chloride. The moment for morpholine is found to be in rough agreement with the Sachse Z-form with the possibility of a small contribution from a less polar form such as the configuration allowing an internal N---H–O bond.

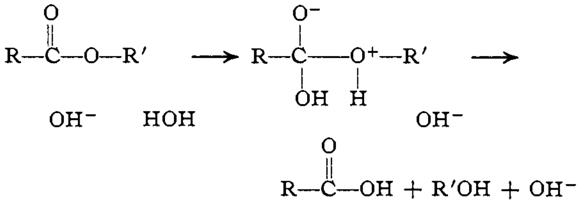
DURHAM, NORTH CAROLINA RECEIVED JUNE 18, 1940

[CONTRIBUTION FROM THE WILLIAM H. CHANDLER CHEMISTRY LABORATORY OF LEHIGH UNIVERSITY]

Kinetics of the Saponification of the Ethyl Esters of Several Phenyl Substituted Aliphatic Acids[1]

BY H. S. LEVENSON AND HILTON A. SMITH

The Lowry mechanism for saponification[2] proposes that the rate-determining step is the addition of hydroxyl to the carbonyl carbon atom of the ester to form an intermediate complex, decomposition of which leads to completion of reaction.



$$R\text{—}\overset{\overset{O}{\|}}{C}\text{—}O\text{—}R' \;\xrightarrow{\quad}\; R\text{—}\overset{\overset{O^-}{|}}{\underset{\underset{OH}{|}}{C}}\text{——}\underset{\underset{H}{|}}{O^+}\text{—}R' \;\xrightarrow{\quad}$$
$$OH^- \quad HOH \qquad\qquad OH^-$$
$$R\text{—}\overset{\overset{O}{\|}}{C}\text{—}OH + R'OH + OH^-$$

Electron sinks which tend to make the carbon atom more positive facilitate addition of the negative hydroxyl, thereby lowering the activation energy, most of which, probably, is required for addition of the hydroxyl.[3] The opposite is produced by electron release. Substituents in the ester molecule, then, affect the reaction velocity through their polarization and polarizability as well as steric effects.

When not part of a conjugated system the phenyl group acts as an electron sink, and this effect (negative inductive, $-I$) has been observed by Dippy and Lewis[4] in the dissociation constants of phenyl substituted monocarboxylic acids. Random data in the literature[5] indicate that this same effect operates in the saponification of esters, the effect of a phenyl substituent being to increase the reaction rate over that for the unsubstituted analog. In continuation of work on the kinetics of saponification there are reported here results obtained in a systematic study of several ethyl esters of phenyl substituted aliphatic acids.

Experimental

All the esters were prepared by esterification of absolute ethanol with the corresponding acid, using sulfuric acid as a catalyst. They were purified by distillation under reduced pressure in a 5 ft. (1.5 meter) Vigreux column, with the exception of ethyl diphenylacetate which was vacuum distilled in a 2 ft. (0.6 meter) Vigreux column. Each ester distilled at constant head temperature, and each sample used was shown, by the method of analysis previously employed,[6] to be, within the precision of the method, 100% pure.

Phenylacetic acid, hydrocinnamic acid, phenylethylacetic acid and **diphenylacetic acid** were obtained from Eastman Kodak Co. **γ-Phenylbutyric acid** was prepared by carbonation of the Grignard reagent of γ-phenylpropyl bromide by the method previously described.[7]

δ-Phenylvaleric acid and **cyclohexylacetic acid** were prepared from γ-phenylpropyl bromide and cyclohexyl bromide, respectively, by malonic ester syntheses carried out in the usual manner.[8]

Hydratropic acid (phenylmethylacetic acid) was prepared from hydratropic aldehyde[9] by oxidation with silver oxide in alkaline medium using the method described by Delépine and Bonnet.[10]

The reaction medium for the saponification experiments was 85% aqueous ethanol prepared in the manner already described.[11] The method of making velocity determinations was similar to that previously employed.[6,11]

Experimental Calculations and Results

The values of k were calculated from the second order reaction rate equation

$$k = x/at(a - x)$$

where a is the initial concentration of each reactant, and x is the concentration of each reactant at the time t. All the saponifications here reported were fast enough so as to make correction for reaction of the reagents with the Pyrex reaction bottles negligible. Table I gives the results

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[1] Most of the material in this paper was presented before the Boston meeting of the American Chemical Society, September 11, 1939.

[2] *Cf.* Waters and Lowry, "Physical Aspects of Organic Chemistry," D. Van Nostrand Co., New York, N. Y., 1937, Chap. XII.

[3] Newling and Hinshelwood, *J. Chem. Soc.*, 1360 (1936).

[4] Dippy and Lewis, *ibid.*, 1008 (1937).

[5] *Cf.*, for example, Kindler, *Ann.*, **452**, 90 (1927).

[6] Levenson and Smith, THIS JOURNAL, **62**, 1556 (1940).

[7] Smith, *ibid.*, **61**, 1176 (1939).

[8] The authors are greatly indebted to Mr. T. E. Ricketts for his aid in the preparation of the cyclohexylacetic acid.

[9] This aldehyde was purchased from Paragon Testing Laboratories, Orange, New Jersey.

[10] Delépine and Bonnet, *Compt. rend.*, **149**, 39 (1909).

[11] Smith and Levenson, THIS JOURNAL, **61**, 1172 (1939).

for a typical run, and the values of *k* for each ester are presented in Table II. These are the averages of individual rate constants obtained in each run between 20 and 80% reaction. The average error for each value of *k* is of the order of 2% or less.

TABLE I

SAPONIFICATION OF ETHYL δ-PHENYLVALERATE AT 45°

a = [NaOH] = [ester] = 0.0500 mole liter^{-1}

t, min.	x	10^3k, liter mole^{-1} sec.$^{-1}$
4	0.00625	11.9
8	.01057	11.2
14	.01593	11.1
23	.02187	11.3
37	.02760	11.1
55	.03242	11.2
87	.03729	11.2
130	.04061	11.1
	Average for 20–80% =	11.2

Figure 1 is a plot of log *k versus* $1/T$ from which the activation energies listed in column 7 of Table II were determined graphically. These were checked by the method of least squares and are reported to the nearest 100 cal.

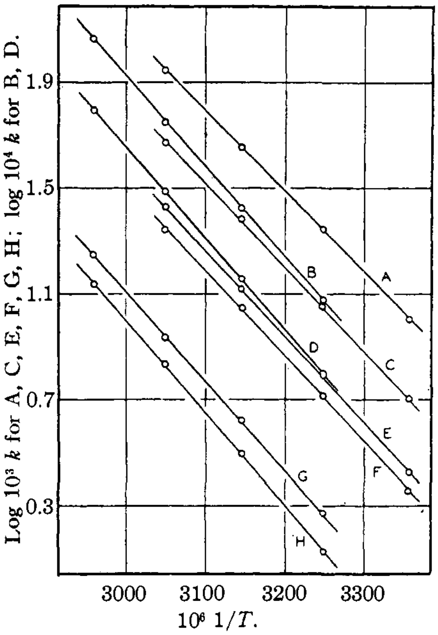

Fig. 1.—Temperature coefficients for saponification reactions: A, ethyl phenylacetate; B, ethyl cyclohexylacetate; C, ethyl hydrocinnamate; D, ethyl phenylethylacetate; E, ethyl γ-phenylbutyrate; F, ethyl δ-phenylvalerate; G, ethyl hydratropate; H, ethyl diphenylacetate.

TABLE II

REACTION RATE CONSTANTS FOR SAPONIFICATION OF ETHYL ESTERS OF PHENYL SUBSTITUTED ACIDS

For all esters, a = [NaOH] = [ester] = 0.0500 mole liter^{-1}

Ethyl ester	10^3k, l. mole^{-1} sec.$^{-1}$					
	t = 25°	t = 35°	t = 45°	t = 55°	t = 65°	E, cal. mole^{-1}
Phenylacetate	10.0	22.2	45.4	89.0		
	10.1	22.2	45.1	87.5		
Average	10.1	22.2	45.3	88.3		14,100
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		14,500
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		14,900
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		14,700
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	15,400
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	15,900
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	16,000
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	15,600

[a] For purposes of comparison these values are extrapolated from the tabulated data.

Discussion

To facilitate comparisons made in the discussion there are listed in Table III k_{25} and activation energies for saponification, under the same experimental conditions as used here, of several ethyl esters of aliphatic acids.

TABLE III

SAPONIFICATION OF ALIPHATIC ETHYL ESTERS

Ethyl ester	10^3k_{25}	E, cal. mole^{-1}
Acetate[11]	6.92	14,700
Propionate[11]	3.55	14,700
Butyrate and higher homologs[11,12]	1.83	14,900

Phenyl Substitution at the End of an Alkyl Chain.—The results for these esters are in accord with what would be expected on the basis of the $-I$ effect of the phenyl group. For ethyl phenylacetate and ethyl hydrocinnamate phenyl substitution has caused a lowering of E from its value for their aliphatic analogs. This effect is no longer found for ethyl γ-phenylbutyrate, and the activation energy for this ester as well as that for ethyl δ-phenylvalerate are both, within experimental error, the same as for ethyl butyrate and higher aliphatic esters. The data indicate the transmission of the negative inductive effect through an alkyl chain with decreasing magnitude as the chain length increases until when four carbon atoms intervene between the phenyl and the seat of reaction the effect becomes inconsequential.

It should be noted that, just as for straight chain aliphatic esters, the values of k decrease as the alkyl chain lengthens until, when a four carbon-atomed chain is reached, k appears to have approached an almost constant value.[13] This is in contrast to what is found in esterification (which for straight and branched chain aliphatic acids has been shown[6] to be analogous to saponification) for which phenylacetic, hydrocinnamic and γ-phenylbutyric acids all have essentially the same k values as for butyric and higher acids.[7]

Phenyl Substitution in the α-Position.—In every case, 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 IV.

TABLE IV

EFFECT OF α PHENYL SUBSTITUTION ON SAPONIFICATION OF ETHYL ESTERS

α Substitution	% change in $k_{25°}$ (+ = increase)	ΔE, cal. mole^{-1}
Acetate ⟶ Phenylacetate	+46	− 600
Propionate ⟶ Hydratropate	−77.5	+ 700
Butyrate ⟶ Phenylethylacetate	−86	+1000
Phenylacetate ⟶ Diphenylacetate	−94.5	+1900

Inductive effect cannot explain these changes; in fact, inductive effect *per se* would predict precisely the opposite.[14] A combination of steric effect with the $-I$ of the phenyl group gives probably the best interpretation.

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^{-1}) 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.[4] 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 −1500 cal. estimated for the inductive effect and the change in E actually found for phenyl substitution, *cf.* Table IV) for ethyl hydratropate and ethyl phenylethylacetate its magnitude is much greater (2200 and 2500 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[4] this $-I$ effect accounts for the very high dissociation constant of diphenylacetic acid (in aqueous solu-

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(12) Evans, Gordon and Watson, *J. Chem. Soc.*, 1439 (1938).

(13) Kindler's data[5] on the saponification of the ethyl esters of phenylacetic, hydrocinnamic and γ-phenylbutyric acids in 87.8% ethanol at 30° show the same trend in k.

(14) 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 $-I$.

tion at 25° $10^5 K_{(\text{therm})} = 11.5$, compared to 1.76 for acetic acid and 4.88 for phenylacetic acid).[15] It may be mentioned here that the high dissociation constant for diphenylacetic acid might also be explained as a steric phenomenon along the lines of reasoning of Smith and McReynolds.[16]

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 V.

TABLE V

KINETICS OF SAPONIFICATION

Ethyl ester	10^3k_{25}	E, cal. mole^{-1}
Cyclohexylacetate	0.509	15,600
Isovalerate[12]	.427	15,700
β-Methylvalerate[6]	.411	15,700

In consideration of the structural similarities of the three esters, it seems probable that here the prime factor governing the influence of substituents is a spatial one. In this connection it is interesting to note that ethyl diisopropylacetate and ethyl dicyclopentylacetate, either of which may be compared structurally with ethyl diphenylacetate, were found by von Braun and Fischer[17] 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.

The general results given here seem to warrant the statement that although the phenyl group does have a negative inductive effect, this may be subservient to a much more powerful steric influence on both reaction rate and activation energy. By analogy it would seem likely that substitution of various alkyl groups in aliphatic esters affects saponification velocity chiefly through their steric effect, rather than by virtue of differences in the positive inductive effect ($-I$) usually attributed to them.

Summary

1. The kinetics of saponification in 85% aqueous ethanol have been studied for ethyl phenylacetate, ethyl hydrocinnamate, ethyl γ-phenylbutyrate, ethyl δ-phenylvalerate, ethyl hydratropate, ethyl phenylethylacetate, ethyl diphenylacetate and ethyl cyclohexylacetate at four temperatures.

2. Evidence of the negative inductive effect attributed to phenyl is indicated.

3. The steric influence of phenyl in the α-position upon the rate and energy of activation for the saponification of these esters is of greater import to the kinetics of the reaction than is any polarization effect due to phenyl.

4. Analogy suggests that alkyl groups substituted in the acyl part of esters of aliphatic acids affect saponification kinetics chiefly through their steric influence.

BETHLEHEM, PA.

RECEIVED JULY 5, 1940

[15] Dippy and Williams, *J. Chem. Soc.*, 161, 1888 (1934).

[16] Smith and McReynolds, THIS JOURNAL, **61**, 1965 (1939).

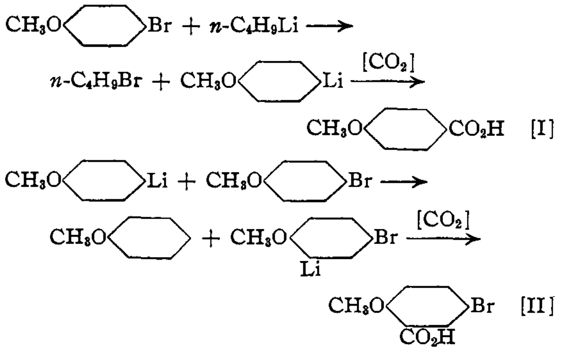
[17] Von Braun and Fischer, *Ber.*, **66**, 101 (1933).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE, AND PANHANDLE AGRICULTURAL AND MECHANICAL COLLEGE]

Some Interconversion Reactions of Organolithium Compounds

BY HENRY GILMAN, WRIGHT LANGHAM AND FRED W. MOORE

The Two-stage Metalation of Some Aryl Halides.—Evidence was presented in an earlier paper for the two-stage metalation of 2-bromodibenzofuran.[1a,b] A similar mechanism is also involved with *p*-bromoanisole and *p*-iodoanisole in their reactions with *n*-butyllithium.[1b]



That is, interconversion first takes place in ac-

[1] (a) Gilman, Cheney and Willis, THIS JOURNAL, **61**, 951 (1939). (b) Gilman, Langham and Willis, *ibid.*, **62**, 346 (1940). (c) The only cases are those noted recently with 2,4,5-triphenyl-3-chlorofuran and phenylethynyl chloride in studies by Messrs. Melstrom and Haubein. (d) Wittig, Pockels and Dröge, *Ber.*, **71**, 1903 (1938); see, also, Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938). (e) Professor Wittig (private communication) has examined the reaction of the halogenoanisoles with phenyllithium. (f) Marvel, Hager and Coffman, THIS JOURNAL, **49**, 2323 (1927).