A Study of the Kinetics of Aliphatic Ester Saponification.

Lehigh University Bethlehem, Pa.

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A STUDY OF THE KINETICS OF ALIPHATIC ESTER SAPONIFICATION

by

Harold Samuel Levenson

A DISSERTATION

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of Lehigh University

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TABLE OF CONTENTS

INTRODUCTION

This investigation is a systematic study of the effect upon saponification velocity of substitution of the phenyl and various alkyl groups in the acyl component of ethyl esters of monobasic aliphatic acids.

The experimental course of such saponifications follows the kinetic expression for second order reactions,

$$-\frac{d(\text{ester})}{dt} = k(\text{ester})(\text{base}). \qquad (1)$$

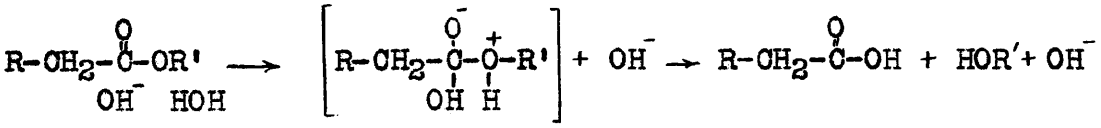
The specific reaction rate constant, k, is a suitable index for comparing the reactivities of different esters. It may, for theoretical reasons, be expressed

$$k = PZ\, e^{-E/RT} \qquad (2)$$

E, the activation energy, is the minimum energy the reacting molecules must possess for reaction to occur. Z is the collision number; it varies only slightly with temperature and for a given medium has essentially the same value for all esters. P, a steric factor, is usually less than unity and accounts for the fact that not every collision between sufficiently activated reactant molecules is necessarily fruitful. Changes in reaction velocity, then, may be due to the effect of a substituent on either or both P and E.

Lowry (20) has postulated the following mechanism for saponification which is supported by a large number of experimental data, and which, at least in its major impli-

cations, is generally accepted.



According to this mechanism addition of the hydroxyl ion is slow and rate determining; this is followed by rapid collision with a water molecule (due to the high concentration of water molecules) and formation of the intermediate complex which undergoes an almost instantaneous electronic rearrangement to yield the final products. Since the coordination of the catalyst ion to the ester molecule is rate determining, the effect of a substituent group, R, on reaction velocity is either to hasten or retard this process. This may be due to a polarity effect of R which makes the carbonyl carbon atom more positive than in the unsubstituted ester and thus more amenable to attack by the negative OH group, or the steric effect of R may effect the velocity by hindering the approach of the hydroxyl group to the ester molecule. The polarization caused by the substituent group may be either an inductive (I) or a tautomeric (electromeric, E) effect.

In this study only substituents capable of exhibiting an inductive effect were used. This effect is produced by a displacement of the electron pair constituting the bond between the substituent and the carbonyl carbon atom of the ester in such a direction as to make the carbon atom more negative (or more positive) than in the unsubstituted molecule (R equals H). R groups having the former tendency are said to have a

positive inductive effect (+I), while to groups producing the opposite is attributed a negative inductive effect (-I). Thus +I groups, by making the carbonyl carbon more negative, hinder the approach of the catalyst OH^- ion, and esters containing such substituents should saponify more slowly than corresponding unsubstituted esters. Since in this instance we are dealing with energy conditions (the passage of OH^- through an electrostatic field) such effects will be indicated by differences in activation energy.

The spatial requirements of R, on the other hand, are noted by variations in P, the steric factor. The two terms E and P, however, are not strictly independent, since in order to meet the steric requirements a reacting molecule or ion (OH^- approaching the ester molecule, in this instance) may need some activation energy in excess of that necessary were no steric hindrance present. This consideration is further amplified in the subsequent discussion.

LITERATURE

Of the available k values for ester saponification in the literature few are suitable for making comparisons such as are intended here. This is due chiefly to variations of experimental conditions (temperature, media, concentration, purity of compounds, etc.) so that no true comparisons can be made. Furthermore, much of the older work was performed at only one temperature, and thus it is not possible to evaluate the influence of substituents upon activation energy.

Olsson has attempted to circumvent these difficulties by using as an indication of reaction velocity the ratio of k for a given ester to that for ethyl acetate determined under identical experimental conditions. The relative k value is arbitrarily assigned the value of 100 for ethyl acetate. Such ratios, although of only qualitative value, make possible a fairly useful comparison of the work of different investigators. In Table I are ratios for esters pertinent to this work which have been extracted from Olsson's compilation (12) of data available up to 1928.

Olsson pointed out the generalizations possible from the then available data. The value of k decreases as one proceeds through a homologous series, and methyl substitution which causes chain branching lowers k considerably from its value for the unbranched ester. This latter effect was ascribed to steric hindrance, but the fact that such branching

Table I
(From Olsson's compilation (12))

Ethyl ester	k(rel)	10^5.k(diss.)
Formate	21,300.	21.4
Acetate	100.	1.8
Propionate	89.6	1.34
Butyrate	52.5	1.5
Valerate	50.	1.6
Hexoate	51.9	1.45
Heptoate	51.5	1.4
Isobutyrate	49.2	1.4
Isovalerate	25.3	1.75
Trimethylacetate	23.2	0.98
Phenylacetate	191.	5.3
Hydrocinnamate	106.2	2.3
Methylphenylacetate	14.1	4.2

has a greater effect in ethyl isovalerate than in ethyl isobutyrate was not explained, although one would expect a priori that steric hindrance is greater for α-substitution than for β-substitution. Olsson also emphasized the analogy, already pointed out by van't Hoff, between the saponification velocity of esters and the acid dissociation constants of the acids forming the esters. This is indicated by the data in Table I where the values for k(diss.) are taken from Olsson (12). The idea of acid groups, which had been used to explain the effect of substituents on acid dissociation constants, was carried over to saponification when it became apparent that those groups which increased k(diss.) had a similar effect upon saponification velocity. The phenyl group then must be considered an acid group. It was realized, of course, that steric hindrance might mask the effect of acid groups, and certain exceptions, such as ethyl hydratropate, were explained in just this fashion. At best, however, the above considerations were not very satisfying and Olsson stated:

> "Betreffs des Einflusses auf die alkalische Hydrolysegeschwindigkeit von der Zusammensetzung der Ester sei erwaehnt, dass eine allgemeine Beziehung bis jetzt nicht existiert."

Kindler (10)(11) published the first data obtained under the same experimental conditions on the kinetics of saponification of a long series of esters. Although the rate constants were determined at only one temperature, the results are more suitable for comparison than any previously available. Kindler chose to consider the saponfication

velocity as a measure of the "Haftfestigkeit" of the organic radical attached to the carbonyl carbon atom of the ester; thus, the smaller the k value the greater is the "Haftfestigkeit" of the organic radical in question. In this manner he prepared the data reproduced in Tables II and III. The values for "Haftfestigkeit" are the reciprocals of what Olsson would have called k(rel). These results confirmed the facts already known, but, having studied a longer homologous series than previous workers, Kindler was able to state definitely that:

> "Die Radikale Butyl, Pentyl, Hexyl und Heptyl seigten nahezu die gleiche Haftfestigkeit."

Kindler discussed his results in the light of a negative valence field which determines "Haftfestigkeit". On this basis, then, negative groups substituted in R decrease the "Haftfestigkeit" of R toward $-COOC_2H_5$. Such is the effect of the phenyl group, and this is indicated by the data for phenyl substituted esters in Table III. However, Kindler, with these ideas, had not advanced fundamental knowledge much beyond that summarized by Olsson. The two factors, energetic and steric, remained to be resolved.

The rise of the electronic theory of organic reactions which explained reactions in terms of polarizations, already briefly mentioned in the Introduction, was accompanied by its fairly successful explanation of the effect of substituents on the velocity of ester saponification. By this theory the mechanism of a reaction is described in terms of fundamental

Table II
Data of Kindler, (10)(11)

(T = 30°; medium: 87.8% aq. ethanol; base: NaOH)

Ethyl ester	k, lit. mole^{-1} min.$^{-1}$
Acetate	0.481
Propionate	.226
Butyrate	.132
Valerate	.126
Hexoate	.131
Heptoate	.130
Octoate	.130
Nonoate	.134
Decoate	.132
Stearate	.111
Isobutyrate	.0483
Trimethylacetate	.00505
Phenylacetate	0.636
Hydrocinnamate	.343
γ-Phenylbutyrate	.199

Table III
(From Kindler (10)(11))

Radical, R	"Haftfestigkeit" toward $COOC_2H_5$ (referred to CH_3 = 100)
CH_3	100
C_2H_5	210
n-C_3H_7	370
n-C_4H_9 to n-C_9H_{19}	370-380
n-$C_{17}H_{35}$	430
$(CH_3)_2CH$	990
$(CH_3)_3C$	9500
$C_6H_5CH_2$	76
$C_6H_5CH_2CH_2$	140
$C_6H_5CH_2CH_2CH_2$	242

changes in the electronic arrangements which constitute chemical bonds. Steric and energy requirements are assigned definite roles, and the effect of substituent groups upon chemical reactivity becomes more clearly visualized.

Evans, Gordon and Watson (8) have analyzed their data on the saponification velocity of substituted aliphatic ethyl esters in the light of this theory. Their results are reproduced in Table IV. The work was performed as part of a study of the influence of alkyl groups upon reaction velocity, and it had already been shown that the kinectics of the prototropy of phenyl alkyl ketones harmonized with the notion of the + I effect of alkyl groups, increasing in the order: Me < Et < sec-Pr < tert-Bu.

This concept was carried over to the saponifications, and Evans, Gordon and Watson concluded that the activation energy increased gradually as the normal series is ascended in accordance with the increasing inductive effect of the methyl, ethyl, propyl, etc. groups. They pointed out that the equality of the activation energy for ethyl propionate and ethyl isobutyrate was anomalous and attempted to explain this result in terms of the Baker-Nathan effect. The Baker-Nathan effect is the postulated electron release by the methyl group. This is assumed to occur also in the isopropyl group, but the net effect is less than in the methyl alone. Superimposed on the general inductive effect, this would tend to make the total electron release, and hence E, for the propyl and isobutyl compounds the same.

Table IV
Data of Evans, Gordon and Watson (8)

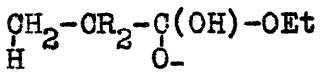
(Medium: 85% aq. ethanol; base: NaOH)

10^3k, lit. mole^{-1} sec.$^{-1}$

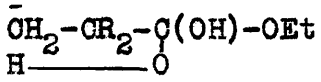
Ethyl ester	25°	35°	50°	E, cal./mole	
Acetate	6.21	13.6	38.7	14,200	
Propionate	3.63	8.31	24.7	14,500	
Butyrate	1.72	3.94	12.2	15,000	
Valerate	1.92	4.42	13.3	14,700	
Hexoate	2.07	4.81	14.5	14,800	
Heptoate	1.79	4.06	12.7	15,000	
Octoate	1.84	4.30	13.3	15,000	
Isobutyrate	0.801	1.84	5.72	15,000	(a)
Isovalerate	.427	1.02	3.34	15,700	
Methylethylacetate	.308	0.735	2.36	15,400	
Trimethylacetate	.0254	.0635	0.241	16,500	
Diethylacetate	.0157	.0409	.154	17,400	

(a) Recalculated value; cf. Smith and McRaynolds, J. Am. Chem. Soc., 61, 1964 (1939), foot-note (5).

The low P factors which were observed for the branched chain esters were clarified by assuming, for chains branched at the α-carbon atom, a possible hydrogen-bond formation between the β-carbon and the carbonyl oxygen in the intermediate complex, which would then be a resonance hybrid including forms I and II.



(I)



(II)

These results appeared at once in direct disagreement with the work of Smith (13) (15) on the kinetics of the esterification of the aliphatic acids in methanol. His results indicated a constancy in E in ascending the homologous series, and he was able to explain them in terms of steric considerations rather than electronic ones. A study of Evans, Gordon and Watson's work, made in view of this discord, then lead to the evaluation of the following criticisms:

(1.) The changes of activation energy in ascending the normal series are well within experimental error. This is indicated by the following considerations. E values were determined from the values for k at three different temperatures. In the case of ethyl propionate the activation energy determined from the 20° and 35° points is 15,100 cal., while that obtained from the 35° and 50° points is 14,340 cal. The difference between these two values is 760 cal., yet Evans, Gordon and Watson in the discussion of their work consider as significant differences of only 200-300 cal.

(2.) The similarity of the activation energy for ethyl propionate and ethyl isobutyrate is wholly fictitious, since Smith and McReynolds (16) upon recalculation of Evans, Gordon and Watson's data found the values of E to be 14,500 cal. and 15,000 cal., respectively.

(3.) The experimental technique, especially for the more volatile esters, is questionable.

The purity of the esters is claimed by no more than a statement that they were subjected to repeated fractional distillation and by boiling points given, in general, to the nearest whole degree. The type of distillation apparatus is not mentioned, and, if a simple distilling flask were employed, such a treatment could not be depended upon for purification, especially in the case of ethyl acetate (b.p. 77.1°) which forms one azeotrope with ethanol boiling at 71.8° and another with ethanol and water boiling at 70.3°(9).

The velocity determinations involved weighing a quantity of ester into a stoppered 100 ml. flask, and subsequent diluting to 75 ml. with alcohol. When ethyl acetate is used, such a method as this may lead to considerable loss of ester due to volatilization as indicated by the following calculation. The weight of ethyl acetate needed for the 0.05 M solutions used is about 0.44g. If the weighings were made at 25° the vapor pressure of the ester would be about 90 mm. Then if the air in the 100ml. flask were saturated with ester by volatilization of the weighed sample, about 0.043 g. or 10% of the ester would

have vaporized. Undoubtedly some of this vaporized ester would be lost upon the addition of alcohol to the flask, thus creating a difference between the amount of ester weighed out and that actually present at the beginning of a run. The error from this source would be considerably lower for ethyl propionate (vapor pressure at 25° is about 35 mm.) and would be essentially negligible for still higher boiling esters.

The only valid conclusion which may be made from the results of Evans, Gordon and Watson is that, in accord with Kindler's findings, the saponification velocities for ethyl butyrate and higher esters are essentially the same. Their conclusion that E increases, due to increasing +I as the normal series (acetate, propionate, butyrate, etc.) is ascended is based upon questionable experimental data and cannot be accepted.

Following Evans, Gordon and Watson, Davies and Evans (3) presented their findings on the saponification of various ethyl esters in 70% acetone (cf. Table V). These results show a quite definite increase in E in the normal series which may be attributed to increasing +I of the alkyl groups. Davies and Evans state that in spite of the criticisms to Evans, Gordon and Watson's work by Smith and Levenson (14) they still

> "believe that there is a trend toward a higher constant value (in E) as the normal series is ascended even in alcohol-water medium."

There is, however, no foundation for this belief. It is well known that an ordered effect, or even a reaction mechanism,

Table V

Data of Davies and Evans (3)

(Medium: 70% aq. acetone: base: NaOH)

Ethyl ester	$10^3 k$, lit. mole^{-1} sec.$^{-1}$ 24.8°	35°	44.70°	E, cal./mole
Acetate	4.65	8.22	13.5	9,800
Propionate	2.20	4.06	6.83	10,600
Butyrate	0.881	1.68	2.99	11,700
Valerate	.659	1.33	2.45	12,400
Heptoate	.608	1.19	2.21	12,400
Isobutyrate	.550	1.03	1.80	11,200
Isovalerate	.218	0.450	0.863	13,300
Trimethylacetate	.0223	.0456	.0874	13,000
Diethylacetate	.0083	.0184	.0371	14,300

may change upon passage from one solvent to another. Baker and Nathan (1) state that their results on the reaction between benzyl bromide and pyridine in dry acetone, 90% aqueous acetone and 90% aqueous ethanol

> "clearly indicate that the effect of such substituent groups (unipolar substituents) upon the velocity of one particular reaction is largely dependent upon the nature of the medium."

Furthermore, there is a definite objection to the assignment of the changes in rate found in these reactions to variation of the general positive inductive effect of alkyl groups. For both ethyl butyrate and ethyl isobutyrate log PZ was practically the same (6.5 and 6.0, respectively); yet, E for the isobutyrate was found to be 500 cal. less than for its normal isomer. This result is in conflict with all ordinary concepts of inductive effects of alkyl groups, which assign to the branched alkyl groups a higher +I than to the normal groups. Davies and Evans resort to the Baker-Nathan effect to explain this anomaly; but, this is not valid. The Baker-Nathan effect is limited to systems in which a methyl group is attached to either a nominally or potentially conjugated double bond system (1). Such is not the case in ethyl isobutyrate.

In summary, the literature shows:

1. Saponification velocity of ethyl esters decreases as the acyl group ascends the normal homologous series until ethyl butyrate is reached, after which k remains essentially constant.

2. Branching at the α-carbon atom of the acyl group decreases the rate of saponification.

3. Available data do not unequivocally indicate the operation of the inductive effect of alkyl groups in saponification in aqueous ethanol medium, although there is some indication of the effect when aqueous acetone is used.

EXPERIMENTAL

Materials:

The medium for all the saponifications was 85% aqueous ethanol. Ordinary 95% ethyl alcohol was shaken with freshly prepared silver oxide (to remove aldehydes) and then fractionated with a reflux ratio of about 5:1 through a five-foot column packed with Fenske glass spirals (22). Middle fractions were collected and then diluted with distilled water to a concentration of 85% by weight ethanol, as indicated by density measurements. This medium was prepared in large batches so as to provide a constant medium for the several series of rate determinations.

All the esters, except ethyl acetate, ethyl propionate, ethyl butyrate and ethyl laurate, were prepared by esterification of the corresponding acid with absolute ethanol, using a small quantity of concentrated sulfuric acid as a catalyst. Precautions were taken to insure the use of a reasonably pure organic acid, and the resulting esters were purified by careful fractionation, with high reflux ratio, in efficient distilling columns.

Ethyl acetate, ethyl propionate and ethyl butyrate were the best grade Eastman Kodak Company products. Approximately 3% of the corresponding acid was mixed with each ester, and a drop of sulfuric acid was added. This was done to esterify any free alcohol which might have been present, and hence prevent the formation of azeotropic mix-

tures. The esters were then fractionated in a five-foot spiral column. No free acid was found in any of the fractions used.

Ethyl laurate, obtained from Eastman Kodak Company, was fractionated in a five-foot Vigreux column under reduced pressure.

The fractions used for the kinetic studies were middle cuts which distilled at constant head temperature. Each sample used was submitted to analysis by complete saponification with excess standard caustic and back titration with standard hydrochloric acid solution. The method, which is similar to that described by Bryant and Smith (2), is estimated to have an accuracy of ± 0.5%.

Table VI contains a summary of some pertinent details of the preparation and distillation of the various esters. Descriptions of the use of the malonic ester synthesis, the carbonation of a Grignard reagent and the silver oxide oxidation of an aldehyde are given in Appendices I, II and III, respectively. Table VII is a summary of the results of the ester analyses.

Kinetic measurements:

Mixtures of the 85% aqueous ethanol and approximately 0.2 M sodium hydroxide in 85% ethanol were made up in glass stoppered bottles so that upon addition of a given quantity of ester the resulting mixture would become 0.0500 M with respect to both ester and caustic. These solutions were

Table VI

Ethyl ester	Source of corresponding acid	Fractionation of ester (boiling points are approx.)
Acetate	(Ester purchased from E.K.Co.,) (a)	I (b) 77.1°/atm.
Propionate	(Ester purchased from E.K.Co.)	I, 99.1°/atm.
Butyrate	(Ester purchased from E.K.Co.)	I, 121.3°/atm.
Laurate	(Ester purchased from E.K.Co.)	II, 186.0°/60mm.
Isocaproate	Malonic ester synthesis (d)(17)	III, 162.6°/atm.
β-Methyl-valerate	Malonic ester synthesis (d)(17)	III, 160.7°/atm.
Diethyl-acetate	Purchased from E.K.Co.	II, 150.8°/atm.
Dipropyl-acetate	Malonic ester synthesis (c)(17)	III, 189.5°/atm.
Dibutyl-acetate	Malonic ester synthesis (c)(17)	III, 122.2°/31mm.
Di-isobutyl-acetate	Malonic ester synthesis (c)(17)	II, 125.8°/67mm.
Phenyl-acetate	Purchased from E.K.Co.	II, 146.8°/68mm
Hydro-cinnamate	Purchased from E.K.Co.	II, 160.0°/65mm.
γ-Phenyl-butyrate	Carbonation of Grignard reagent (e)	II, 172.0°/57mm.
δ-Phenyl-valerate	Malonic ester synthesis (e)	II, 151.0°/13mm.
Hydra-tropate	Alkaline oxidation of the aldehyde with silver oxide (e)(f)	II, 141.8°/54mm.
Phenylethyl-acetate	Purchased from E. K. Co.	II, 156.5°/66mm.
Diphenyl-acetate	Purchased from E. K. Co.	III, 191°/12mm.
Cyclohexane-carboxylic acid	Purchased from E.K.Co.	II, 112.6°/57mm.
Cyclohexyl-acetate	Malonic ester synthesis(g)	II, 127.8°/55mm.

Table VI continued

(a) Eastman Kodak Company, Rochester, N. Y.

(b) I: Five-foot spiral column.
II: Five-foot Vigreux column.
III: Two-foot Vigreux column.

(c) The author is grateful to Dr. H. A. Smith, who made this acid available to him.

(d) This acid was prepared by Mr. A. S. Raff to whom the author extends his gratitude.

(e) Cf. Appendices

(f) Hydratropic aldehyde was purchased from Paragon Testing Laboratories, Orange, N. J.

(g) The author is grateful to Mr. T. E. Ricketts for preparing this acid.

Table VII

Analysis of Esters
(Accuracy of analytical method is ca.±0.5%)

Ethyl ester	Percentage Purity
Acetate	100.4
Propionate	100.1
Butyrate	99.5
Laurate	99.9
Isocaproate	100.2
β-Methylvalerate	99.8
Diethylacetate	99.6
Dipropylacetate	99.7
Dibutylacetate	99.6
Di-isobutylacetate	100.1
Phenylacetate	99.9
Hydrocinnamate	100.2
γ-Phenylbutyrate	100.2
δ-Phenylvalerate	100.2
Hydratropate	99.6
Phenylethylacetate	99.7
Diphenylacetate	100.4
Cyclohexane-carboxylic acid	99.9
Cyclohexylacetate	99.7

allowed to come to temperature equilibrium in electrically controlled water thermostats maintained within ± 0.02° of the desired temperature. All temperatures were checked with a Bureau of Standards calibrated thermometer. At zero time the ester was added, and the subsequent course of reaction was followed by pipetting from the reaction mixture, at various intervals, 10 ml. samples. These samples were delivered into 10 ml. (excess) of standard hydrochloric acid solution. The mixture was then titrated to a brom-thymol-blue end-point with standard carbonate-free aqueous sodium hydroxide. The data in Table VIII is typical of those obtained in the various runs.

The method of adding the ester varied somewhat. In the work with the more volatile esters, especially ethyl acetate, it was essential to reduce vaporization losses to a minimum. Therefore, for ethyl acetate, ethyl propionate, and ethyl butyrate one ml. pipettes were calibrated so that the exact amount of ester delivered from the pipette at 20° was known. This value was found to be reproducible to ± 0.15%. At zero time the ester was withdrawn from a sample maintained at 20° and delivered into the reaction mixture from the pipette. All times were recorded at half-delivery of the pipette.

In order to make sure that none of the esters was lost by vaporization during delivery from the pipette, two runs were made with ethyl acetate at 50° in which the weighed quantity of ester was added to the reaction mixture in a sealed glass ampoule. At a given instant the ampoule was crushed under the surface of the liquid, the contents of the bottle thoroughly mixed by shaking, and the reaction followed in the usual manner. The

Table VIII

Run No. 148 - Saponification of Ethyl δ-Phenylvalerate at 45°

a = [Ester] = [NaOH] = 0.0500 M

NaOH = 0.0415 M ; 10 ml. HCL = 16.29 ML. NaOH

Interval, min.	Back-titre, ml. NaOH	(a - x)	X	$10^3 k$ lit. mole^{-1} sec.$^{-1}$
4	5.76	0.04375	0.00625	11.9
8	6.80	.03943	.01057	11.2
14	8.09	.03407	.01593	11.1
23	9.52	.02813	.02187	11.3
37	10.90	.02240	.02760	11.1
55	12.06	.01758	.03242	11.2
87	13.23	.01271	.03729	11.2
130	14.03	.00939	.04061	11.1

Average for 20-80% 11.2

results of these runs, which are indicated by an asterisk in Table X, are, within experimental error, indentical with those obtained when the ester was added by pipette.

For the higher boiling esters precautions to prevent volattilization were not necessary. These esters were weighed out in open glass capsules shortly before starting a run and were introduced into the reaction mixture by simply dropping in the capsule at zero time.

Calculations:

The velocity of saponification may be expressed

$$\frac{dx}{dt} = k\,(a - x)(b - x) \qquad (3)$$

where, a = initial concentration of ester,

b = initial concentration of sodium hydroxide,

x = amount of reaction in the interval of time, t, and

k = specific reaction rate constant.

When the initial concentrations of ester and base are the same, as in this work, $a = b$, and the integrated expression assumes the form

$$k = x / a\,t\,(a - x). \qquad (4)$$

The values of k reported here, except for ethyl diethylacetate, ethyl dipropylacetate and ethyl dibutylacetate at 45° and 55°, have been calculated from this equation, and they are measured in units of liters $mole^{-1}$ $second^{-1}$.

The reactions were carried out in either soft glass or Pyrex glass stoppered bottles. In all but the above excepted instances any side reaction between the glass reaction vessel and the sodium hydroxide was found to be negligible. For these

special cases the rate of reaction was so slow that at the higher temperatures the amount of glass reaction over the long period of time necessary to complete a run became appreciable, and a correction for it had to be applied in calculating the rate constants. This was done in the following manner.

Assuming that the glass reaction and the saponification occur simultaneously and independently of each other, the rate of total reaction is

$$\frac{dy}{dt} = k_s (a - x)(b - y) + k_g (b - y) \qquad (5)$$

where, $\underline{a}$ = initial concentration of ester,

$\underline{b}$ = initial concentration of sodium hydroxide,

$\underline{x}$ = amount of ester reacted,

$\underline{y}$ = total amount of sodium hydroxide reacted,

$\underline{k_s}$ = reaction rate constant for the saponification of the ester,

$\underline{k_g}$ = unimolecular reaction rate constant for the reaction of the caustic with the glass.

The rate of the reaction of ester is

$$\frac{dx}{dt} = k_s (a - x)(b - y). \qquad (6)$$

Solution of the two simultaneous differential equations, 5 and 6, using the experimental conditions that $\underline{a} = \underline{b}$ and that $\underline{x} = 0$ when $\underline{y} = 0$, yields the result

$$y = x + 2.303 \frac{k_g}{k_s} \log \frac{b}{(b - x)} \qquad (7)$$

For the glass reaction

$$k_g = \frac{2.303}{t} \log \frac{b}{(b - y)} \qquad (8)$$

The values of k_g were determined by the graphical method from the data of blank runs in which no ester was present. These values were found to be:

	45^0	55^0
k_g (sec.$^{-1}$)	1.4×10^{-7}	9.6×10^{-7}

Using the uncorrected k value as a first approximation to k_s the curve representing equation 7 was drawn. From this curve the value of x corresponding to each experimentally determined y was picked; and, this value of x used in equation 4 gave, to a first approximation, the value of k. The data in Table IX show the effect of the correction upon the reaction rate constants.

Tables X and XI contain the values of K for all the esters studied. Because small experimental errors may cause large errors in k during the beginning and end of a run, the recorded values are the average of individual rate constants obtained in each run between 20 and 80% reaction, except where corrections for the glass reaction were made. For these only, figures for 20 to 60% reaction were averaged since the corrections are approximate, and they become relatively large after 60% reaction. The average error for each value of k is of the order of 2%.

Figures 1, 2 and 3 contain plots of log k *versus* 1/T for the various esters. From the slopes of these lines the energies of activation were calculated by means of the Arrhenius equation,

$$\frac{d(\ln k)}{dT} = \frac{E}{RT^2} \qquad (9)$$

which in the integrated form gives the linear relationship

$$\log k = -\frac{E}{2.303\ RT} + \text{constant} \qquad (10)$$

Table IX

Run No. 96 - Saponification of Ethyl Dipropylacetate at 55°

$a = [Ester] = [NaOH] = 0.0500$ M

t, min.	y	x	$10^3 k$, lit. mole^{-1} sec.$^{-1}$ Uncor.	Cor.
460	0.01028	o.0096	0.188	0.172
1230	.02052	.0184	.189	.157
1860	.02610	.0232	.196	.155
2820	.03237	.0282	.217	.153
4290	.03859	.0331	.263	.152

Average for 20-60% 0.154

Table X

Reaction Rate Constants for Saponification of Ethyl Esters of Alkyl-Substituted Aliphatic Acids

In all cases $a = [\text{Ester}] = [\text{NaOH}] = 0.0500$ M

$10^3 K$, lit. mole^{-1} sec.$^{-1}$

Ethyl ester	t = 20°	t = 25°	t = 30°	t = 35°	t = 40°	t = 45°	t = 50°	t = 55°
Acetate	4.56		11.0		22.9		47.6	
	4.51		10.8		23.0		47.6	
							47.7*	
							48.7*	
Average	4.53	6.92[a]	10.9		22.9		47.9	
Propionate	2.32		5.28		11.9		23.9	
	2.33		5.32		11.5		24.4	
Average	2.32	3.55[a]	5.30		11.7		24.2	
Butyrate	1.18		2.79		6.31		13.4	
	1.18		2.79		6.23		13.2	
Average	1.18	1.83[a]	2.79	4.25[a]	6.27	9.18[a]	13.3	19.0[a]
Laurate		1.81		4.11		9.31		18.6
		1.86		4.10		9.23		18.8
Average		1.84		4.11		9.27		18.7
Isocaproate		1.85		4.34		9.01		18.9
		1.87		4.28		9.06		18.9
Average		1.86		4.31		9.04		18.9
β-Methyl-valerate		0.414		0.968		2.20		4.67
		.407		.959		2.19		4.62
Average		.411		.963		2.20		4.65
Diethyl-acetate		,0151		.0385		0.0955		0.216
		.0152		.0387		.0966		.211
		.0159		.0381		.0981		.217
Average		.0154		.0384		.0968		.215
Dipropyl-acetate		.0105		.0283		.0644		.154
		.0107		.0280		.0669		.154
Average		.0106		.0282		.0656		.154
Dibutyl-acetate		.0101		.0254		.0629		.153
		.0099		.0256		.0640		--
Average		.0100		.0255		.0635		.153
Di-isobutyl-acetate		.0031[b]						

(a) Interpolated (or extrapolated) value.

(b) Approximate value.

Table XI

Reaction Rate Constants for Saponification of Ethyl Esters of Phenyl-Substituted Aliphatic Acids

In all cases $a = [Ester] = [NaOH] = 0.0500$ M

Ethyl ester	$10^3 k$, lit. mole^{-1} sec.$^{-1}$ t = 25°	t = 35°	t = 45°	t = 55°	t = 65°
Phenylacetate	10.1	22.2	45.4	89.0	
	10.0	22.2	45.1	87.5	
Average	10.1	22.2	45.3	88.3	
Hydrocinnamate	5.03	11.2	24.5	46.7	
	5.05	11.5	23.9	47.4	
Average	5.04	11.3	24.2	47.1	
γ-Phenylbutyrate	2.68	6.26	13.2	26.6	
	2.69	6.12	13.2	27.1	
Average	2.69	6.19	13.2	26.8	
δ-Phenylvalerate	2.27	5.24	11.3	21.9	
	2.29	5.18	11.2	22.0	
Average	2.28	5.21	11.3	21.9	
Hydratropate		1.86	4.14	8.73	17.5
		1.87	4.20	8.60	17.7
Average	0.802[a]	1.87	4.17	8.67	17.6
Phenylethylacetate		0.635	1.43	3.06	6.33
		.625	1.44	3.10	6.24
Average	0.264[a]	.630	1.43	3.08	6.28
Diphenylacetate		1.36	3.17	6.89	13.9
		1.33	3.11	6.70	13.5
Average	0.560[a]	1.35	3.14	6.79	13.7
Cyclohexylacetate		1.21	2.68	5.60	11.5
		1.19	2.64	5.70	11.7
Average	0.509[a]	1.20	2.66	5.65	11.6
Cyclohexanecarboxylic acid		0.850	1.90	4.06	8.16
		.845	1.92	4400	8.22
Average	0.360[a]	.848	1.91	4.03	8.19

(a) Extrapolated.

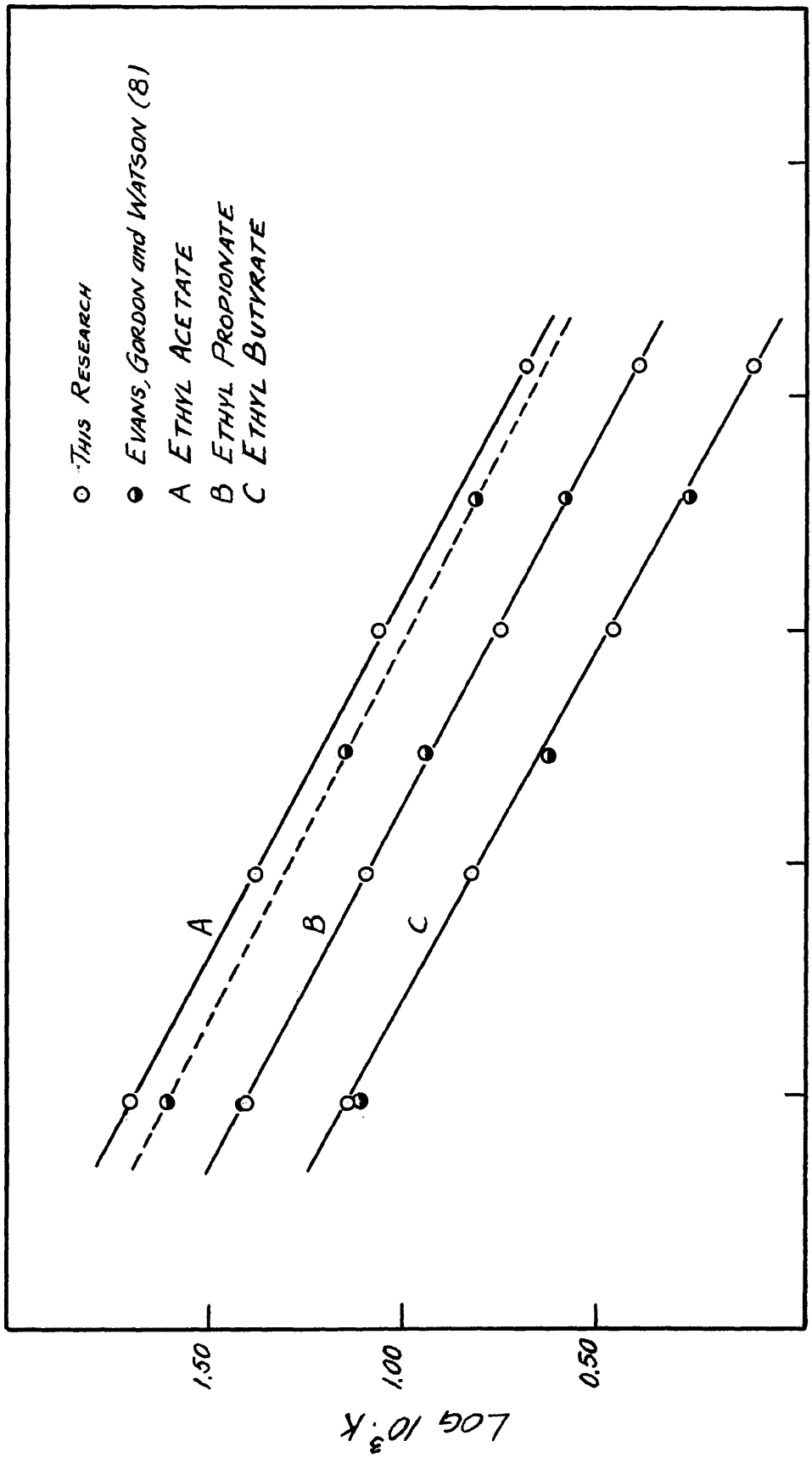

This Research
Evans, Gordon and Watson (8)
A Ethyl Acetate
B Ethyl Propionate
C Ethyl Butyrate
A
B
C
1.50
1.00
0.50
Log 10³·k
3100
3200
3300
3400
3500
10⁶·1/T

FIGURE 1.

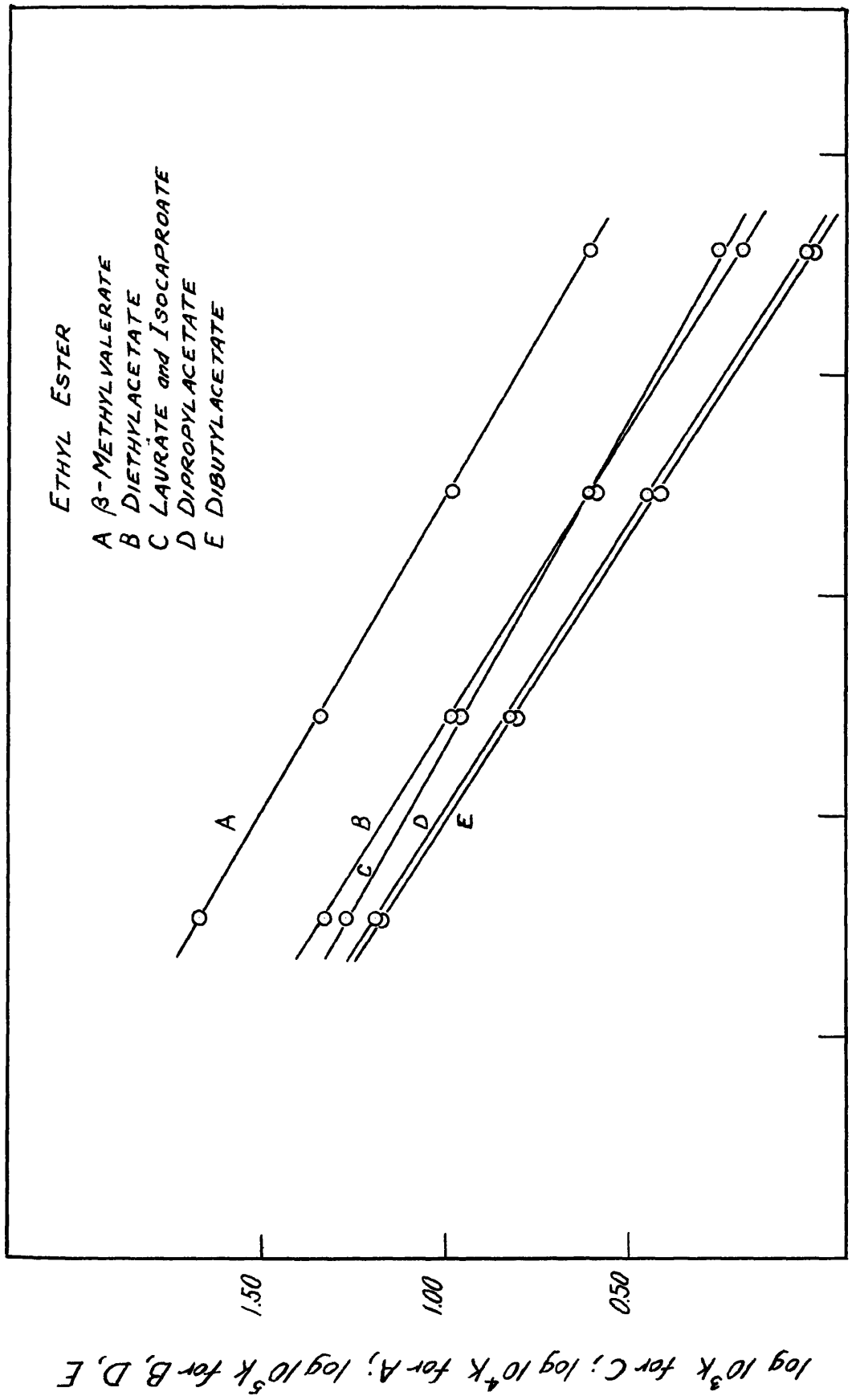

Ethyl Ester
A β-Methylvalerate
B Diethylacetate
C Laurate and Isocaproate
D Dipropylacetate
E Dibutylacetate
A
B
C
D
E
1.50
1.00
0.50
3000
3100
3200
3300
3400
log 10³k for C; log 10⁴k for A; log 10⁵k for B, D, E
10⁶. 1/T

FIGURE 2.

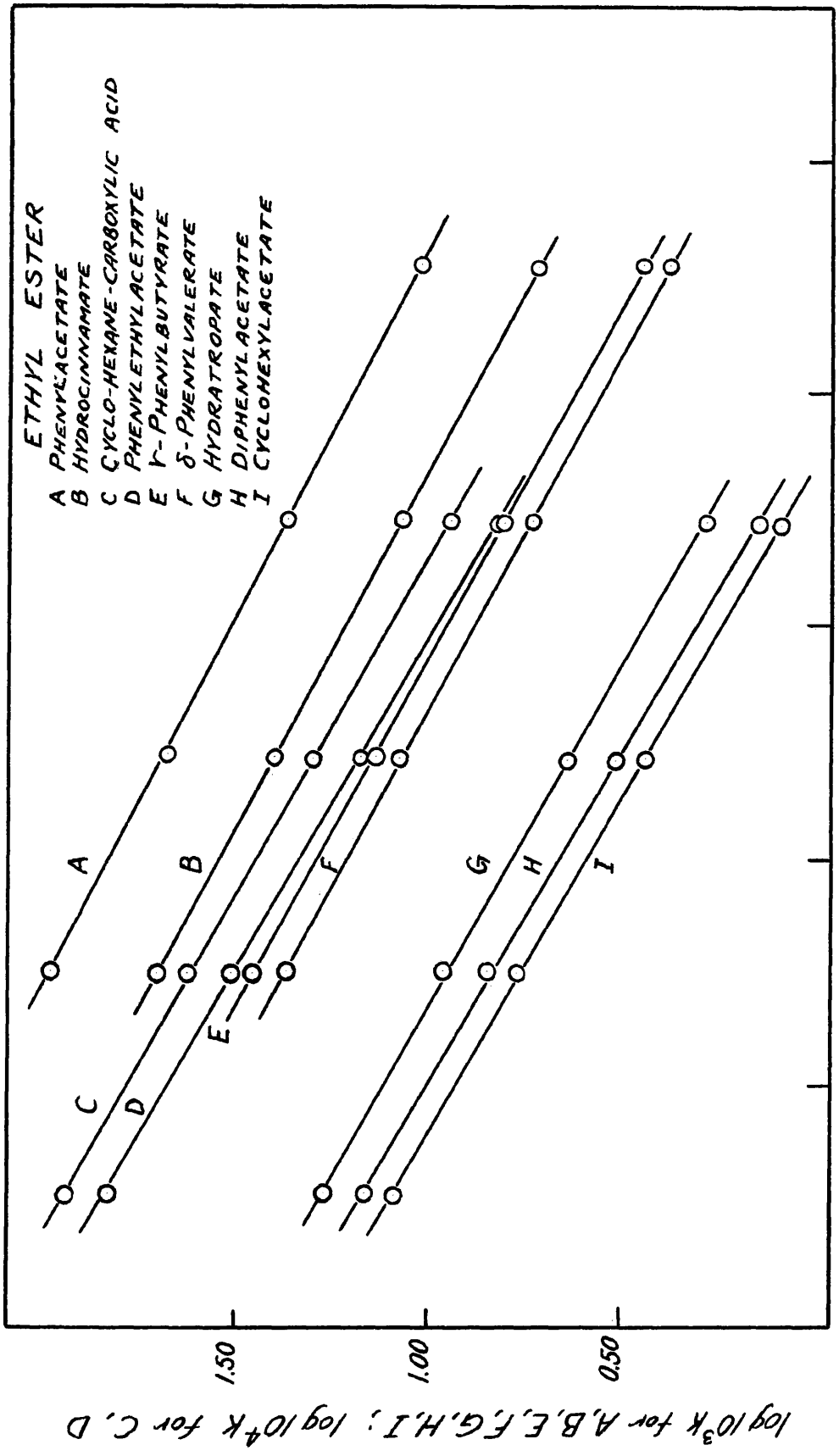

ETHYL ESTER
A PHENYLACETATE
B HYDROCINNAMATE
C CYCLO-HEXANE-CARBOXYLIC ACID
D PHENYLETHYLACETATE
E γ-PHENYLBUTYRATE
F δ-PHENYLVALERATE
G HYDRATROPATE
H DIPHENYLACETATE
I CYCLOHEXYLACETATE
A
B
C
D
E
F
G
H
I
1.50
1.00
0.50
3000
3100
3200
3300
3400
log 10³k for A, B, E, F, G, H, I; log 10⁴k for C, D
10⁶. 1/T

FIGURE 3.

The slopes, - $\underline{E}/2.303\ \underline{R}$, were calculated from the four experimental points by the method of least squares. The values of $\underline{E}$ are recorded, to the nearest 100 cal./mole, in Table XII. Consideration of the various experimental errors involved in their determination indicates that the error in the values of the activation energies is of the order of $\pm$ 200 cal./mole.

Table XII

Activation Energy for Saponification of Ethyl Esters

Ethyl ester	E, cal./ mole
Acetate	14,700
Propionate	14,700
Butyrate	15,100
Laurate	15,100
Isocaproate	15,000
β-Methylvalerate	15,700
Diethylacetate	17,200
Dipropylacetate	17,200
Dibutylacetate	17,700
Phenylacetate	14,100
Hydrocinnamate	14,500
γ-Phenylbutyrate	14,900
δ-Phenylvalerate	14,700
Hydrotropate	15,400
Phenylethylacetate	15,900
Diphenylacetate	16,000
Cyclohexane-carboxylic acid	15,600
Cyclohexylacetate	15,600

DISCUSSION

Normal and Branched Chain Alkyl Esters

Comparison of the results of Evans, Gordon and Watson with those of the present research is indicated in Fig. 1. It is evident that agreement is good for ethyl propionate and is fair for ethyl butyrate, the difference in the 50° *k* values being about 8%.

In the case of ethyl acetate, however, there are marked differences in both the values of *k* and the activation energy. At 50° the *k*'s differ by almost 25%, and *E* determined in this work is some 500 cal. greater than theirs. These differences are well outside of experimental error, and it is believed that vaporization of the ester is probably responsible for the generally lower values of Evans and coworkers.

The data in Table XIII indicate, then, that for the straight chain esters the activation energy for the homologous series is, within experimental error, constant and does not gradually increase as Evans, Gordon and Watson state. All the values of *k* are within 200 cal. (the estimated experimental error) of the mean value, 14,900 cal. These results show that, although alkyl groups may exert a positive inductive effect, increasing in the order Me < Pr < Bu, in 85% ethanol the +*I* is small and is not significant in determining the activation energies. Furthermore, variation in inductive effect cannot be attributed to differences in chain branching since it is found that, within experimental error, the values of *E* are

Table XIII

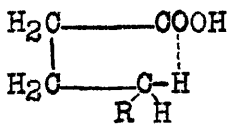
Activation Energies for Saponification of n-Ethyl Esters in 85% Ethanol

Ethyl ester	$10^3 k_{25°}$	E
Acetate	6.92	14,700
Propionate	3.55	14,700
Butyrate	1.83	15,100
Valerate (8)	1.92	14,700
Hexoate (8)	2.07	14,800
Heptoate (8)	1.79	15,000
Octoate (8)	1.84	15,000
Laurate	1.84	15,100
	Average	14,900 ± 160

the same for n-butyrate, isobutyrate and isocaproate, and for β-methylvalerate and isovalerate (cf. Tables IV, X), although in each group different normal and branched chain groups are present.

The values of $\underline{k}$ for the normal series of esters decrease up to ethyl butyrate. From here on, insofar as can be experimentally determined, the values remain constant. This phenomenon is found not only for saponification, as shown by the results of the present work as well as those of Evans, Gordon and Watson and of Kindler, but also in the similar type reactions of esterification of normal aliphatic acids with methanol and hydrolysis of esters in 70% aqueous acetone (cf. Tables XIV, XV). The constancy of activation energy in all three instances makes it probable that the variations of $\underline{k}$ can best be explained in terms of some type of "steric hindrance" arising in the aliphatic chain. Such steric considerations have been used by Smith (15) in treating his esterification results, and his ideas may be carried over to the saponifications. By doing this the perfect analogy between the kinetics of esterification of alkyl acids with methanol and the saponification of their ethyl esters in 85% ethanol is clarified.

Smith postulated that when a chain of four carbon atoms had been reached ring formation might occur, probably through hydrogen bonding.



Further increase in chain length would not appreciably change

Table XIV

Acid Hydrolysis in 70% Aqueous Acetone (3)

Ethyl ester	$10^5 k_{24.8^\circ}$ lit.mole^{-1} sec.$^{-1}$	E, cal./mole
Acetate	4.47	16,200
Propionate	3.70	16,200
n-Butyrate	1.96	16,100
n-Valerate	1.79	16,500
n-Hexoate	1.77	16,200
n-Heptoate	1.64	16,200
n-Octoate	1.55	16,300

Table XV

Esterification with Methanol Catalyzed by H^+ Ions (13)

Acid	k_{20° lit.mole^{-1} sec.$^{-1}$	E,cal./mole
Formic	0.632	
Acetic	.0440	Constant within experimental error. Mean value = 10,000
Propionic	.0400	
Butyric	.0211	
Valeric	.0214	
Hexoic	.0219	
Nonoic	.0211	

this structure, and normal acids higher than butyric (or esters higher than ethyl butyrate) would, as far as steric considerations are concerned, behave kinetically the same. Since the carbonyl group is the seat of reaction in esterification, saponification and acid hydrolysis the formation of the hydrogen bond accounts for the sudden decrease in rate at the four carbon-atom compound found in all three processes.

On the basis of this postulate one would expect alkyl substitutions on the γ-carbon atom or other carbons farther removed from the carbonyl group to produce no appreciable effect on the kinetics of saponification; such esters would have a structure analogous to ethyl butyrate, and their rate of saponification should be almost the same. This is actually true as shown by the data for ethyl isocaproate (cf. Table X). It is a striking rule which applies in esterification as well as saponification that only when substitution of a methyl group for a hydrogen in a normal alkyl chain takes place in the α or β-position is the reaction velocity appreciably affected. (Cf. data in Table XVI).

Substitution on an α or β-carbon atom in a normal alkyl chain may be any one of three kinds:

1. The substituent has no effect on the possibility of ring formation; e.g., ethyl propionate $\rightarrow$ ethyl isobutyrate.

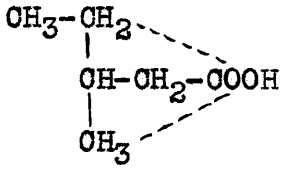
2. The substituent introduces a second way in which the ring (one ring being already possible) may form; e.g., ethyl valerate $\rightarrow$ ethyl β-methylvalerate.

Table XVI

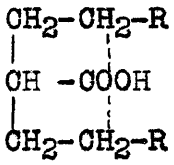
Effect of Methyl Substitution on Reaction Velocity (a)

Position in which methyl substitution takes place	% Change Ester.(k_{20})	Sapon.(k_{25})	ΔE(sapon.)
α			
Acetate → propionate	10	49	0
Propionate → isobutyrate	62	78	+ 300
Butyrate → methylethylacetate	88	83	+ 300
β			
Propionate → butyrate	47	49	+ 400
Butyrate → isovalerate	76	77	+ 600
Valerate → β-methylvalerate	78	77	+ 1000
γ			
Butyrate → valerate	1	5	-400
Valerate → isocaproate	5	3	+ 300

(a) Data from present work, (8), (13), (15), (17).



3. The substituent mades possible simultaneous occurrence of two rings; e.g., ethyl butyrate $\longrightarrow$ ethyl diethylacetate.



Introduction of an α-methyl group never increases the possibilities for closure of a four carbon-atom ring; it invariable causes a lowering of the rate constant, presumably by its effect on P in the equation $k = PZ\, e^{-E/RT}$, since there is produced no significant changes in E (300-400 cal.), even when the methyl involves formation of a branched chain.

A methyl in the β-position always increases by one the number of ways in which the ring can be formed. When the new methyl makes possible two ways of ring closure there is found, accompanying the decrease in k, a larger increase in E than occurs when only one method of ring closure is available. This increment in E amounts to 600 cal. for the change butyrate $\longrightarrow$ isovalerate and to 1000 cal. for the change valerate $\longrightarrow$ β-methylvalerate. The effect may be attributed to increasing steric resistance, which requires an energy of activation, to the approach of the hydroxyl ion in the saponification. Further evidence for this concept is furnished by the data for the diethyl-, dipropyl- and dibutylacetates.

When there are two ethyl or higher groups substituted on the α-carbon atom it is feasible to have two rings occurring simultaneously. The results for such esters, summarized in Table XVII, confirm this postulate since it is found that (just as in esterification) there is a much larger decrease in k when the chains are lengthened from isobutyrate to diethylacetate than is caused by the change from acetate to isobutyrate. Further lengthening of the two chains simultaneously results in relatively smaller changes in saponification velocity. This is to be expected since the greater length no longer affects the two rings which are already present.

The k values for the saponification of ethyl di-isobutylacetate are not included in Table XVII. This compound saponifies so slowly that the glass reaction correction becomes quite large. All that can be said with certainty is that this ester saponifies about one-third as fast as does dibutylacetic acid ester. This result, again, is similar to what Smith has found in esterification.

The changes in the activation energies for these esters also parallel those found by Smith (17) in esterification studies. The values of E are consistently several thousand calories higher than for the normal esters or for the branched chain esters in which simultaneous existence of two rings is impossible. The only logical way to explain this fact is to assume again an energy requirement for the surpassing of the steric hindrance created by the given substituents. It might be argued that a certain amount of energy is required for

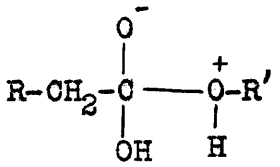
Table XVII

Effect of Chain Length of Ethyl Esters of Di-substituted Acetic Acids on Their Velocity of Saponification

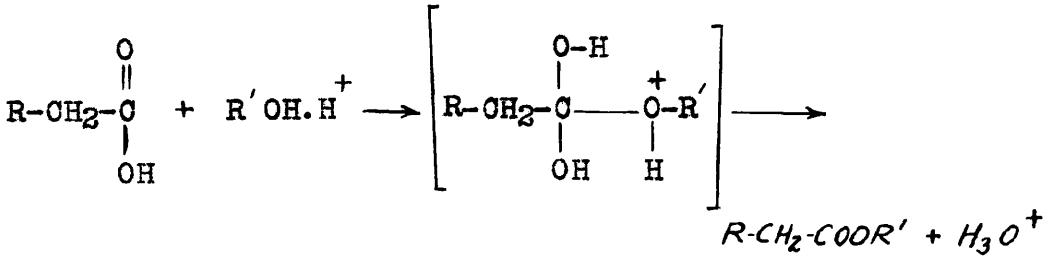
Ethyl ester	$10^3 k_{25}$	E
Acetate	6.92	14,700
Isobutyrate(cf.Table IV)	0.801	15,000
Diethylacetate	.0154	17,200
Dipropylacetate	.0106	17,200
Dibutylacetate	.0100	17,700

breaking the hydrogen bonds involved in the rings in order to allow formation of an intermediate complex, but, in view of the small energies usually associated with hydrogen bonds and of the transitory existence which they undoubtedly possess in such structures as postulated here, such energies could not account for the large differences found.

The parallelism of the effect of the character of the alkyl chain upon reaction velocity in both saponification and esterification gives further evidence of the similarities in the mechanisms of the two processes as already discussed by Waters and Lowry (20). In their treatment it is pointed out that both reactions probably proceed through the same type of intermediate complex of the structure



In saponification the rate determining step and the spatial requirements are associated with the approach and coordination of the catalyst ion; in esterification the hydronium ion $R\text{-}OH_2^+$ is the catalyst, which plays a role similar to the OH^- ion in saponification. The analogy may be visualized by comparison of the following scheme for esterification with that given on page 1. for saponification.



It is readily seen that in both reactions formation of the intermediate complex (the rate determining step) is subject to the same steric factors as well as being facilitated by electron recession from the carbonyl carbon atom (-I effect of substituents R); the rate determining process in both reactions is the coordination of a nucleophilic reagent with the carbonyl carbon atom.

Phenyl-Substituted Ethyl Esters

When not part of a conjugated system the phenyl group acts as an electron sink, and therefore insofar as its polarization effect is concerned one would expect the phenyl group to increase the velocity of saponification. This -I effect of phenyl has been observed by Dippy and Lewis (6) in the dissociation constants of phenyl-substituted monocarboxylic acids (cf. Table XVIII). The role of the phenyl in these instances is presumably to decrease the work required for the loss of a proton and thus increase the acid strength. Kindler's data (cf. Table II) gives some indication of the negative inductive effect operating in the saponification of straight chain phenyl-substituted esters, although since activation energies were not determined, the increase in rate constants over those for the unsubstituted analogs cannot be definitely attributed to the inductive effect. The results of this work show the effect of the phenyl group when it is at the end of an alkyl chain and when it is substituted in the α-position and that the net effect is apparently different.

Phenyl substitution at the end of an alkyl chain:

The results for these esters are in accord with expectations based upon the -I effect of the phenyl group (cf. Table XIX). For ethyl phenyl acetate and ethyl hydrocinnamate phenyl substitution causes a lowering of E from its value for the aliphatic analog. The activation energy for ethyl γ-phenyl-

Table XVIII

Acid Dissociation Constants in Aqueous Solution at 25° (5) (6)

Acid	10^5K(therm.)
Acetic	1.76
Phenylacetic	4.88
β-Phenylpropionic	2.19
γ-Phenylbutyric	1.75
Diphenylacetic	11.5
Cyclohexane-carboxylic	1.34 (a)

(a) K (classical)

Table XIX

Effect of Phenyl Substitution at the End of an Alkyl Chain

Ethyl ester	$10^3 k_{25}$	E
Acetate	6.92	14,700
Phenylacetate	10.1	14,100
Propionate	3.55	14,700
Hydrocinnamate	5.04	14,500
Butyrate	1.83	15,100
γ-Phenylbutyrate	2.69	14,900
Valerate (8)	1.92	14,700
δ-Phenylvalerate	2.28	14,700

butyrate and that for ethyl δ-phenylvalerate are both, within experimental error, the same as for ethyl butyrate and higher aliphatic esters. The negative inductive effect is apparently transmitted through the alkyl chain with decreasing magnitude as the chain length increases. When four carbon atoms intervene between the phenyl and the seat of reaction the effect becomes small and has no appreciable effect on the kinetics of saponification. This is in agreement with a large number of observations which have shown that the polarization effect of a substituent atom or group decreases progressively as it becomes farther removed from the functional part of the molecule. For the dissociation constants of chloro-substituted aliphatic acids Derick (4) has shown that the magnitude of the effect due to the chlorine atom decreases in the ratio 0.680: 0.189: 0.063: 0.024 accordingly as the halogen is in the α, β, γ and δ-positions. He concluded:

> "in all cases except where the substituent is of great negativity the effect of the substitution of negative radicals.....has fallen to a constant value by the γ-position....which(effect) is approximately that of the corresponding unsubstituted acid. A slight residual effect is always present so that the ionization of the substituted acid. never completely falls to that of the corresponding unsubstituted acid."

Similarly, in saponification once the phenyl is beyond the γ-position it has little effect upon the kinetics of the reaction.

It is interesting to note that, just as for the straight chain aliphatic esters, the values of $\underline{k}$ decrease as the alkyl chain lengthens until, when a four carbon-atomed chain is reached $\underline{k}$ appears to have approached an almost constant value.

Kindler's results (cf. Table II) show the same trend in k. This is in contrast to what is found in esterification (which has already been shown to be analogous to saponification for straight and branched chain aliphatic acids) for which phenylacetic, hydrocinnamic and γ-phenylbutyric acids all have essentially the same k values as do butyric and higher acids (15). Similarly, in acid hydrolysis both k and E have practically the same values for ethyl butyrate and ethyl phenylacetate (3). It is probable that in the two acid catalyzed processes there is a compensation of steric and energetic effects which does not occur in saponification.

Phenyl substitution in the α-position:

In every instance, except that of ethyl phenylacetate, the effect of introducing a phenyl group into the α-position is to lower k and increase E. This is shown in Table XX.

Inductive effect cannot explain these changes; in fact, inductive effect perse would predict precisely the opposite. It should be noted that in none of the esters studied is the phenyl part of a conjugated system, which precludes operation of a tautomeric effect which would produce the opposite result to that of -I. (It is such a tautomeric effect, indicated in the figure below, which undoubtedly accounts for the slow rate of saponification of ethyl benzoate, as well as esterification of benzoic acid. $10^3 k_{25^\circ}$ (sapon.) = 0.621 lit. mole^{-1} sec.$^{-1}$; E = 17,700 cal./mole (7))

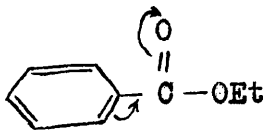


Table XX

Effect of α-Phenyl Substitution on Saponification of Ethyl Esters

α-Substitution	% change in k_{25} (+ = increase)	ΔE
Acetate → Phenylacetate	+46	-600
Propionate → Hydratropate	-77.5	+700
Butyrate → Phenylethylacetate	-86	+1000
Phenylacetate → Diphenylacetate	-94.5	+1900

A combination of steric effect with the -I of the phenyl group gives probably the best interpretation of the results of this investigation.

Assuming the same general steric influence of a six-membered ring in both ethyl phenylacetate and ethyl cyclohexylacetate, the difference in the energy of activation for their saponification (1500 cal./mole) may be accepted as an approximation to the inductive effect due to a phenyl in the α-position, since saturation of the benzene nucleus probably destroys its polarization effect (6). On this basis the change in E on going from ethyl acetate to ethyl phenylacetate should be much greater than that actually found. The difference must be due to the influence of phenyl through some type of steric hindrance which requires an energy of activation. The same reasoning then applies to ethyl hydratropate and ethyl phenylethylacetate; the decrease in E due to +I of the phenyl is counteracted by the steric effect.

Although for ethyl phenylacetate this latter effect accounts for some 900 cal. (the difference between-1500cal. estimated for the inductive effect and the change in E actually found for phenyl substitution, cf. Table XX), for ethyl hydratropate and ethyl phenylethylacetate its magnitude is much greater (2200 and2500 cal., respectively). This is in accord with what might be expected since in the latter two esters the phenyl is not the only substituent on the α-carbon atom. The additional substitution of methyl or ethyl on the same carbon atom would certainly enhance any steric effect due to the phenyl alone.

The steric effect must be quite large in ethyl diphenylacetate, since inductive effect, caused by the substitution of two phenyls in the α-position, operating alone would predict very rapid saponification. According to Dippy and Lewis (6) this -I effect accounts for the very high dissociation constant of diphenylacetic acid (cf. Table XVIII).

Ethyl Cyclohexylacetate

The kinetics of the saponification of ethyl cyclohexylacetate are strikingly similar to those for ethyl isovalerate and ethyl β-methylvalerate, as indicated in Table XXI. The fact that E for cyclohexylacetate is the same as for the two branched chain esters seems to give further indication that the inductive effects of aliphatic groups play no role in determining the reaction velocity, since the cyclization of the two branching ethyl groups in the cyclohexylacetate should certainly cause significant change in the polarization and hence in E, if inductive effects were an important factor in the saponification of these esters. Yet this is not found. The structural similarities of the three esters, moreover, make it seem most probable that the prime factor governing the influence of the substituents is a spatial one. In this connection it is interesting to note that ethyl di-isopropylacetate and ethyl di-cyclopentylacetate, either of which may be compared structurally with ethyl diphenylacetate, were found by von Braun and Fischer (19) to be practically unsaponifiable. That ethyl diphenylacetate saponifies at all, then, may be attributed solely to the magnitude of the -I due to two phenyls, which causes a lowering in E.

Table XXI

Ethyl ester	$10^3 k_{25}$	E
Cyclohexylacetate	0.509	15,600
Isovalerate (8)	.427	15,700
β-Methylvalerate	.411	15,700

Ethyl Cyclohexanoate(Ethyl ester of cyclohexane-carboxylic acid)

The kinetics of the saponification of ethyl cyclohexanoate are treated separately since these results give strong additional evidence that the ring structures postulated for aliphatic aicds and esters actually do exist. It has already been shown that the existance of two simultaneous rings in ethyl diethylacetate and higher di-substituted acids readily explains the very low saponification velocity and high energy of activation (as well, also, of the rates of esterification of the corresponding acids with methanol). For ethyl isobutyrate, in which no rings are possible, a much higher rate of reaction is found.

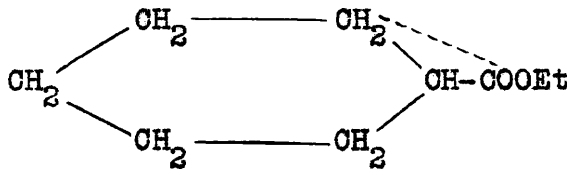
Now, any structural change which might be made in the acyl part of ethyl diethylacetate so as to prevent the formation of the postulated rings should produce a compound much like ethyl isobutyrate as far as reaction velocities are concerned. This could be easily detected as the difference between ethyl isobutyrate and ethyl diethylacetate is so marked.

Such a structural change is found when the two terminal carbon atoms of diethylacetic acid are joined by a methylene group. The six carbon atoms of the resulting ring do not lie in one place as is indicated by the existance of *cis* and *trans* forms of its disubstituted derivatives. Due to this the carbon valencies can occur with their natural angle, 109.5^{o}, and the ring is of the so-called strainless type. The mono-

substituted cyclohexanes exist in only one form, probably the cis (21), and there seems to be no reason to believe that any other significant changes other than that of the relative positions of the groups with reference to the carboxyl would be caused by this change.

The data for ethyl cyclohexanoate are in full agreement with these expectations (cf. Table XXII). The results of esterification studies which are included in Table XXII show again the parallelism between saponification and esterification.

It is quite apparent that the behavior of ethyl cyclohexanoate is much more like that of ethyl isobutyrate than that of ethyl diethylacetate. The value of k for this ester is about half that for ethyl isobutyrate, but it is more than twenty times as great as k for ethyl diethylacetate. Exact agreement with ethyl isobutyrate is not expected. A model of the cyclohexanoate molecule shows that the structure is such that there exists the possibility of a ring as indicated below.



If this were true, closer agreement would be expected with ethyl methylethylacetate than with ethyl isobutyrate. Furthermore, even if the geometry of the molecule does not permit full formation of this ring, it is quite certain that considerable steric hindrance does occur in this region. The result

Table XXII

Ethyl ester	$10^3 k_{25}$(sapon.)	E	k_{20}(esterification of the acid in methanol)	E (18)
Isobutyrate	0.801 (8)	15,000(16)	0.0147	9,800
Cyclohexanoate	.360	15,600	.00886	10,000
Diethylacetate	.0154	17,200	.000351	12,400

of this hindrance would be in the same direction but of a smaller magnitude than of a ring. Actually, the values for ethyl cyclohexanoate are intermediate between those for ethyl isobutyrate and ethyl methylethylacetate (cf. Table IV).

The difference in kinetics noted in Table XXII might be attributed to an alteration of inductive effect due to the union of the two ethyl groups to form the cyclohexyl ring. This is not likely, since, as has already been pointed out, there are no significant differences in the kinetics of saponification of ethyl cyclohexylacetate, ethyl isovalerate and ethyl β-methylvalerate. Furthermore, if any inductive effect may be attributed to the cyclohexyl group, it would undoubtedly be $+ \underline{I}$; then one would expect ethyl cyclohexanoate to saponify considerably slower, with a higher activation energy, than ethyl cyclohexylacetate. Actually this is not found.

SUMMARY

For the saponification of the ethyl esters of monocarboxylic aliphatic acids in 85% aqueous ethanol it has been shown that:

1. Inductive effects of alkyl groups are not significant in determining the saponification kinetics.

2. For all normal aliphatic esters E is, within experimental error, constant. In ascending the homologous series k decreases up to ethyl butyrate and assumes an essentially constant value beyond that member.

3. Substitution of a methyl group affects k only when such substitution occurs in an α or β-position, but not when in the γ-position.

4. Ethyl diethylacetate and higher α-disubstituted ethyl esters saponify much more slowly than other branched chain esters.

5. The values of k and E for ethyl cyclohexylacetate are essentially the same as for ethyl isovalerate and for ethyl β-methylvalerate which have similar structures.

6. Substitution of a phenyl group at the end of an alkyl chain increases reaction velocity by virtue of the negative inductive effect of the phenyl group.

7. When substituted in an α-position the phenyl group decreases k and increases E chiefly through its steric

effect which may be partially counteracted by the polarization of the phenyl group.

8. The effect of aliphatic substituents on the kinetics of saponification of these esters is parallel to what has been found for esterification of the corresponding acids in methanol.

9. Associated with increased steric effect is an increase in energy of activation.

The resultsof this research are unified on the basis of the postulate of the presence of a four carbon-atomed ring formed with the oxygens of the carbonyl group by hydrogen bonding which was proposed by Smith (15) (16) to explain the results of esterification studies. The kinetics of the saponification of ethyl cyclohexanoate (ethyl ester of cyclohexanecarboxylic acid) are in agreement with this concept.

APPENDIX I

Preparation of γ-Phenylbutyric Acid

γ-Phenyl-n-propyl bromide:

$$3\ C_6H_5(CH_2)_2CH_2OH + PBr_3 \longrightarrow 3\ C_6H_5(CH_2)_2CH_2Br + P(OH)_3$$

In a two-liter three-neck flask provided with a vertical condenser, a dropping funnel and a stirrer connected through a mercury seal was placed 478.5 g. (1.77 moles) of phosphorous tri-bromide. Over a period of two hours 461.5 g (3.38 moles) of γ-phenyl-n-propyl alcohol was added with constant stirring. Reaction occurred with evolution of heat, and after all the γ-phenyl-n-propyl alcohol had been added the mixture was refluxed on a water-bath for one hour, whereupon the solution became cloudy. The mixture was poured over a large quantity of cracked ice. The emulsion which formed was then extracted with ether, and the ether layer, after being washed with sodium bicarbonate solution and dried over fused calcium chloride, was distilled from a one-liter Claisen flask until the temperature of the vapor rose to 68°. Arrangements for vacuum distillation were then attached and the residue of γ-phenyl-n-propyl bromide was distilled off into a separate receiver under a pressure of about 28 mm. The amount of product was 560 g. (2.81 moles) which is 83% of the theoretical yield.

γ-Phenylbutyric acid:

$$C_6H_5(CH_2)_2CH_2Br + Mg \longrightarrow C_6H_5(CH_2)_2CH_2MgBr$$

$$2\ C_6H_5(CH_2)_2CH_2MgBr + 2\ CO_2 + H_2SO_4 \longrightarrow$$

$$C6H_5(CH_2)_3COOH + MgSO_4 + MgBr_2$$

Sixty-five g. (2.71 moles) of activated magnesium turnings and 1200 ml. of anhydrous ether was placed in a dry two-liter three-neck flask which was provided with a vertical condenser, a mechanical stirrer connected through a mercury seal and a dropping funnel. To this was added, with stirring, 560 g. (2.81 moles) of γ-phenyl-n-propyl bromide over a period of one hour and forty minutes. Reaction started readily, and after all the magnesium had dissolved the mixture was refluxed with stirring for one-half hour. The solution was then poured over a large quantity of cracked "Dry Ice"; a gray, viscous mass with a faint skunk-like odor formed.

After all the "Dry Ice" had disappeared dilute (1-1) sulphuric acid was added until the solution became acidic to litmus. A brownish ether layer above contained the γ-phenylbutyric acid, while a white precipitate of magnesium sulphate settled to the bottom. The ether layer was separated, and the aqueous layer was extracted twice with ether. The combined ether layers were neutralized with potassium carbonate, and the aqueous layer was separated and extracted with ether to remove non-acidic impurities. Upon acidification of the aqueous layer with dilute (1-1) sulphuric acid γ-phenylbutyric acid rose to the surface as a light yellow oil. This was extracted with and crystallized from benzene. The product was in the form of yellowish platelets; it analyzed 98% acid by titration with standard base. The yield was 187.5 g.

(1.14 moles) or 41% of the theoretical amount.

The crude γ-phenylbutyric acid this obtained was neutralized; a large excess of water was added and distilled off. A considerable amount of impurity came over with the steam. The residue was then extracted with benzene to remove any non-acidic impurities. It was then acidified, and the acid extracted with benzene and distilled in a five-foot Vigreux column at a pressure of 10 mm. The pure fractions analyzed 99.8% by titration and melted at 51.2°.

Referance: Rupe, Ber., 43, 177 and 1233 (1910).

APPENDIX II

Preparation of δ-Phenylvaleric Acid

$$CH_2(COOC_2H_5)_2 + C_2H_5ONa + n\text{-}C_6H_5(CH_2)_3Br \longrightarrow$$

$$C_6H_5(CH_2)_3CH(COOC_2H_5)_2 + C_2H_5OH + NaBr$$

$$C_6H_5(CH_2)_3CH(COOC_2H_5)_2 + 2\ H_2O \longrightarrow$$

$$C_6H_5(CH_2)_3CH(COOH)_2 + 2\ C_2H_5OH$$

$$C_6H_5(CH_2)_3CH(COOH)_2 \longrightarrow C_6H_5(CH_2)_4COOH + CO_2$$

A one-liter three-neck flask was provided with a vertical condenser, a dropping funnel and a mechanical stirrer, and the apparatus was set in a water-bath so as to furnish cooling facilities in case reaction became violent. The flask was rinsed with alsohol, and then 350 ml. absolute ethanol (500 ml. per mole of sodium) was introduced. To this was carefully added 15.3 g. (0.66 moles) of sodium cut into small pieces. When all the sodium had reacted (if the flask becomes too cold a gel may form which can be redissolved by addition of a little ethanol or by gentle warming) 110 g. (0.67 moles; 2% excess) of diethyl malonate was added with stirring, and then 132 g. (0.66 moles) of γ-phenyl-n-propyl bromide was added very slowly. After some time mild reaction began as indicated by the precipitation of the white solid, sodium bromide (a). Stirring was continued under reflux on the water-bath until the solution became neutral. The alcohol was now distilled off until the temperature of the

(a) It is interesting to note that in this reaction the sodium bromide is white; in most malonic ester syntheses the precipitate is yellow in color.

vapor reached 110°; about 200 ml. of residue remained. One hundred ml. of water was added to this residue (if too much water is added troublesome emulsions may form), the mixture was swirled lightly, and the upper layer of γ-phenyl-n-propyl diethyl malonate was separated. The yield of crude product was 183 g. (0.65 moles). This is 98% of the theoretical yield.

Fifty-three g. (1.33 moles) of sodium hydroxide (a) was dissolved in 100 ml. water plus 100 ml. ethanol, and the mixture was then introduced into a one-liter three-neck flask. A vertical condenser was attached. The alcoholic solution was set to refluxing on a water-bath, and 183 g. (0.65 moles) of γ-phenyl-n-propyl diethyl malonate was slowly added when a white precipitate of the sodium salt formed. Reflux was continued for two hours, and the excess alcohol and water was then distilled off until the temperature of the boiling solution reached 95°. The residue was acidified with dilute (1-1) sulphuric acid, and the oily layer which formed was separated. (This γ-phenyl-n-propyl malonic acids forms emulsions with water very readily, and for this reason it must not be washed with water.)

In order to remove any last traces of water the acid was treated with 15 ml. of benzene which was then distilled off. After all the benzene and its water azeotrope had distilled over heating was continued, whereupon decarboxylation, accompanied by frothing, occurred. When decarboxylation was

(a) An uhsuccessful attempt was made to half-saponify the ester using half the required quantity of caustic, with the belief that the monobasic acid-ester might form which would possibly yield directly ethyl δ-phenylvalerate upon decarboxylation.

complete the residue in the flask was mixed with 75 ml. absolute ethanol and 1 ml. conc. sulphuric acid and transferred to the pot of a five-foot Vigreux column. This mixture was refluxed for two and one-quarter hours, after which it was fractionally distilled in vacuo. Approximately 71 ml. of pure, constant-boiling ethyl δ-phenylvalerate was obtained.

Reference: Borsche, Ber., 45, 620 (1912); v. Braun and Kruber, ibid., 387 (1912).

APPENDIX III

Preparation of Hydratropic Acid (Phenylmethylacetic Acid)

$$C_6H_5(CH_3)CHCHO + [O] \longrightarrow C_6H_5(CH_3)CHCOOH$$

One hundred eighty-two g. (1.21 moles) of hydratropic aldehyde was mixed with 451 g. (2.66 moles) of silver nitrate dissolved in water, and enough ethanol was added to make the mixture homogeneous. This solution was placed in a three-liter three-neck flask provided with a vertical condenser, a dropping funnel and a mechanical stirrer. Two hundred twenty-four g. (4.00 moles) of potassium hydroxide dissolved in water was then slowly added with constant stirring. A brown-black precipitate of silver oxide formed, and there was considerable evolution of heat. After all the potassium hydroxide had been added stirring was continued for one hour; the reaction mixture was then filtered through a Buechner funnel. Alcohol and water were distilled from the filtrate until the distillate became cloudy (probably due to steam distillation of some unchanged hydratropic aldehyde). The residue was extracted with benzene, and the aqueous layer acidified with dilute (1-1) sulphuric acid. The oily layer of hydratropic acid which formed was separated and fractionally distilled in a five-foot Vigreux column. About 60 ml. of pure product were obtained.

Reference: Delépine and Bonnet, Compt. rend., 149, 39 (1909).

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VITA

Harold Samuel Levenson was born in Allentown, Pa. on July 12, 1916 the son of Oscar H. and Annie May (Brobst) Levenson. He completed his elementary and secondary education in the schools of Allentown. On June 15, 1937 he received the degree Bachelor of Science in Chemical Engineering with Honors from Lehigh University, and on June 13, 1939 the same institution granted the degree Master of Science. He married Alice Augusta Nathan on June 26, 1938. He has taught General Chemistry and Qualitative Analysis for three years at Lehigh University in the capacity of Graduate Assistant. With Dr. Hilton A. Smith he is co-author of the following papers which appeared in the Journal of the American Chemical Society:
"Kinetics of the Saponification of the Ethyl Esters of Normal Aliphatic Acids"-Vol. 61, 1172 (May, 1939),
"The Saponification of Ethyl Esters of Aliphatic Acids" - Vol. 62, 1556 (June, 1940).
"Kinetics of the Saponification of the Ethyl Esters of Several Phenyl-Substituted Aliphatic Acids" - Vol. 62, 2324 (Sept., 1940).
"Kinetics of the Esterification of Cyclohexanoic Acid and of the Saponification of its Ethyl Ester" - Vol. 62, 2733 (Oct., 1940).
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