

STUDIES OF RACEMIZATION RATES
IN METHYLETHYL KETONE

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TABLE OF CONTENTS

	PAGE
Approval Sheet	ii
Acknowledgments	iii
Table of Contents	iv
List of Tables	v
Chapter I: Introduction	1
Chapter II: Preparation of Materials ..	7
Chapter III: Procedure	9
Chapter IV: Results	11
Chapter V: Summary	18
BIBLIOGRAPHY	19
APPENDIX I	20

LIST OF TABLES

TABLE	PAGE
I. Dependence of Rate on LiBr Concentration (Concentration of Ester, 0.1348 M; t = 25.0°C.)	11
II. Dependence of Rate on LiBr Concentration (Concentration of Ester, 0.1348 M; t = 35.0°C.)	13
III. Heat of Activation and Collision Frequency Factors	14
IV. Dependence of Rate on Ester Concentration (LiBr, 0.01038 M; t = 25.0°C.)	14

STUDIES OF RACEMIZATION RATES

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CHAPTER I

INTRODUCTION

The role of the solvent in chemical reactions has been the subject of many investigations. Van't Hoff¹ suggested that the use of the ratio of the concentration to the solubility in the rate equation would yield more concordant results for the rates in different solvents. This was found to be quite satisfactory for the velocity of isomerization of methyl-5-hydroxy-1-phenyltriazole-4-carboxylate. This reaction was studied by Dimroth² in a number of common organic solvents. It has been observed that the ratio does not serve any useful purpose for many other reactions, and in many the variation in the rate constant is increased.

Brønsted³ employs a ratio of activity coefficients of the reactants and the intermediate complex in his theory. The activity coefficients must be estimated for ions and the intermediate complex, usually by means of the Debye-Hueckel theory. Scatchard⁴ has developed the effect of the solvent on the reaction rate between ions, taking the

¹J. H. Van't Hoff, Vorlesungen I, 219 (1898).

²O. Dimroth, Annalen, 377, 127 (1910).

³J. N. Brønsted, Zeits f. physik. Chemie, 102, 169 (1922); 115, 337 (1925).

⁴G. Scatchard, Chem. Rev., 10, 229 (1932).

solvent into account by means of its dielectric constant. The result, which is called the Brønsted-Christiansen-Scatchard equation, includes the charge on the ions and the radius of the intermediate complex as parameters. Support for the equation has been given by the data of Amis and LaMer⁵ on the fading of bromphenol blue in alkaline solutions. The solvents employed were methanol-water and ethanol-water mixtures. Amis and Jaffe⁶ have derived an equation for the rate of reaction between ions and dipolar molecules.

The preceding theories assume that the solvent exerts its influence by the forces associated with its dielectric constant. The fact that electrostatic effects of this type are often overshadowed by specific solvent effects has been recognized by many workers. Dimroth⁷ found no correlation between the dielectric constant of the solvents and the rate of the reaction mentioned above. Soper and Richardson,⁸ and Glasstone, Laidler and Eyring⁹ have discussed the effect of the internal pressure of the solvent on the rate of reaction. The viscosity of the solvent has been employed by Moelwyn-Hughes¹⁰ to derive the collision number for some reactions.

⁵E. S. Amis and V. K. LaMer, J. Am. Chem. Soc., 61, 905 (1939).

⁶E. S. Amis and G. Jaffe, J. Chem. Phys., 10, 598 (1942).

⁷O. Dimroth, loc. cit.

⁸M. Richardson and F. G. Soper, J. Chem. Soc., 1873 (1929).

⁹S. Glasstone, K. J. Laidler and H. Eyring, The Theory of Rate Processes, (New York: McGraw-Hill Book Co., Inc., 1941).

¹⁰E. A. Moelwyn-Hughes, J. Chem. Soc., 1932, 95.

For a more complete discussion of the above theories the reader is referred to Glasstone, Laidler, and Eyring.¹¹ The fact that the early and some current theories have failed almost as often as they have succeeded cannot escape mention. Olson and Simonson¹² have found some evidence that both the Debye-Hueckel theory and the Brønsted theory are in need of very close examination to test whether they are valid. Their work on the reaction between bromopentammine cobaltic ion and mercuric ion in the presence of inert salts combined with the results of others has given rise to an interpretation of salt effects which does not depend on the ionic strength of the solvent. The introduction of activity coefficients was found unnecessary.

The need for a thorough understanding of a particular reaction in a number of solvents of widely different physical and chemical properties has given rise to the present work. It is part of a larger program of research whose aim is to understand and interpret one reaction so that the results may be used to interpret others.

Holmberg¹³ has shown that the rate of racemization of l-bromo-succinic acid by bromide ion in water solution is first order with respect to each reactant. Olson and Long¹⁴ have made a more detailed study of the reaction with bromide and chloride ion in water solutions

¹¹S. Glasstone, K. J. Laidler, and H. Eyring, loc. cit.

¹²A. R. Olson and T. R. Simonson, J. Chem. Phys., 17, 1167 (1949).

¹³B. Holmberg, J. Prakt. Chem., 195, 456 (1913); 196, 553 (1913); Ber., 60, 2194 (1927).

¹⁴A. R. Olson and F. A. Long, J. Am. Chem. Soc., 56, 1294 (1934); 58, 393 (1936).

and proved that inversion of the asymmetric carbon atom occurs with every bromide or chloride ion substitution.

A study of the reaction with lithium and sodium bromides in methyl alcohol, glacial acetic acid and acetone solutions was made by Olson and Voge.¹⁵ The rates in glacial acetic acid, methyl alcohol and water were found to be approximately the same and to have an activation energy of 20,000 calories. The rate in acetone was 300 times as fast and the activation energy was 17,000 calories. They found no correlation between the rates and the dielectric constant or the dipole moments of the solvents, but pointed out that the rate was greater and the activation energy was less in acetone than the other solvents which are all capable of forming hydrogen bonds with the bromide ions. They also found that the addition of 0.45 M water to the acetone solutions decreased the rate by 50% and increased the activation energy by 1,000 calories.

Spieth¹⁶ investigated the rate of racemization of l-bromosuccinic acid by lithium bromide in acetone solutions, taking into consideration the fact that lithium bromide is a weak electrolyte in acetone with an ionization constant of about 10^{-4} . She found that the specific rate varied with both the lithium bromide concentration and the l-bromosuccinic acid concentration. The acid exhibited an inhibiting effect on the rate which could be expressed by the equation $k = k_0/(1 + b(\text{BrS}))$ where k_0 is the rate at zero concentration of the bromosuccinic acid

¹⁵Ibid., p. 1690.

¹⁶Francis J. Spieth, Ph.D. Dissertation, University of California, 1947.

and b is a constant. Tartaric and succinic acids produced similar inhibiting effects. She assumed that both lithium bromide molecules and bromide ions react at the carbon bromine bonds and calculated the concentrations of these from an equilibrium constant evaluated from conductance data.

Spieth also made exploratory runs with the dimethyl ester of l-bromosuccinic acid and found that the ester also inhibited the reaction, but to a much smaller degree. Frashier¹⁷ studied the racemization of dimethyl l-bromosuccinate by lithium bromide in anhydrous acetone and aqueous acetone. The pseudo unimolecular rate was explained by assuming that the lithium bromide molecules and bromide ions react. The rate for the ester was found to be about fifty times greater than the acid rate. The inhibiting effect of the ester was explained by assuming that the bromide ions and lithium bromide molecules have a tendency to associate with the ester group dipoles. The activation energy for both the processes (ion and molecule reactions) was found to be 16,000 calories. The addition of approximately 0.15 M water was found to decrease the rate by one-half. The effect of the addition of lithium perchlorate to the solutions was also studied by Frashier. The major effect was repression of the ionization of the lithium bromide. The inhibitory effect of the ester was also decreased. It was suggested that the latter effect was due to the tendency of perchlorate ion to associate itself with the dipoles of the ester, thus decreasing the tendency of the

¹⁷L. D. Frashier, Ph.D. Dissertation, University of California, 1949.

lithium bromide to enter into such association.

The present work is concerned with the rate of racemization of dimethyl 1-bromosuccinate by lithium bromide in the solvent methylethyl ketone. The main emphasis is placed on the dependence of the rate constant on the concentration of lithium bromide and the ester.

CHAPTER II

PREPARATION OF MATERIALS

The preparation of the dimethyl ester of l-bromosuccinic was accomplished in two steps, using l-asparagin as a starting material. Forty-five grams of l-asparagin were refluxed with 200 ml. of saturated hydrobromic acid for two hours. The solution was cooled to 0° C., diluted to 300 ml., and treated with 135 grams of sodium bromide and 43 grams of sodium nitrite. The nitrite was added in small quantities over a period of one hour. Ten minutes after the last addition of sodium nitrite, 100 ml. of 12 N sulfuric acid was added to the solution and it was stirred for ten minutes. The product was extracted from the aqueous solution with two 100 ml. portions of ether. The ether was evaporated in an air stream and the acid was recrystallized from acetone.

The ester was prepared from the acid by refluxing the acid in a large excess of methyl alcohol to which two ml. of concentrated sulfuric acid had been added. Water was then added to the solution and the product was extracted with ether. The ether was removed by evaporation and the ester was heated for one hour at 60° C. to remove most of the water and alcohol. The ester was then dried over calcium sulfate for one day and distilled under high vacuum. At the beginning of the vacuum distillation, the ester was heated gently and none of the product was condensed. The specific rotation was found to agree with Frashier's value $[\alpha]_{5461}^{25} = -69.5^\circ$ in acetone.¹

¹L. D. Frashier, Ph.D. Dissertation, University of California, 1949.

C.P. lithium bromide was dissolved in a small quantity of water and filtered. The solution was then cooled and the crystals of the dihydrate were removed by filtration. The dihydrate was then heated to 44° C. and the resulting monohydrate removed from the mother liquor by suction filtration. The monohydrate was then dried at 100° C. under high vacuum (10^{-4} mm. Hg). The lithium bromide was then dissolved in acetone, filtered, and dried under vacuum at 100° for two days. The resulting anhydrous salt is a finely-divided, white powder. It is extremely hygroscopic.

The methylethyl ketone was treated with potassium permanganate and potassium hydroxide, then distilled. It was then kept in contact with calcium sulfate in an evacuated system for two hours and distilled at room temperature. Final drying was accomplished by passing the vapors over phosphorous pentoxide suspended on packing made of short pieces of glass tubing. This distillation was also carried out at room temperature in a closed system.

CHAPTER III

PROCEDURE

Methylethyl ketone solutions of the lithium bromide were prepared in a dry box. The atmosphere of the box was tank nitrogen which was constantly being replaced while the box was in use. The need for a dry atmosphere in handling lithium bromide cannot be overemphasized, since the salt is very hygroscopic and the effect of water on the rate of the reaction is large. Solutions for individual runs were made by transferring portions of the stock solution of the lithium bromide and the pure ester to a volumetric flask and diluting to volume with the dry solvent. The concentrations were adjusted so that the variation with temperature was accounted for. The dried methylethyl ketone was not kept for more than three days before use, and during this period, it was kept in a stoppered flask in the dry box.

The polarimeter used is a Bellingham and Stanley model A. It can accommodate a tube four decimeters in length, however a three decimeter tube was used to allow space for the constant temperature bath. The scale is calibrated at quarter-degree intervals with a vernier attachment which allows direct readings to one-hundredth of one degree. The light source was an A-H₄ mercury lamp. A Wratten No. 61 filter was used to isolate the 5461 Å line. The constant temperature bath was situated between the polarizer and analyzer of the polarimeter and was large enough to allow room for several tubes. The temperature was controlled by intermittent heating through a thermostat and continuous cooling by circulation of water through a copper coil immersed in the bath.

The pseudo-unimolecular rate constants were determined by plotting the logarithm of the rotation against the time and reading the slope from the graph. The pseudo-unimolecular rate constant, k , is calculated from the equation

$$k = - \frac{2.303}{2} \frac{d \log \alpha}{dt} .$$

Analytical determination of the slope by the method of least squares was made as a check on several runs, and was found to agree with the graphical method to within one per cent. The data for one of the runs is plotted in Figure 1.

CHAPTER IV

RESULTS

The series of experiments summarized in Table I, below, in which the concentration of lithium bromide was varied and the concentration of the ester was constant at 0.1348 M, correspond to the pseudo-unimolecular specific rates shown in the third column of that table. The rates are given in units of minute^{-1} . When these rates are plotted against the gross concentrations of lithium bromide, the points of curve 1 of Figure 2 are obtained.

TABLE I

Dependence of Rate on LiBr Concentration
(Concentration of Ester, 0.1348 M; $t = 25.0^\circ \text{C}$)

LiBr $\times 10^3$	$k \times 10^3$		$\Delta k\%$
	Exp.	Calc.	
0.04312	0.270	0.271	-0.4
0.2156	0.885	1.08	-18.0
0.4312	1.83	1.83	0.0
1.038	3.36	3.37	-0.3
5.190	8.87	9.22	-3.8
10.38	13.96	13.94	+0.2
15.58	21.3	17.81	----
2.076	3.89	5.33	----

Conductance measurements¹ have revealed that lithium bromide is a weak electrolyte in acetone. The ionization constant in that solvent is about 6×10^{-4} . Further, Spieth² and Frashier³ have been able to fit their data on the rate of racemization of l-bromosuccinic acid and dimethyl l-bromosuccinate only by assuming that the rate can be expressed in terms of both the concentrations of the lithium bromide molecule and the bromide ion. In conformity with these two assumptions, equation (1) below was formulated and the success of the correlation is illustrated by curve 1 in Figure 2.

$$(1) \quad k = k_1(\text{LiBr}) + k_2(\text{Br}^-)$$

$$\text{where: } k_1 = 0.138$$

$$k_2 = 6.94$$

By assuming that the ionization constant of LiBr is about the same in methylethyl ketone as in acetone, the concentrations of the ion and the molecule were calculated. By adjusting the values of the two constants the curve could be duplicated by the equation over a wide range of values of the ionization constant. In the present work, however, the procedure was to adjust the value of K_1 and use two points from the curve to solve for the constants (see Appendix). The value used for the ionization constant at 25° C was 4×10^{-4} . Frashier⁴ used the value $K_1 = 3.6 \times 10^{-4}$

¹J. F. J. Dippy, H. O. Jenkins, and J. E. Page, J. Chem. Soc., 1386 (1939).

²F. J. Spieth, Ph.D. Dissertation, University of California, 1947.

³L. D. Frashier, Ph.D. Dissertation, University of California, 1949.

⁴Ibid.

for the ester reaction in acetone at 24.9°. The present value is preferred for methylethyl ketone although the difference is not of great significance.

The results shown in Table II are for the reaction at 35° C. The rate constants are again the pseudo-unimolecular specific rates. The value for the ionization constants and the constants in Equation (1) are also given.

TABLE II

Dependence of Rate on LiBr Concentration
(Concentration of Ester, 0.1348 M; t = 35° C)

LiBr x 10 ³	k x 10 ³		Δk%
	Exp.	Calc.	
1.394	10.51	10.59	-0.9
2.885	17.07	16.92	+1.2
6.970	28.03	28.14	-0.7
7.137	28.65	28.47	+0.7

$k_1 = 0.351$; $k_2 = 17.8$; $K_1 = 4 \times 10^{-4}$

The activation energies and frequency factors in the Arrhenius equation may be calculated for the ion and molecule rates from the values of k_1 and k_2 given in Tables I and II. Their values are listed in Table III.

TABLE III

Heat of Activation and Collision Frequency Factors

	$E_{act.}$	S
k_1	17,060	$0.4 \cdot 10^{13} \text{sec}^{-1}$
k_2	17,200	$3.98 \cdot 10^{13} \text{sec}^{-1}$

The data for the experiments in which the concentration of LiBr was kept constant and the concentration of the ester varied are presented in Table IV and plotted in Figure 3.

TABLE IV

Dependence of Rate on Ester Concentration

(LiBr, 0.01038 M; $t = 25.0^\circ \text{C}$)

Ester	$k \times 10^3$		1/k	$\Delta k\%$
	Exp.	Calc.		
0.1078	14.20	14.00	70.4	+1.4
0.1348	13.96	13.94	71.6	+0.2
0.1678	13.33	13.40	75.0	-0.5
0.2696	11.46	11.53	87.4	-0.6

$k_0 = 17.64 \cdot 10^{-3}$; $b = 1.96$; $k_3 = 0.175$; $k_4 = 8.74$

It may be seen on inspection that the rate decreases slightly as the concentration of the ester increases. The rates for the acid were found by Spieth⁵ to decrease greatly with increasing concentration. Her data were fitted to an equation of the form

$$k = k_0/(1 + bm)$$

The constant k_0 is the rate at zero concentration of acid, b is a constant, and m is the molar concentration of the ester. The expression $1/(1 + bm)$ represents the fraction of the activated complexes that react to give products. The same form of equation was used by Frashier.⁶ He gives a different explanation of the form of the equation, calling $1/(1 + bm)$ the fraction of LiBr which is not associated with the ester-group dipoles, and b the association constant for the ester-group dipoles. He finally arrives at an equation expressing the pseudo-unimolecular specific rate in terms of the lithium bromide molecule, bromide ion, and ester concentrations. An equation of the same type was used to advantage in this work. Specifically, it is

$$(2) \quad k = \frac{k_3(\text{LiBr}) + k_4(\text{Br}^-)}{1 + bm}$$

The values of k_3 , k_4 , and b are found in Table IV, and are directly proportional to the constants k_1 and k_2 mentioned earlier. This gives the final equation

$$(3) \quad k = \frac{0.175(\text{LiBr}) + 8.74(\text{Br}^-)}{1 + 1.96(\text{ester})},$$

⁵J. Spieth, loc. cit.

⁶L. D. Frashier, loc. cit.

from which all of the values of k at 25° C can be calculated within the experimental error. The values of k_3 and k_4 in acetone were 0.303 and 6.32, respectively. The difference in the values of k_3 in the two solvents is not significant since the value in methylethyl ketone cannot be determined accurately with the available data. The major portion of the rate is due to the bromide ion rate. An explanation of the increased rate in methylethyl ketone has been presented in the introduction.

It is of considerable interest that Olson and Simonson⁷ used an equation of this same form to obtain a fit to data, and to explain the effect of the addition of inert salts on the rate of reaction between ions.

The value of the association constant obtained by Frashier for the rate of racemization of dimethyl l-bromo succinate in anhydrous acetone was 0.74. This is much smaller than the value of 1.96 found in the present work. Since the dielectric constant of methylethyl ketone is smaller, one would expect the association constant to be larger, but perhaps not as much as the 260% increase found. The activation energies for the ion and molecule rates were found to be about 16,000 calories each in acetone as compared to a value of 17,000 calories in methylethyl ketone. This greater value in the latter case suggests that solvation of the bromide ions is greater. The increase in size of the solvent molecules is possibly of importance, since steric factors would hinder the approach to the carbon-bromine dipole. The rate in methylethyl ketone is higher than in acetone, thus the increase in the collision frequency factors more than compensates for the larger activation energy.

⁷A. R. Olson and T. R. Simonson, J. Chem. Phys., 17, 1167 (1949).

If the concept of the steric or probability factor is valid, the size and shape of the solvent-ion and solvent-molecule complexes would again enter the picture.

The same value was used for the ionization constant of lithium bromide at 25° and 35° C. This means that ΔH for the ionization is zero. If the same intermediate complex is formed in both paths, the activation energies should be the same. This is true within the accuracy with which the activation energies can be determined by these data.

With the data available, the values of the ion and molecule rates cannot be assigned precise values. Further research into this reaction with the addition of lithium perchlorate to the solutions should firmly establish these rates.

CHAPTER V

SUMMARY

The racemization of dimethyl 1-bromosuccinate by lithium bromide in anhydrous methylethyl ketone solutions has been studied. The observed rates may be explained by assuming that both the lithium bromide molecules and the bromide ions react. The ester has some inhibiting effect on the reaction. This may be accounted for by assuming that both the ion and the molecule become associated at the ester group dipoles. A constant for this association was determined.

The activation energies for the ion and molecule rates were found to be 17,000 calories each.

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APPENDIX I

Calculation of the constants k_1 and k_2 from experimental data.

In the equation $k = k_1(\text{LiBr}) + k_2(\text{Br}^-)$ it is required to find the concentrations of the lithium bromide molecules and the bromide ions from the gross concentration of lithium bromide. To do so requires the assumption of an ionization constant. If the value is available, it may be used; however, the value necessary to obtain a fit may not be the same. In the present work, the data were not available, but the value used by Frashier for acetone was used as an approximation, since methyl-ethyl ketone has similar properties. The values of these concentrations are then inserted in the above equation. Two rate constants and their conjugate concentrations are required. The constants are then obtained by solving the determinants

$$k_1 = \frac{\begin{vmatrix} K'' & b'' \\ K' & b' \end{vmatrix}}{\begin{vmatrix} a'' & b'' \\ a' & b' \end{vmatrix}}$$

and

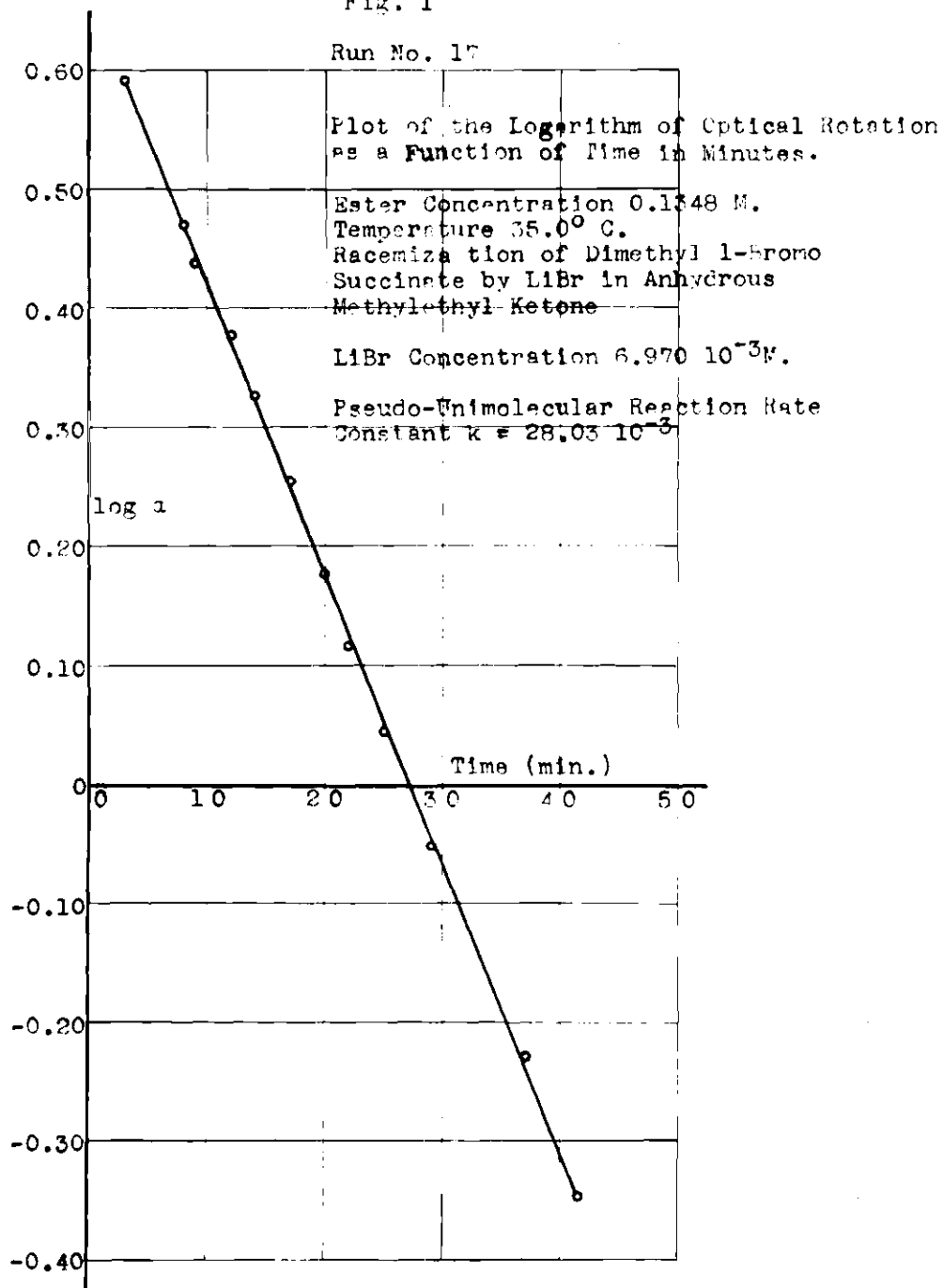
$$k_2 = \frac{\begin{vmatrix} a'' & K'' \\ a' & K' \end{vmatrix}}{\begin{vmatrix} a'' & b'' \\ a' & b' \end{vmatrix}}$$

where:

K'' , K' are two different rate constants, and the concentrations of lithium bromide and bromide ion are a'' , a' and b'' , b' respectively. To test the constants, one needs simply to insert the constants and values for (LiBr) and (Br^-) in the equation and solve for k . This may then be

compared with the experimental result. If the concentrations are over a wide range, several attempts may be required to obtain a fit.

Fig. 1



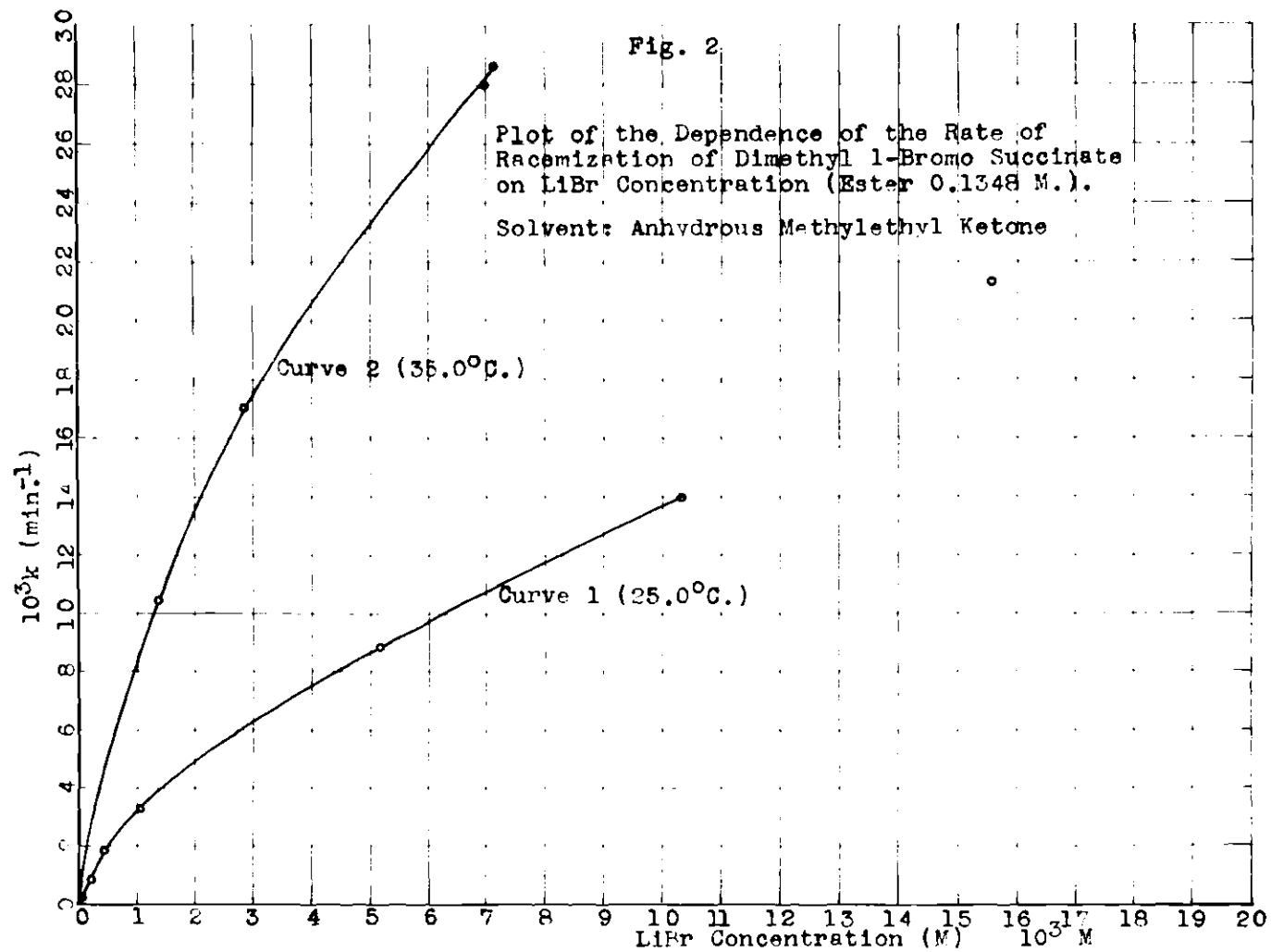


Fig. 3

