between salts of the type $COOH(CH_2)_nCOONa$ and $CH_3(CH_2)_nCOONa$, a difference which is marked in spite of the anomalous behavior of sodium caproate[6] at high concentration (probably due to micelle formation). Along with this difference between the two types of salts are to be noted the very low values of the activity coefficients of the salts now under investigation, suggesting that the hydrogen malonate, succinate and adipate ions belong to the same category as the nitrate, chlorate and primary phosphate ions. Thus, although "localized hydrolysis" may be a factor resulting in decreasing dispersion of the curves of the sodium and potassium salts as we proceed from the malonate to the adipate, there must be another factor of larger magnitude which lowers the curves of both the sodium and the potassium salts. It is difficult to explain this effect for the nitrate ion and it is equally difficult to understand why it should occur with ions of the hydrogen malonate type; furthermore, it is difficult to find a common factor between nitrates and malonates apart from their low activity coefficients.

I wish to thank Professor N. S. Bayliss for his kind permission to use the facilities of his department.

Summary

Isopiestic measurements have been made on solutions of the primary sodium and potassium salts of malonic, succinic and adipic acid and the osmotic and activity coefficients calculated.

Although these salts are derived from weak acids, their activity coefficient curves are in the order Na > K; in this respect they differ from the sodium salts of monobasic fatty acids. Moreover, their activity coefficients are very low and have an unexpected resemblance in this respect to sodium and potassium nitrate and the primary phosphates.

NEDLANDS, WESTERN AUSTRALIA
RECEIVED FEBRUARY 4, 1948

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(6) E. R. B. Smith and R. A. Robinson, *Trans. Faraday Soc.*, **38**, 70 (1942).

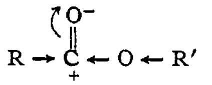
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

Effect of Structure on Reactivity.[1] I. Ammonolysis of Esters with Special Reference to the Electron Release Effects of Alkyl and Aryl Groups

BY MAXWELL GORDON,[2] JOHN G. MILLER AND ALLAN R. DAY

In the interest of augmenting present knowledge of the effect of structure on reactivity, it was decided to measure the rates of ammonolysis of several homologous series of esters. Although several reports have appeared in the literature on the effect of structural variations on the rate of ammonolysis of esters, they have embraced only limited numbers of esters, the possibility of ester interchange in working in alcoholic solution was often overlooked, no calculations of rate constants or activation energies were made in many cases, and the conclusions derived from these studies were, in some instances, conflicting. Most of the references in the literature on this subject have been discussed by Gorvin.[3] Additionally it has been shown by Komatsu and Nakayama[4] that ethyl phenylacetate reacts with ammonia fifteen times as rapidly as does ethyl benzoate.

The present study of the ammonolysis of esters was undertaken in an effort to show the effect of various R and R′ groups in the ester RCOOR′, with special emphasis on tracing the electron release effects in various homologous series. Most of the mechanisms which have been postulated for ammonolysis or hydrolysis of esters[5] indicate that the reactivity of the ester depends on the polarization of the carbonyl group in the ester which then provides the center for nucleophilic attack at the carbon of the carboxyl group. From this representation it may be seen that the greater

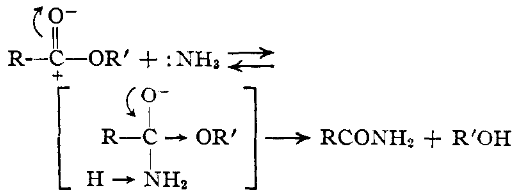


$$R \rightarrow \overset{O^-}{\underset{+}{\overset{\|}{C}}} \leftarrow O \leftarrow R'$$

the electron release of the R or R′ group, the slower should be the rate of ammonolysis of the ester since the positive charge on the carbonyl carbon would be reduced in magnitude.

One may consider two possible mechanisms for the ammonolysis of esters

(I)[5,6]



$$R-\overset{O^-}{\underset{+}{\overset{\|}{C}}}-OR' + :NH_3 \rightleftharpoons \left[\begin{matrix} & O^- & \\ R- & C & \rightarrow OR' \\ H \rightarrow & NH_2 & \end{matrix}\right] \longrightarrow RCONH_2 + R'OH$$

Betts and Hammett[7] suggested that both the am-

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[1] From a thesis submitted by M. Gordon to the Department of Chemistry and Chemical Engineering of the University of Pennsylvania, Dec. 1947, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] National Institute of Health Predoctoral Research Fellow, 1946–1948.

[3] Gorvin, *J. Chem. Soc.*, 732 (1945).

[4] Komatsu and Nakayama, *J. Chem. Soc. (Japan)*, **54**, 558–569 (1933).

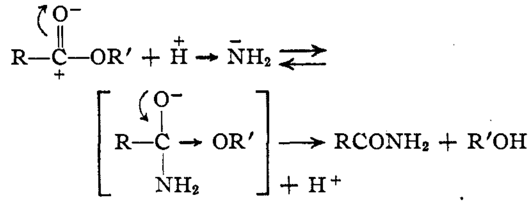
[5] H. Meyer, *Monatsh.*, **27**, 31 (1906); Holmberg, *Ber.*, **45**, 2997 (1912); Ingold and Ingold, *J. Chem. Soc.*, 758 (1932); Polanyi and Szabo, *Trans. Farad. Soc.*, **30**, 508 (1934); Day and Ingold, *ibid.*, **37**, 689 (1941); Watson, *ibid.*, **37**, 712 (1941).

[6] Chattaway, *J. Chem. Soc.*, 355 (1936).

[7] Betts and Hammett, THIS JOURNAL, **59**, 1568 (1937).

monia amide ion and molecular ammonia are the attacking reagents in ammonolysis.

(II)



Both mechanisms involve the addition of a nucleophilic agent to the carbonyl carbon atom. The fact that the presence of a polar (ionizing) solvent is necessary for ammonolysis to occur readily suggests that (II) is more probable than I. It is not necessary to postulate free amide ions $(NH_2)^-$ although they may exist to some extent. It is possible that through hydrogen bonding the polarization of the H—NH_2 bond may be increased to the point that it simulates ionization.

Experimental

It was originally hoped to carry out the ammonolysis of esters in anhydrous media, but preliminary experiments showed that ammonolysis of most esters will not proceed at a useful rate in anhydrous dioxane or methanol. This result confirms the work of Grant and Hinshelwood[8] and others.[9]

As Gorvin[3] has noted, aqueous ammonia is not suitable for accurate kinetic studies owing to the complicating factors introduced by the low solubility of the ester. This difficulty may be overcome by the use of suitable organic diluents in the reaction mixtures. The principal solvent employed in this study was 1,4-dioxane. This compound was used for all series of esters except where all of the esters of a series contained the same alcohol component, in which case that alcohol was used as the diluent. Alcohol was used as a diluent where possible because ammonolysis proceeds roughly twice as rapidly in primary alcohols as in dioxane, provided water is present in each case. Dioxane was selected for use as a result of a process of elimination. Alcohols, generally speaking, were unsatisfactory due to the possibility of ester interchange. There was no method immediately evident for ascertaining the extent of this side reaction. Other solvents react with either the esters or ammonia, or interfere with the subsequent titrations of the reaction mixtures, or are not soluble in water.

In the establishment of conditions for this study three major experimental factors had to be considered: (1) the kinetics of the reaction, which involves making the rate of reaction great enough to minimize the experimental errors involved in the measurements; (2) miscibility of the components, which means adjusting concentrations so that the entire series of reaction mixtures is kept homogeneous; (3) stability of ammonia solutions, which involves addition of sufficient water to avoid loss of ammonia in the course of the manipulations of the study. Since the above three factors are more or less mutually exclusive, it was only on the basis of a great deal of trial and error that a satisfactory set of conditions was arrived at that would hold for substantially all of the esters employed.

The dioxane used, a product of Carbide and Carbon Chemicals Corp., was purified by distillation from sodium metal. Alcohols used were freed from water by the method of Lund and Bjerrum.[10] Most of the esters used[11] were available commercially with the exception of methyl isobutyrate, methyl trimethylacetate, *n*-propyl benzoate, *t*-butyl benzoate, *t*-butyl acetate, β-naphthyl acetate, and *t*-butyl lactate. These esters were synthesized by a variety of methods, all of which have been described in the literature. Of special interest is the method of Richard[12] for esterifying sterically hindered acids. This procedure is seldom encountered in contemporary chemical literature.

An azeotrope of methanol and methyl trimethylacetate was encountered which is believed not to have been hitherto described. Its composition was 12.8% of ester by weight; b. p. 65.0° at 760 mm.

The esters, whether synthesized or obtained commercially, were dried over magnesium sulfate and fractionated in all-glass apparatus using an efficient column. The high boiling esters were distilled under reduced pressure. Refractive indices were used to ascertain final purity of esters employed.

Boiling points or melting points and refractive indices (D line) of the esters used were as follows: methyl acetate, b. p. 57.1° at 755 mm., n^{20}D 1.3610; ethyl acetate, 77° at 760 mm., 1.3728 at 20°; *n*-propyl acetate, 101–101.5° at 750 mm., 1.3844, 20°; isopropyl acetate, 88.5–89.0° at 750 mm., 1.3771, 20°; *n*-butyl acetate, 126.5° at 750 mm., 1.3938 at 20°; isobutyl acetate, 116.5–117.0° at 750 mm., 1.3900 at 20°; *s*-butyl acetate, 112.0–112.5° at 755 mm., 1.3885 at 20°; *t*-butyl acetate, 97.5–98.0° at 755 mm., 1.3860 at 20°; *n*-amyl acetate, 148.0–148.5° at 755 mm., 1.4025 at 20°; benzyl acetate, 93° at 7 mm., 1.5020 at 20°; phenyl acetate, 78° at 10 mm., 1.5033 at 20°; vinyl acetate, 69–70° at 755 mm., 1.3941 at 20°; α-naphthyl acetate, m. p. 44–45°; β-naphthyl acetate, m. p. 68°; methyl benzoate, 85° at 10 mm., 1.5170 at 20°; ethyl benzoate, 90° at 10 mm., 1.5058 at 20°; *n*-propyl benzoate, 101.0–101.5° at 9 mm., 1.5000 at 20°; isopropyl benzoate, 94° at 10 mm., 1.4947 at 20°; *t*-butyl benzoate, 105° at 16 mm., 1.4896 at 25°; phenyl benzoate, m. p. 70°; benzyl benzoate, 110° at 0.5 mm., 1.5685 at 20°; methyl formate, 31.5° at 760 mm., 1.3438 at 20°; methyl propionate, 79° at 750 mm., 1.3770 at 20°; methyl isobutyrate, 92.0–92.5° at 755 mm., 1.3840 at 20°; methyl trimethylacetate, 99.5–100.5° at 760 mm., 1.3908 at 20°; methyl crotonate, 119–120° at 755 mm., 1.4250 at 20°; methyl phenylacetate, 79° at 5 mm., 1.5090 at 16°; methyl lactate, 50° at 17 mm., 1.4140 at 20°; ethyl lactate, 54° at 12 mm., 1.4131 at 20°; *n*-propyl lactate, 71° at 20 mm., 1.4170 at 20°; isopropyl lactate, 51° at 8 mm., 1.4102 at 20°; *n*-butyl lactate, 77° at 13 mm., 1.4215 at 20°; isobutyl lactate, 58° at 3.5 mm., 1.4184 at 20°; *s*-butyl lactate, 42° at 1 mm., 1.4168 at 20°; *t*-butyl lactate, 40° at 6 mm., 1.4085 at 30°; *n*-amyl lactate, 66° at 1 mm., 1.4261 at 20°; allyl lactate, 55° at 3 mm., 1.4369 at 20°; *n*-butyl hydracrylate, 69° at 0.5 mm., 1.4288 at 20°.

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[8] Grant and Hinshelwood, *J. Chem. Soc.*, 1351 (1933).

[9] Very recent work in this laboratory indicates that by working in ethylene glycol and related compounds, amides can be obtained in good yield under anhydrous conditions. This material is part of the next paper of this series which will be ready for publication in the near future.

[10] Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

[11] We are indebted to Dr. C. H. Fisher of the Eastern Regional Laboratory, U. S. Department of Agriculture, for generous samples of lactic acid esters.

[12] Richard, *Ann. chim. phys.*, **21**, 323–406 (1910).

TABLE I

BIMOLECULAR REACTION RATES FOR AMMONOLYSIS OF ACETIC ACID ESTERS AT 25°

Time, hr.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.
Acetate →	Methyl		Ethyl		*n*-Propyl		Isopropyl		*n*-Butyl		Isobutyl	
100	33.0	0.00148	13.4	0.000530	12.1	0.000504	5.2	0.000231	7.2	0.000273	5.1	0.000201
200	50.0	.00142	22.0	.000450	19.2	.000436	7.5	.000202	11.3	.000240	7.0	.000166
300	62.0	.00140	28.1	.000420	24.6	.000370	11.5	.000180	13.6	.000209	9.5	.000153
400	72.0	.00138	32.6	.000390	28.5	.000302	14.5	.000156	16.0	.000178	11.1	.000136
500	80.6	.00140	36.0	.000380	31.6	.000240	16.0	.000135	17.3	.000146	14.0	.000128
Acetate →	*s*-Butyl		*t*-Butyl		*n*-Amyl		Benzyl		α-Naphthyl		β-Naphthyl	
100	5.0	0.000146	4.0	0.000111	7.0	0.000258	21.9	0.000960	1.6	0.000070	1.9	0.000082
200	5.5	.000122	4.0	.000100	11.0	.000230	36.3	.000950	2.5	.000065	2.8	.000070
300	5.9	.000101	4.5	.000090	13.0	.000205	48.0	.000950	3.2	.000060	3.2	.000060
400	6.0	.000090	5.3	.000080	16.3	.000179	58.0	.000950	3.8	.000054	3.7	.000050
500	6.2	.000080	5.3	.000068	18.1	.000154	67.4	.000950	4.2	.000049	4.1	.000046

Phenyl acetate,[a] 0.5 hr., ammonalysis 86.6%, const. 2.02

Vinyl acetate,[a] 0.5 hr., ammonalysis 75.3%, const. 1.34

[a] Ammonolysis was too rapid for a satisfactory rate study, time, 0.5 hour.

In carrying out the ammonolyses, equivalent molar quantities of the various esters were measured into 10-ml. glass ampoules by means of a 1-ml. glass syringe graduated in 0.01 ml. subdivisions and fitted with a #16 gage 3-inch stainless steel needle. The use of the above device made possible the introduction of the esters into the ampoules without wetting the necks of the containers. It was found by a series of control experiments that the quantities of ester delivered by this method were reproducible with an error of less than one-tenth of one per cent. In the case of the volatile esters the opening of the ampoule was tightly closed by means of half a gelatin capsule of appropriate size, then the needle was pushed through the top of the capsule into the ampoule. In all cases the ampoules were closed off by means of intact capsules after the introduction of the esters and were then chilled in ice.

Reproducible results were obtained in the manipulation of the aqueous dioxane–ammonia solutions only by filling eight ampoules from each 100-ml. buretful of solution, using the first and last 10 ml. of each buretful as controls. These control portions of ammonia solution were run into 4% boric acid solution and titrated directly with half-normal hydrochloric acid using methyl red as the indicator. Following the introduction of both ester and ammonia the ampoules were again cooled in ice and then rapidly sealed off in a hot flame, first removing the gelatin closure. This chilling procedure cut down the loss of ammonia during the sealing operation and reduced the likelihood of leaks developing in the sealed ampoules. The ampoules were then shaken thoroughly and placed in a constant temperature bath.

A series of duplicate reaction mixtures was started for each ester. At intervals the ampoules were removed from the thermostat and again chilled. The ampoules were then opened, rinsed into 4% boric acid solution, and titrated directly with standard acid as in the case of the blank runs. The accuracy of the method was ascertained by setting up a series of reaction mixtures and titrating them at intervals as before, but omitting the ester. These blank runs showed that the error in the rest of the method was less than that involved in titrating the solutions.

The amount of competing hydrolysis occurring in the ammonolysis of the acetates was determined by the method of Pucher[13] as modified by French.[14] Results of this direct analytical method corroborated the results obtained in estimating ammonia consumed by difference.

Determination of activation energies for methyl acetate and the lactates was carried out by setting up parallel reaction mixtures of the various esters and running half of them at 25° and the rest at 30 or 35°. Determination of the activation energies for the benzoates, for the methyl esters other than acetate and formate, and for the acetates above methyl, was omitted because their low reaction velocity made the accurate measurement of temperature coefficients impossible. The ammonolysis of methyl formate proceeded too rapidly for the determination of activation energies with any accuracy.

Sources of Error

A major consideration in working with aqueous ammonia solutions is the possibility of simultaneous hydrolysis and ammonolysis of the ester. This matter will be discussed after presentation of the data.

The possibility of reversibility of the reaction was eliminated when it was found that acetamide will not react with alcohols in aqueous dioxane-ammonia solutions at the temperatures of the experiments. Other side reactions such as the formation of amines or double amides have been ruled out by various investigators. This aspect of the problem has been fully discussed by Betts and Hammett.[7] The possibilities for manipulative error were discussed in the description of the experimental method employed, and it is believed that the maximum error for any single determination is about 2%. The over-all errors persisting in any of the rate constants obtained graphically probably amount to less than 5%.

Results

The values found for the second order rate constants in the ammonolysis of esters of acetic acid at 25° are listed in Table I. Also tabulated are the percentages of total reaction for the times indicated. The amount of ester employed in all of the reaction mixtures of this investigation was 0.007 mole per 10 ml. reaction vessel, or 0.7 mole per liter. The ammonia concentration in every

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[13] Pucher, Vickery and Leavenworth, *Ind. Eng. Chem.*, *Anal. Ed.*, **7**, 152 (1935).

[14] French, Johnson and Ratekin, THIS JOURNAL, **58**, 1346 (1936).

TABLE II

RELATIVE REACTION RATES FOR AMMONOLYSIS OF ACETIC ACID ESTERS AT 25°

Ester	100 hr.	200 hr.	300 hr.
Phenyl acetate[a]	1365	1422	1443
Vinyl acetate[a]	909	944	957
Methyl acetate	1.00	1.00	1.00
Benzyl acetate	0.649	0.662	0.678
Ethyl acetate	.358	.317	.300
n-Propyl acetate	.341	.307	.264
n-Butyl acetate	.185	.169	.149
n-Amyl acetate	.174	.163	.148
Isopropyl acetate	.156	.142	.128
Isobutyl acetate	.136	.117	.109
s-Butyl acetate	.0986	.0859	.0721
t-Butyl acetate	.0750	.0655	.0643
β-Naphthyl acetate	.0554	.0493	.0429
α-Naphthyl acetate	.0473	.0458	.0429

[a] Reaction has gone to completion by the time 100 hours is reached, but this ester is included for purposes of comparison.

TABLE III

BIMOLECULAR REACTION RATES FOR AMMONOLYSIS OF BENZOATES AT 25°

Ester	Rate constant	Comparative rate
Phenyl benzoate[a]	0.0620	376
Methyl benzoate	.000165	1.00
Benzyl benzoate[b]	.000087	0.527
Ethyl benzoate	.000084	.509
n-Propyl benzoate	.000065	.391
Isopropyl benzoate	.000056	.341
t-Butyl benzoate	.000019	.116

[a] Owing to the high molecular weight of this ester only 0.467 mole/l. was used. Any greater amount led to separation of layers. Reaction time in this case was twenty-four hours. [b] 0.467 mole/l. of this ester was used.

case was between 2.5 and 2.8 moles/liter. All of the reaction mixtures contained ten moles of water/liter. The diluent used for this series was 1,4-dioxane. The rate constants are bimolecular and are expressed in liters/mole/hour.

Table II lists the relative rate constants for the acetates. All of the rate constants have been divided through by the corresponding rate for methyl acetate so that the latter always has the value unity in the tabulation, and the comparative rates of the other esters may be seen accordingly.

The ammonolysis of benzoic acid esters proceeded so slowly that, in most cases, a satisfactory kinetic study was impractical. The differences in ammonia content found on successive titrations over a period of several days were often so small as to be within the limits of experimental error of the method. Accordingly, only one titration was carried out on each ester after reacting with aqueous dioxane–ammonia for 618.5 hours. Dioxane was used as the diluent. Bimolecular rate constants and comparative rates of ammonolysis of the benzoates are given in Table III.

Second order rate constants and percentages of total reaction in the ammonolysis of lactic acid esters at 30° are listed in Table IV. The diluent for this series was dioxane.

The values found for the second order rate constants and the percentages of total reaction in the ammonolysis of the methyl esters of various acids at 25° are listed in Table VI. The diluent used for this series was absolute methanol.

The compilation in Table VIII is taken from Tables II, III and V in an effort to determine what correlation may be found between structure and reactivity.

The extent of ammonolysis and hydrolysis of acetic acid esters is shown in Table IX.

From the temperature coefficients of ammonolysis an approximate evaluation of the activation energies was possible using the integrated form of the Arrhenius equation. Calculations of PZ factors from the equation $k = PZe^{-A/RT}$ showed that errors in the values of activation energies were too great to permit the use of entropy changes to show the validity of structure–reactivity correlations.

TABLE IV

BIMOLECULAR REACTION RATES FOR AMMONOLYSIS OF LACTIC ACID ESTERS AT 30°

Time, hr.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.
Lactate →	Methyl		Allyl		Ethyl		*n*-Propyl		*n*-Butyl			
10	55.0	0.0397	54.0	0.0370	25.9	0.0155	16.6	0.00780				
20	78.0	.0372	77.5	.0370	37.0	.0135	26.1	.00760				
30	88.0	.0363	88.0	.0362	45.2	.00950	33.6	.00740	34.0	.00740		
50	94.0	.0361			57.8	.00800	45.0	.00710	46.0	.00710		
100					78.5	.00780	66.2	.00610	66.1	.00608		
150									75.1	.00470		
Lactate →	*n*-Amyl		Isobutyl		Isopropyl		*s*-Butyl		*t*-Butyl		*n*-Butyl hydracrylate[a]	
30	32.5	0.00504	28.2	0.00493	11.1	0.00242	11.0	0.00200	1.10	0.00042	8.5	0.00167
50	42.0	.00500	38.3	.00483	16.0	.00188	16.1	.00184	1.79	.00040	12.0	.00140
100	60.9	.00497	57.5	.00460	25.2	.00137	21.0	.00132			18.4	.00100
150	76.0	.00482	71.0	.00440	31.3	.00108	24.9	.00087			24.0	.00080

[a] Inserted for comparison with *n*-butyl lactate.

TABLE V

RELATIVE REACTION RATES FOR AMMONOLYSIS OF LACTIC ACID ESTERS AT 30°

Ester	30 hr.	50 hr.
Methyl lactate	1.00	1.00
Allyl lactate	0.997	
Ethyl lactate	.262	0.221
n-Propyl lactate	.204	.197
n-Butyl lactate	.204	.197
n-Amyl lactate	.139	.139
Isobutyl lactate	.136	.134
Isopropyl lactate	.0667	.0521
s-Butyl lactate	.0551	.0509
n-Butyl hydracrylate[a]	.0460	.0398
t-Butyl lactate	.0116	.0111

[a] Tabulated for comparison with *n*-butyl lactate.

TABLE VI

BIMOLECULAR REACTION RATES FOR AMMONOLYSIS OF METHYL ESTERS AT 25°

Time, hr.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.	Ammonolysis, %	Rate const.
Methyl →	Formate		Lactate		Acetate		Phenylacetate		Crotonate	
50	79.3[a]	1.54	94.0[b]	0.0361	45.0	0.00500	40.0	0.00469	29.0	0.00290
100					63.5	.00480	59.3	.00435	52.8	.00332
150					74.9	.00453	71.0	.00408	71.3	.00370
200					81.3	.00420	77.0	.00375	82.6	.00403
300							84.2	.00315		
Methyl →			Propionate		Benzoate		Isobutyrate		Trimethylacetate[c]	
50			25.0	0.00282	16,0	0.00188	10.0	0.000880	0	0
100			36.8	.00233	18.3	.00110	13.3	.000725	0	0
150			46.0	.00196	20.8	.00075	16.6	.000600	0	0
200			54.0	.00173	23.1	.00058	20.0	.000500	0	0
300			67.4	.00160	27.7	.00043	25.0	.000390	1.43[d]	.0000147

[a] Ammonolysis is too rapid for a satisfactory rate study; time, 0.5 hour. [b] This rate is for dioxane diluent. In methanol the rate is approximately twice this value. [c] Ammonolysis is too slow for a satisfactory rate study. [d] Time, 388 hours.

TABLE VII

RELATIVE REACTION RATES FOR AMMONOLYSIS OF METHYL ESTERS AT 25°

Ester	50 hr.	100 hr.	200 hr.
Methyl formate	308[a]	321[a]	367[a]
Methyl lactate	7.2	7.5[b]	7.9[b]
Methyl acetate	1.00	1.00	1.00
Methyl phenylacetate	0.938	0.906	0.893
Methyl crotonate[c]	.580	.692	.881
Methyl propionate	.564	.485	.412
Methyl benzoate	.376	.239	.138
Methyl isobutyrate	.176	.151	.119
Methyl-trimethylacetate	.00294[d]	.00306[d]	.00350[d]

[a] This ratio is obtained from the rate constant after one-half hour and is used here for purposes of comparison. [b] Taken from data for 50 hours. [c] The reaction of this ester results primarily in 1,4-addition of ammonia. [d] Taken from data for 388 hours.

Possible errors in activation energy calculations were estimated by substituting probable maximum and minimum values of the various rate constants in the integral form of the Arrhenius equation.

Activation energies for the ammonolysis of methyl acetate and the lactates are listed in Table X.

Discussion

While the comparative rates for similar esters of different acids (Table VIII) show that the correlation of structure and reactivity is still far from quantitative, they do show that the relative magnitude of effects may be determined. The variations in reaction rates of most of the esters studied are at least qualitatively predictable from the known electronegativity of the groups attached. While it is true that probably both steric and polarization effects contribute to the variations in rate constants among the reactions of this study, the fact that, except for the case of the naphthyl esters to be discussed later, an explanation based on polarization effects has been found to be adequate has led to the emphasis on the latter. The relative rates for the ammonolysis of the different esters agree in the main with published values obtained in alkaline and acid hydrolysis of esters.[15]

TABLE VIII

COMPARATIVE RATES OF SIMILAR ESTERS OF DIFFERENT ACIDS

Alcohol component	Acetic acid[a]	Benzoic acid[b]	Lactic acid[c]
Methyl	1.00	1.00	1.00
Ethyl	0.358	0.509	0.221
n-Propyl	.341	.391	.197
Isopropyl	.156	.341	.0521
t-Butyl	.0750	.116	.0111

[a] This comparison is for a reaction time of 100 hours. [b] Reaction time is 618.5 hours. [c] Reaction time is 50 hours.

In all of the ester series where the acid component was held constant, we noted that the reactivity of the ester toward ammonia decreased with increase of the molecular weight of the alcohol

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[15] Skrabal, *Monatsh.*, **45**, 148 (1924), *et seq.*; Palomaa, *Ber.*, **71B**, 480 (1938); Kindler, *Ber.*, **69B**, 2792 (1936); Sudborough, *J. Chem. Soc.*, **75**, 467 (1899).

TABLE IX

EXTENT OF AMMONOLYSIS AND HYDROLYSIS OF ACETATES

Ester	% Hydrolysis	% Ammonolysis	Time, hr.
Methyl acetate	1.1	75.9	579.5
Methyl acetate	1.1	78.6	699.5
Methyl acetate	0.7	83.9	792.5
Ethyl acetate	1.1	35.4	698.5
n-Propyl acetate	4.3	26.0	862.5
Isopropyl acetate	3.3	7.6	1127
n-Butyl acetate	3.6	23.9	1127
Isobutyl acetate	4.4	17.1	1127
s-Butyl acetate	2.9	3.6	1127
t-Butyl acetate	2.9	2.9	1127
n-Amyl acetate	4.3	20.3	1127

TABLE X

ACTIVATION ENERGIES FOR AMMONOLYSIS

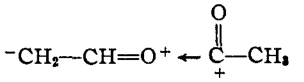
Ester	Activation energy, cal./mole
Methyl acetate	12,700 ± 2000
Methyl lactate	11,800 ± 1000
Ethyl lactate	10,500 ± 1000
n-Propyl lactate	10,700 ± 1000
Isopropyl lactate	9,900 ± 1000
n-Butyl lactate	9,400 ± 1000
Isobutyl lactate	11,800 ± 1000
s-Butyl lactate	11,800 ± 1000
n-Amyl lactate	10,200 ± 1000
Allyl lactate	11,100 ± 1000

component, and, to an even greater extent, with increased branching of the alcohol. Generally speaking, esters of primary alcohols ammonolyze more readily than those of secondary alcohols, and the latter in turn react with ammonia more rapidly than the esters of tertiary alcohols: $CH_3 > C_2H_5 > CH_3CH_2CH_2 > (CH_3)_2CH > (CH_3)_3C$. These results are in accord with accepted electron release effects of alkyl groups.

In the acetate series we found that vinyl acetate had several hundred times the reactivity of ethyl acetate. Writing the resonance forms for vinyl acetate, we see that the positive charge on the oxygen tends to make the carbonyl carbon more

$$CH_2{=}CH{-}O{-} \longleftrightarrow {}^{-}CH_2{-}CH{=}O^{+}{-}$$

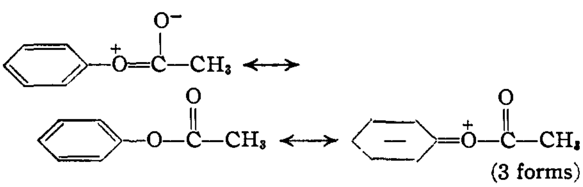
electrophilic, which in turn greatly enhances the reactivity of this carbon toward a nucleophilic



$${}^{-}CH_2{-}CH{=}O^{+} \leftarrow \underset{+}{\overset{\overset{O}{\|}}{C}}{-}CH_3$$

attacking species. The latter, in this case, is probably either the ammonia amide ion or a hydrogen bonded water–ammonia complex.

The very great reactivity of phenyl acetate toward ammonia, compared to the other acetates, is likewise attributable to resonance, in this case mainly between the benzene ring and the oxygen bound to it. Writing the various resonance forms we see that all of the charged structures have a positively charged center adjoining the carbonyl carbon. The effect of this charge concentration on the reactivity of phenyl acetate is the same as that discussed above for vinyl acetate.



(3 forms)

On the basis of resonance it might further be anticipated that the naphthyl acetates would have similarly enhanced reactivities. However, these esters react very slowly with ammonia. This phenomenon can be partly attributed to the large size of the naphthyl groups. Atomic models indicate the reduced susceptibility of the carbonyl carbon to attack due to steric hindrance. In the forms of phenyl acetate in which there is resonance with the benzene ring, there is the spatial requirement that the carbonyl carbon be coplanar with the ring. The decreased likelihood of this restriction being complied with in the naphthyl acetates may further account for their low reactivity toward ammonia.

It was noted that benzyl acetate ammonolyzed twice as rapidly as ethyl acetate and allyl lactate reacted with ammonia five times as rapidly as did *n*-propyl lactate. From these results it must be concluded that the benzyl group is less electron releasing than the ethyl, and the allyl less than the *n*-propyl. These relationships would seem to be at odds with the well-known behavior of the halides of these compounds. For example, benzyl chloride is known to be more reactive than ethyl chloride and this phenomenon is popularly attributed to the greater polarization of the carbon–halogen bond in the benzyl chloride, from which one would have to conclude that the benzyl group is more electron releasing than the ethyl. Similarly the greater reactivity of allyl chloride over *n*-propyl chloride would lead one to believe that the allyl group is more electron releasing than the *n*-propyl.

However, reference to dipole moments shows that precisely the reverse is true. The relative dipole moments of ethyl bromide[16] and benzyl bromide[17] are 2.12 (in benzene) and 1.85 (in benzene), respectively, indicating that the carbon-halogen bond is less polarized in the latter, and that the electron release effect of the benzyl group must be less than that of the ethyl group. Similarly the relative dipole moments of *n*-propyl bromide[16] and allyl bromide[18] are 2.00 (in benzene) and 1.79 (in benzene), respectively, again leading to a conclusion supporting the results of this investigation, namely, that the allyl group is relatively less electron releasing than the *n*-propyl.

The usual high reactivity attributed to allyl halides, alcohols, etc., in unimolecular displacements, when compared to the corresponding saturated

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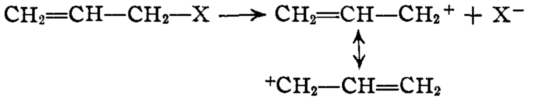
[16] Daily, *Phys. Rev.*, [ii] 34, 548 (1929).

[17] Smyth and Walls, THIS JOURNAL, 54, 1854 (1932).

[18] Parts, *Z. physik. Chem.*, B12, 312 (1931).

alkyl compounds, is due to stabilization of the carbonium ion through resonance. However, only after ionization does this stabilizing influence



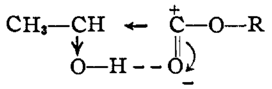
$$\begin{array}{l} CH_2{=}CH{-}CH_2{-}X \longrightarrow CH_2{=}CH{-}CH_2^+ + X^- \\ \qquad\qquad\qquad\qquad\qquad \updownarrow \\ \qquad\qquad\qquad\qquad {}^+CH_2{-}CH{=}CH_2 \end{array}$$

operate, so that while the allyl compound is in the un-ionized form it is perfectly consistent to say that the polarization of the carbon–halogen bond in allyl halides is lower than in *n*-propyl halides.

There is abundant evidence in the literature, well summarized by Branch and Calvin,[19] to show the great effect of resonance stabilization by cations such as allyl and benzyl groups in bimolecular ($S_N{}^2$) displacements.

The fact that the reactivity of benzyl halides is greater than that of ethyl halides is due to the presence of the allylic system in the former. So we see that the influence on reactivity attributed to the allyl and benzyl groups in this investigation is not incompatible with the normal behavior of these compounds in displacement reactions, since in ammonolysis there is no cleavage of the alkyl–oxygen bond.

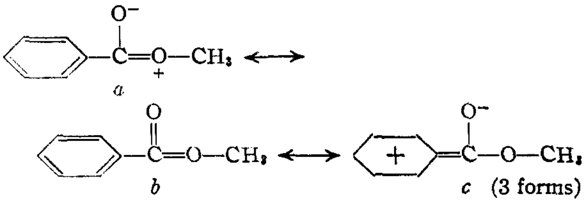
In the case of the saturated aliphatic esters of benzoic and lactic acids the same generalizations apply as in the case of the acetates. The high reactivity of allyl lactate, as compared to *n*-propyl lactate, was noted above. The rate for vinyl esters is much greater than that of allyl esters due to the absence of resonance in the un-ionized form of the latter. *n*-Butyl hydracylate is less than one-fourth as reactive as *n*-butyl lactate because the electron attracting hydroxyl group is farther removed, in *n*-butyl hydracrylate, from the reactive center of the molecule. In general, all of the lactates have from ten to twenty times the reactivity toward ammonia that is exhibited by the corresponding acetates. Here again the difference is due, in part, to the presence of an electron attracting group in the lactic acid esters. Furthermore, to the extent that it occurs, hydrogen bonding in the lactates and hydracrylates could contribute to the electrophilic activity of the carbonyl carbon atom since it assists in the polarization of the carbonyl carbon–oxygen bond. However, hydrogen bonding of the hydroxyl hydrogen to the carbonyl oxygen probably reduces the inductive effect of the hydroxyl group, so that the over-all contribution of hydrogen bonding to the



rate of ammonolysis of the lactates is open to question.

The methyl esters of the various acids show that the variation of R groups in the ester RCOOR′ results in a change in reactivity analogous to that obtained by varying the R′ groups as discussed earlier. However, methyl trimethylacetate has a much lower rate, compared to methyl acetate, than *t*-butyl acetate has compared to methyl acetate. The greater retardation effect of the R_3C grouping in methyl trimethylacetate can be attributed to the closer proximity of that group to the carbonyl carbon than is the case in *t*-butyl acetate. The oxygen, due to its unshared electrons, is probably an efficient conductor of inductive forces, but since the inductive effect falls off rapidly with distance, replacing a given R group in the ester RCOOR′ by any given radical will have greater effect on the rate of ammonolysis of the ester than replacing the corresponding R′ group by the same radical.

In methyl benzoate, unlike phenyl acetate, the conjugation of the carbonyl group with the benzene ring decreases the reactivity toward ammonia. It should be noted that the oxygen attached to the methyl group of methyl benzoate is less positive than that of methyl acetate due to resonance with the ring in the former ester. Writing the resonance structures of methyl benzoate we can see the reasons for the reduced electro-



philic nature of the carbonyl carbon atom. Methyl acetate has only the forms corresponding to *a* and *b* above and would therefore be expected to ammonolyze more rapidly than methyl benzoate.

In the reaction of methyl crotonate Morsch[20] reported predominantly 1,4-addition of ammonia to give methyl 3-aminobutyrate, which he isolated. In this laboratory these results were confirmed by titrating starting mixtures and reaction products by the bromate–bromide method, whereby about 96% of the product was found to be saturated. These results probably account for the rise in reaction rate constants observed with this ester, as compared with the downward drift in the purely ammonolytic reactions.

In the ammonolysis of methyl formate it was found that the competing hydrolytic reaction may account for as much as 40% of the ester consumed, but nevertheless the ammonia reaction was still several hundred times as rapid as in the case of methyl acetate. Work which had been planned with other formic acid esters was dropped due to the great amount of competing hydrolysis. Another objection to the use of formates was the fact that reaction with ammonia was so rapid as to make accurate kinetic studies exceedingly difficult.

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(19) Branch and Calvin, "Theory of Organic Chemistry," 1941, p. 436.

(20) Morsch, *Monatsh.*, **60**, 50 (1932);

The amount of hydrolysis found in the case of esters of acetic acid has been given in Table IX. It should be appreciated that hydrolysis figures presented represent extreme upper limits in view of the length of reaction time. These extreme periods of time were specifically employed because the amounts of hydrolysis obtained over periods of time comparable to those used in the ammonolytic studies were of the same order of magnitude as the experimental error of the method and hence meaningless. Since the extent of hydrolysis in all cases tabulated could not be evaluated for periods comparable to those used in the ammonolytic determinations, we were unable to apply any correction to the calculations for the rates of ammonolysis in order to account for the side reaction. In view of the original objectives of this study, an additional expenditure of time on the further study of the hydrolysis of esters was considered unwarranted.[21]

The relative extent of hydrolysis in these experiments, even for extreme periods of reaction time, is well below that encountered by other investigators[14,22] owing to the lower concentrations of water (18%) employed in this Laboratory.

From the foregoing remarks it should be clear that, for the periods of time used in ammonolysis in this study, the amount of hydrolysis is within the limits of experimental error and hence not significant in its effect on the structure–reactivity correlations.

The second order rate constants for the ammonolysis of esters have been found to drift downward with time. The only exception was the case of methyl crotonate, in which, as discussed earlier, the principal reaction was not ammonolysis. The downward drift of rate constants is attributable to two causes; first, to the accumulation of ammonium ions from the competing hydrolytic reaction, the ammonium ions acting to retard the principal reaction and, second, to the fact that reactions were carried out in concentrated solutions in which we would expect to find considerable deviation from ideality.

Summary

The rates of ammonolysis of several series of esters have been determined and have been found to be regulated by the electron release effects of both the R and R′ groups in the ester RCOOR′, with variations of R having the greater effect due to the rapid falling off of the inductive effect with distance.

A kinetic study has revealed the following order of reactivity of acetates with aqueous ammonia: phenyl > vinyl > methyl > benzyl > ethyl > *n*-propyl > *n*-butyl > *n*-amyl > isopropyl > isobutyl > *s*-butyl > *t*-butyl > β-naphthyl > α-naphthyl.

A study of the reactivity of benzoates indicated the following order: phenyl > methyl > benzyl > ethyl > *n*-propyl > isopropyl > *t*-butyl.

The following order of reactivity in the ammonolysis of lactates was observed: methyl > allyl > ethyl > *n*-propyl > *n*-butyl > *n*-amyl > isobutyl > isopropyl > *s*-butyl > *t*-butyl.

By utilizing a series of methyl esters of different acids the effects of structural variations on the acid side of the ester molecule were observed. The following order of ammonolysis of methyl esters was obtained: formate > lactate > acetate > phenylacetate > propionate > benzoate > isobutyrate > trimethylacetate.

In general the relative rates of ammonolysis obtained by varying the alcohol and acid components of the ester follow the anticipated electron release effects and confirm the results obtained by other investigators in the acid and alkaline hydrolysis of esters.

An azeotrope of methanol and methyl trimethylacetate has been described.

PHILADELPHIA, PENNSYLVANIA

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(21) Results of unpublished work show that the same qualitative structure-reactivity correlations are obtained by working in anhydrous ethylene glycol–ammonia, in which hydrolysis is improbable, as are reported in this paper for aqeuous solutions.

(22) French and Wrightsman, THIS JOURNAL, **60**, 50 (1938).