first order in malonate, first order in methoxide, and zero order in methanol. The ratio of the rate constants, k_I/k_{II}, for the two transesterifications per malonate is 3.0 ± 0.3:1. This reaction is ideally suited for gas chromatography because the relative rates of the two steps enable collection of sufficient data from a single run to calculate rate constants for both steps. Energies and entropies of activation have been obtained from the temperature dependence of the reaction rates. A mechanism is proposed consistent with known enolization of the malonate in the presence of methoxide.

Gas chromatography is firmly established as an analytical tool in many fields, but it is hardly more important to a study than the investigation of the kinetics of consecutive organic reactions. The real beauty of its data outlay is the simultaneous array of concentration parameters for each reactant, intermediate, and product as they exist concurrently during the course of a reaction. This completeness of the data often enables the establishment of a rate law for each step of the reaction. These advantages of gas chromatography have been utilized in this study to follow the kinetics of the methoxide-catalyzed methanolysis of diethyl malonate at 20, 30, and 40°, and ethyl-substituted malonates at 30 and 40°. The reactions are two-step substitutions in which species of methanol consecutively replace the two ethoxy groups of the esters. Each step is an example of a Lewis base attack on an ester.

Of the many examples of Lewis base attack on malonate (*e.g.*, the acidic[1-4] and basic[5-7] hydrolyses and the condensation with urea to form barbituric acid), particularly related here are the alcoholysis rate studies which have been reported. Patel and Watson[8] used dilatometry and 0.05 *M* HCl at 30° to determine first-order velocity constants of 39.5 min^{-1} for the ethanolysis of dimethyl malonate and 142 min^{-1} for the methanolysis of diethyl malonate. Carroll[9] used titrimetry to show that the uncatalyzed alcoholysis of diethyl malonate is first order in malonate with primary and secondary alcohols and second order with tertiary alcohols.

While these studies reveal that the rate constants for the two transesterifications differ considerably, the rate constants for the methoxide-catalyzed methanolysis of diethyl malonate reported here have the ratio of 3.0 ± 0.3:1 for the two steps. This makes the application of gas chromatography to this reaction ideal because the rates of the two steps are sufficiently close together to allow the collection of rate data for both steps almost from the same chromatograms. On the other hand, the first step is fast enough to allow the use of relatively simple kinetic expressions to determine rate laws for both steps.

Experimental Section

Materials. Diethyl malonate (Matheson and K&K, bp 73–75° (5 mm), $n^{24}D$ 1.4124), dimethyl malonate (Matheson, bp 76–78° (15 mm), $n^{23}D$ 1.4119), diethyl ethylmalonate (Eastman White Label, bp 85–87° (5 mm) $n^{24}D$ 1.4146), and diethyl diethylmalonate (Eastman White Label, bp 93–94° (5 mm), $n^{24}D$ 1.4226) were purified just prior to making a run by taking the middle fraction[6] of a vacuum distillation in all-glass apparatus over potassium carbonate and magnesium sulfate.[10] Vacuum distillation alone does not remove the acid formed when diethyl malonate is allowed to stand for several months. Potassium carbonate was Baker ACS anhydrous; magnesium sulfate was Baker anhydrous. Methanol (Fisher electronic grade absolute) was bubbled with dry nitrogen (Airco, oil pumped, dew point −31°) and stored under the nitrogen atmosphere in automatic burets. Clean sodium metal was allowed to react with methanol to form the sodium methoxide stock solution which was stored in automatic burets under dry nitrogen. The methoxide concentration was determined with standardized hydrochloric acid to the phenolphthalein end point.

Apparatus. A Perkin-Elmer Model 811 gas chromatograph equipped with a hot wire detector and a Sargent SRL recorder was used for all runs. The columns were 15-ft × 0.25-in. copper tubing packed with 10% Apiezon M[11] (Wilkens) on 70/80 ABS silanized Anakrom (Analabs). Chromosorb P was unsatisfactory as it appeared to absorb the methanol and cause reaction on the column. The column and injection temperatures were 150 and 220° for diethyl malonate and 185 and 240° for diethyl ethylmalonate and diethyl diethylmalonate, respectively. The carrier gas was helium with a flow rate of *ca.* 60 cc/min, measured with a bubble meter at room temperature and atmospheric pressure.

Kinetic Procedure. The diethyl malonate and the solution of sodium methoxide in methanol were thermostated separately at the reaction temperature for at least an hour prior to beginning a run. To start a typical run, 50 ml of the sodium methoxide and methanol solution was pipetted into a 125-ml Florence flask followed by 10 ml of diethyl malonate. The timer was started when half of the malonate had entered the reaction flask. At appropriate times, 2-ml samples were withdrawn and quenched with concentrated hydrochloric acid issued from a calibrated capillary tube containing sufficient acid to neutralize the methoxide and give a slight excess of acid. The quenching was apparently effective because the eight random samples tested gave peak areas reproducible within ±1% over a 2-hr span, which was the longest time a sample had to remain

(1) M. G. Ter Horst, *Rec. Trav. Chim.*, **53**, 312 (1934).
(2) G. Vavon and J. Ducasse, *Bull. Soc. Chim. France*, 10, 325 (1943).
(3) G. A. Holmberg, *Acta Acad. Aboensis, Math Phys.*, **16**, 138 (1948).
(4) G. A. Holmberg, *ibid.*, 17, 14 (1950).
(5) R. Gane and C. K. Ingold, *J. Chem. Soc.*, 10 (1926).
(6) W. J. Svirbely and A. D. Kuchta, *J. Phys. Chem.*, **65**, 1333 (1961).
(7) N. V. Sapozhnikova, N. I. Darienko, and Z. G. Maizel, *Izv. Vysshikh Uchebn. Zavedenii, Khim. i Khim. Tekhnol.*, 9, 410 (1966).
(8) Z. H. Patel and H. E. Watson, *J. Indian Inst. Sci.*, **16A**, 55 (1933).
(9) M. F. Carroll, "Proceedings of the XIth International Congress of Pure and Applied Chemistry, London, 1947," Vol. II, 1951, p 39.
(10) C. P. Smyth and W. S. Walls, *J. Am. Chem. Soc.*, **53**, 527 (1931).
(11) A. T. James, *Fette, Seifen, Anstrichmittel*, **59**, 73 (1957).

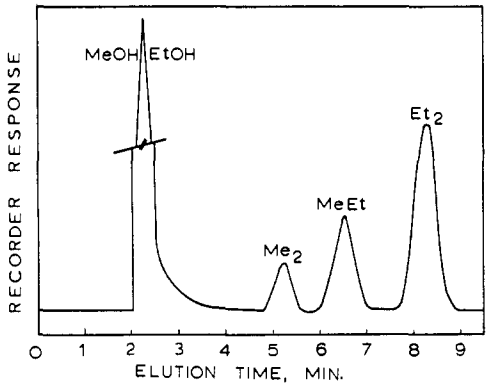


Figure 1. Typical gas chromatogram for the methanolysis of diethyl malonate during the early part of the reaction: injector temperature, 220°; column temperature, 150°; flow rate of helium, 60 cc/min; 10% Apiezon M, silanized 70/80 ABS Anakrom column.

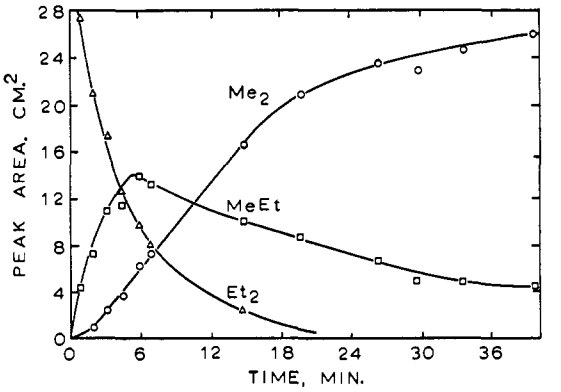


Figure 2. Peak area *vs.* reaction time for the three malonate components in the methanolysis of diethyl malonate at 30°: initial mole ratio, methanol/diethyl malonate = 18.8:1; methoxide concentration, 0.008 *M*; sample size, 0.025 ml.

quenched before being chromatographed; 25-μl aliquots were injected to produce chromatograms similar to Figure 1.

The diethyl and dimethyl malonate peaks were chromatographically proved by the enhancement of the respective peaks when diethyl malonate or dimethyl malonate was added separately to a reaction mixture and a portion chromatographed. It is obvious that the middle peak is methyl ethyl malonate since the total area of the three peaks is constant throughout a run. The areas of the peaks were computed by multiplying the height of the peak by its width at half-height. The areas of the dimethyl and diethyl malonate peaks plotted *vs.* the amount of pure compound injected were each shown to be linear to at least 15 μl, which was the maximum amount of malonate in a 25-μl aliquot of the reaction mixture.

Results and Discussion

The stepwise replacement of the two ethoxy groups of diethyl malonate by methoxide ions is a two-step reaction in which the intermediate is methyl ethyl malonate and the final product is dimethyl malonate. A molecule of ethanol is a product of each step. A typical separation of the five molecular components of the reaction is shown in the chromatogram of Figure 1. Although the alcohols are not separated in this chromatogram, the columns give excellent separation of the alcohols at lower column temperatures and slower flow rate. Since these conditions necessitate longer elution times and the alcohols are not used in the calculations, no effort was made to cleanly separate them when obtaining data for a kinetic run.

The variation of the peak areas of the malonates with time is shown in Figure 2. Diethyl malonate diminishes rapidly and is negligible near equilibrium when compared to the concentration of dimethyl malonate. The dimethyl malonate undergoes the initiation period typical of reactions dependent upon generation of the starting substance.

Each step of the reaction is first order in malonate, first order in methoxide, and independent of the methanol concentration. The pseudo-first-order rate constants shown in Table I for the conversion of diethyl malonate to methyl ethyl malonate were calculated according to the equation[12a]

$$k_I = k_{+1} + k_{-1} = \frac{2.303}{t} \log \frac{A_0 - A_e}{A_t - A_e}$$

(12) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1961: (a) p 186; (b) p 23; (c) p 99. In the derivation of k_{II}, since A is negligible well before the second step is completed (*cf.* Figure 2), then $B_t = A_0 - C_t$ and $B_e = A_0 - C_e$ which allow C_e to be substituted for A_0 according to $A_0 = C_e(k_{+2} + k_{-2})/k_{+2}$. B is the peak area of methyl ethyl malonate; the other symbols are consistent with the rest of the paper.

where A_0, A_t, and A_e are peak areas of diethyl malonate at time = 0, t, and ∞ and k_I, k_{+1}, and k_{-1} are the effective pseudo-first-order constant and the pseudo-first-order rate constants for the forward and reverse reactions, respectively. The derivation of this equation assumes that the final product, dimethyl malonate, is negligibly small compared to the initial concentration of diethyl malonate. Figure 2 clearly shows that sufficient points are obtained for diethyl malonate before dimethyl malonate is too great to be neglected. Typical first-order plots for different methoxide concentrations are shown in Figure 3.

Table I. Pseudo-First-Order Rate Constants for the Methanolysis of Diethyl Malonate, Diethyl Ethylmalonate, and Diethyl Diethylmalonate

Temp, °C	Initial molar ratio MeOH/Mal	Methoxide, $M \times 10^3$	k_I[a]	σ_{k_I}[a]	k_{II}[a]	$\sigma_{k_{II}}$[a]
		Diethyl Malonate				
20	11.2/1	8	0.91	0.07	0.65	0.15
	18.8/1	8	1.01	0.05	0.30	0.09
	41.3/1	8	1.33	0.09	0.43	0.11
30	3.76/1	8	2.07	0.16	0.62	0.12
	11.2/1	8	1.73	0.14	0.61	0.15
	18.8/1	2	0.45	0.02	0.15	0.05
		4	1.15	0.05	0.39	0.05
		6	1.56	0.33	0.55	0.19
		8	2.08	0.31	0.64	0.09
		10	2.82	0.28	0.99	0.15
	41.3/1	8	2.35	0.14	0.80	0.12
40	11.2/1	8	3.05	0.24	0.99	0.25
	18.8/1	4	2.13	0.17	0.25	0.13
		8	3.62	0.15	0.98	0.04
	41.3/1	8	3.74	0.29	1.29	0.30
		Diethyl Ethylmalonate				
30	22.6/1	8	0.11	0.01	0.073	0.018
40	22.6/1	8	0.23	0.02	0.108	0.026
		Diethyl Diethylmalonate				
30	27.2/1	8	0.00009			

[a] Values × 10^1 min^{-1}.

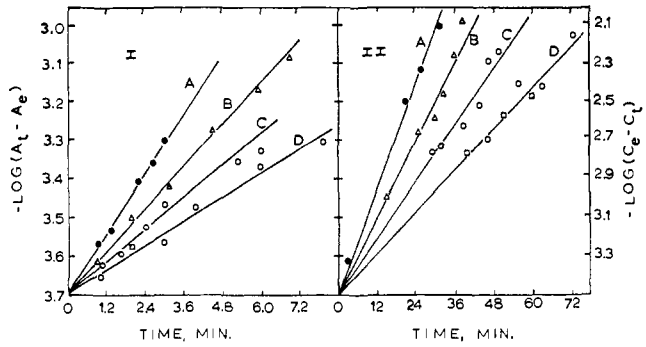


Figure 3. First-order plots at 30° and different methoxide concentrations: (A) 0.010 *M*; (B) 0.008 *M*; (C) 0.006 *M*; (D) 0.004 *M*; set I, methanolysis of diethyl malonate; set II, methanolysis of methyl ethyl malonate.

The pseudo-first-order rate constants for the second step were calculated according to the equation[12a]

$$k_{II} = k_{+2} + k_{-2} = \frac{2.303}{t} \log \frac{C_e}{C_e - C_t}$$

where C_t and C_e are the peak areas of dimethyl malonate at time = t and ∞ and k_{II}, k_{+2}, and k_{-2} are the effective pseudo-first-order rate constant for the second step and the pseudo-first-order rate constants for the forward and reverse reactions, respectively. Typical first-order plots for the conversion of methyl ethyl malonate to dimethyl malonate at different methoxide concentrations are shown in Figure 3. The values of k_I and k_{II} calculated from the expressions above are shown in Table I with their standard deviations.

The ratio of k_I to k_{II} is 3 ± 0.3:1 and is independent of the concentration of the components and the temperature. This ratio is considerably lower than the ratios found for the alkaline hydrolysis of diethyl malonate,[6] which indicates the basicity of the attacking group is a prominent factor on the rate of substitution of the second group on the molecule of malonate.

The rate constants are independent of the methanol concentration, but they are a function of the methoxide concentration. Figure 4 clearly reveals both steps are first order in methoxide since the plots of log k *vs.* log methoxide concentration are linear with calculated slopes of 1.03 ± 0.02. When the pseudo-first-order rate constants k_I and k_{II} are divided by the methoxide concentration, the second-order rate constants, k_{IS} and k_{IIS}, obtained in l./mole sec are 0.23 (±0.04) and 0.076 (±0.015) at 20°, 0.44 (±0.03) and 0.15 (±0.02) at 30°, and 0.76 (±0.11) and 0.23 (±0.04) at 40°, respectively. Without the methoxide, the reaction is negligibly slow.

The plot of the log of these second-order rate constants, k_S, *vs.* the reciprocal of the absolute temperature according to the Arrhenius equation[12b]

$$\log k_S = -E_a/2.303RT + \log A$$

is linear for each step of the reaction. R is the gas constant. The energy of activation, E_a, and the frequency factor, A, calculated with this equation are given in Table II.

The enthalpies of activation, ΔH^*, and entropies of activation, ΔS^*, shown in Table II were calculated

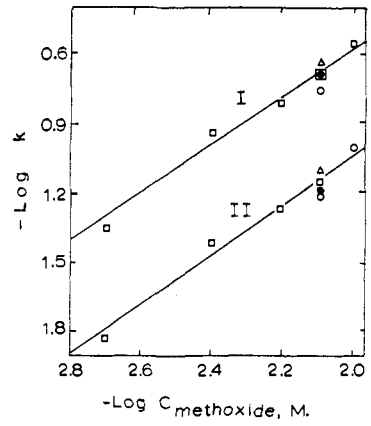


Figure 4. Effect of methoxide and alcohol on the first-order rate constant, k, at 30°. (I) Methanolysis of diethyl malonate; (II) methanolysis of methyl ethyl malonate; initial mole ratio, methanol/diethyl malonate: ●, 3.76:1; ○, 11.2:1; □, 18.8:1; Δ, 41.3:1.

Table II. Energy of Activation, E_a, Frequency Factor, A, Enthalpy of Activation, ΔH^*, and Entropy of Activation, ΔS^*, for the Methanolysis of Diethyl Malonate and Diethyl Ethylmalonate

Formation of	E_a, kcal/mole	A, cc/mole sec × 10^{-10}	ΔH^*, kcal/mole	ΔS^*,[a] eu
Methyl ethyl malonate	11.2 (±0.4)	4.2	10.6	−11.8
Dimethyl malonate	11.7 (±1.2)	6.4	11.1	−12.3
Methyl ethyl ethylmalonate	13.4 (±0.6)	9.6	11.1	−10.5

[a] Standard state for ΔS^* = 1 mole/cc.

from the equations[12c]

$$\Delta H^* = E_a - RT$$

$$\log k_S = \log (RT/Nh) - \Delta H^*/RT + \Delta S^*/R$$

where N is Avogadro's number and h is Planck's constant. ΔS^* is given for the standard state of 1 mole/cc.

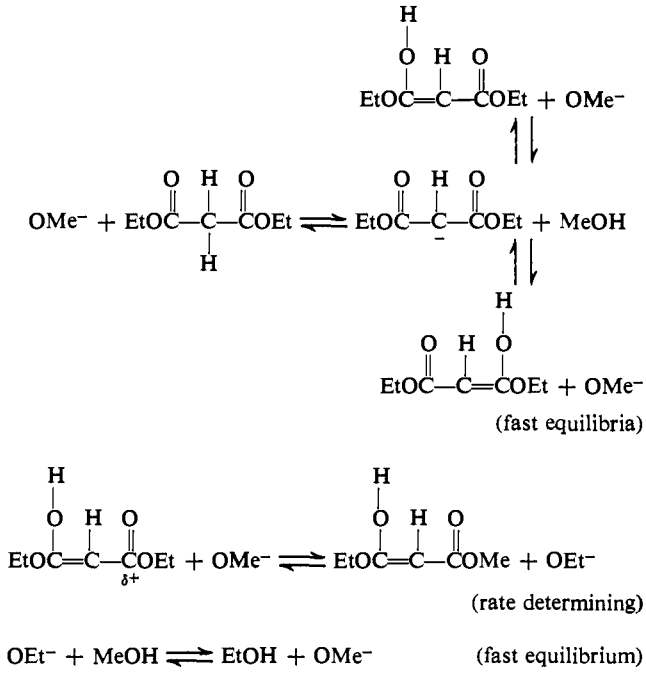
Mechanism. Although a specific mechanism for the methoxide-catalyzed methanolysis of diethyl malonate has not been reported, the addition–elimination mechanism for the saponification of esters is well established.[13a] The data for the methanolysis of diethyl malonate confirm that the reaction is first order in malonate, first order in methoxide, and zero order in methanol for each substitution. This suggests that the rate-determining step must involve a methoxide and a specie of malonate. Although enolization of malonate in methanol without methoxide is very small,[14] it is widely known that malonate and methoxide form enolate ions readily.[13b,15] Among the enolate ion, the enol molecule, and the keto molecule, the specie of malonate most likely to undergo a nucleo-

(13) D. J. Cram and G. S. Hammond, "Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1959: (a) p 305, (b) p 22.
(14) A. Gero, *J. Org. Chem.*, **19**, 1960 (1954).
(15) M. L. Bender and J. Figueras, *J. Am. Chem. Soc.*, **75**, 6304 (1953).

philic attack by methoxide could be the enol molecule, provided the shifting of electrons from the α carbon to enolize one acyl carbon decreases the electron density at the other acyl carbon atom. This would render the nonenolized acyl carbon more electropositive and, hence, more susceptible to nucleophilic attack than any acyl carbon on the keto molecule or the enolate ion. In any event, the enolate ion would not be expected to react appreciably with methoxide because of its charge and limited low concentration. However, enolate would likely participate as an intermediate in fast equilibria with the enol and keto molecular forms. With the molar ratio of methanol to methoxide at least 15,000:1, any equilibria involving enolate, enol, and keto would be shifted toward the molecular species. This means virtually all the malonate could be converted to enol since methoxide is regenerated when enolate becomes enol. The rate of methanolysis should be enhanced with diethyl ethylmalonate because alkyl groups substituted on the α carbon increase the enolization slightly.[16] However, steric effects from the α-substituted ethyl group[17] outweigh any enhancement from increased enolization. The reaction proceeds very slowly with diethyl diethylmalonate because enolization is eliminated and steric hindrance is increased.[18]

A mechanism consistent with the rate law and with enol molecules as the favored reactive specie is summarized in Scheme I. For the formation of dimethyl malonate, the series of reactions is repeated with methyl ethyl malonate in place of diethyl malonate.

Scheme I



Acknowledgment. The authors wish to express their gratitude to Dr. Paul Langford and Dr. Charles Richmond for their helpful suggestions and criticisms during the course of this study.

(16) Y. M. Chang, K. Tsai, Y. L. Wang, and F. K. Lu, *Hua Hsueh Hsueh Poa*, **30**, 587 (1964).
(17) M. H. Miles, E. M. Eyring, W. W. Epstein, and R. E. Ostlund, *J. Phys. Chem.*, **69**, 467 (1965).
(18) P. Dumesnil, *Compt. Rend.*, **172**, 1043 (1921).

Absorption, Rotatory Dispersion, and Circular Dichroism Studies on Some Hydroxy and Amino Acids[1]

Leonard I. Katzin and Elsie Gulyas

Contribution from the Chemistry Division, Argonne National Laboratory, Argonne, Illinois. *Received February 9, 1967*

Abstract: Comparative data are presented on the absorption, rotatory dispersion, and circular dichroism spectra of lactic, malic, and tartaric acids, as well as alanine, serine, valine, leucine, aspartic and glutamic acids, ornithine, lysine, arginine, proline, and asparagine. Effects are found related to molecular structure and to the state of ionization of the species, with the fully protonated forms as reference states. The influence of vibrational fine structure on the absorption–CD relation is shown, and some examples of the utility of comparing the three spectra directly are pointed out.

In an optically active molecule, all electronic transitions show a difference in absorption coefficient for right and left circularly polarized light, the "circular dichroism." In such a molecule an atomic grouping with a fairly characteristic absorption (a "chromophore") will have associated with it a circular dichroism (CD) with characteristic relation to its absorption spectrum for unpolarized light. The rotatory dispersion (ORD) for some compounds bearing the carboxyl chromophore, namely tartaric acid and the amino acids, recently has been reanalyzed in terms of the Drude equation.[2,3] The Drude parameters are in principle related to the parameters which characterize circular dichroism. One purpose of this investigation is to compare the findings of direct observations in the absorption region of these compounds with the parametric behavior of the Drude analyses in order to evaluate the latter. A more general purpose is to seek

(1) Based on work performed under the auspices of the U. S. Atomic Energy Commission.
(2) L. I. Katzin and E. Gulyas, *J. Phys. Chem.*, **66**, 494 (1962).
(3) L. I. Katzin and E. Gulyas, *J. Am. Chem. Soc.*, **86**, 1655 (1964).