[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

A Kinetic Study of the Ammonolysis of Phenylacetic Esters in Methanol Solution[1]

BY RAYMOND L. BETTS AND LOUIS P. HAMMETT

We have investigated the rate and mechanism of the reaction of acid amide formation by treating a group of methyl esters of derivatives of phenylacetic acid with ammonia in methanol solution. The reaction is of interest for preparative purposes, and even more because of the probability that its mechanism is similar to that of the alkaline hydrolysis of an ester. The phenylacetic esters were used because we wished to determine the effect of structural changes at a point in the molecule considerably removed from the reacting group, and because the rate of reaction of benzoic esters is so small as to be practically unmeasurable. The temperature of 25° was used because of the availability of accurately determined ionization constants[2] at that temperature and of carefully measured hydrolysis rates[3] at a not very different temperature.

Experimental

Materials.—The methanol, a product of the Commercial Solvents Corporation, was dried according to the method described by Lund and Bjerrum[4] and distilled from an all-glass apparatus with a bulb stillhead, yielding a product of density 0.78668 at 25°. The density was found to increase slowly on standing but no sample used in the preparation of reaction mixtures had a density greater than 0.78688.

The ammonia was the anhydrous product of the Matheson Company and qualitative tests on its solution in methanol for primary amines were negative.

The methyl esters were purified by extracting their ether solutions with aqueous sodium carbonate, drying over phosphorus pentoxide in a partial vacuum and recrystallizing or distilling through a Vigreux stillhead in an all-glass apparatus and collecting a constant boiling fraction: methyl phenylacetate, b. p. 218°, ester content by saponification, 99.8%; methyl *p*-nitrophenylacetate, m. p. 56°, ester, 100.8%, prepared by esterification of the acid; methyl *p*-chlorophenylacetate, b. p. 114–115° at 6 mm., ester, 100.1%, prepared from *p*-chlorobenzyl chloride by the method described by Adams and Thal[5] for ethyl phenylacetate.

Ammonium chloride and sodium chloride were crystallized, the former was dried at 110°, the latter was fused. The ultimate acidimetric standard for titrations was Bureau of Standards potassium acid phthalate.

Method.—The reaction mixtures were made up by weighing directly into a volumetric flask a suitable quantity of the ester, adding the required amount of an approximately 0.6 molar methyl alcoholic solution of ammonia and finally making to the mark with methanol. After mixing, the contents were transferred to the reaction flask which was placed in a thermostat operating at 25 ± 0.02°. The initial concentration of the ammonia was determined in triplicate by adding 5-ml. portions of the mixture, by means of a sampling pipet, to an aqueous methanol solution containing an excess of standard acid and back titrating with standard alkali, using brom cresol purple as an indicator. The same analytical procedure was used to follow the reaction by determining the amount of ammonia remaining after definite intervals of time.

The sampling pipet was equipped with a two-way stopcock and a ground-glass stopper to fit the reaction flasks which were made of Pyrex glass and possessed standard ground-glass joints. While samples were being taken, the pipet was connected to a drying tube containing concentrated sulfuric acid and another tube filled with soda lime to prevent access of moisture and carbon dioxide to the contents of the flask.

Sources of Error.—The greatest danger of error lies in the possibility of a simultaneous hydrolysis of the ester by traces of water (possibly as much as 0.06 molar) present in the solution. In the case of all the esters reported here and also with methyl acetate we showed that the amide rather than the ammonium salt is the major product of the reaction by isolation and identification of the reaction product. When the work was nearly completed a method for the determination of ammonia and ammonium ion in the presence of acid amides was published by French, Johnson and Ratekin.[6] This involves distillation in the presence of magnesium oxide. We have adapted this method to the micro-Kjeldahl apparatus of Pregl,[7] and verified the completeness of the separation on known materials. Using this method, we found, on six different samples of reaction mixtures prepared from ammonia and ester, that hydrolysis amounts to less than 2% of the total reaction. On reaction mixtures to which sodium methylate had been added, this rose to 8 to 11% for reasons which are not apparent.

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(1) Dissertation submitted by Raymond L. Betts in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

(2) Dippy and Williams, *J. Chem. Soc.*, 161 (1934).

(3) Kindler, *Ann.*, **452**, 90 (1927).

(4) Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

(5) Adams and Thal, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, 1932, pp. 101 and 265.

(6) French, Johnson and Ratekin, THIS JOURNAL, **58**, 1346 (1936).

(7) Pregl, "Quantitative Organic Microanalysis," translated by Fyleman, P. Blakiston's Son Co., Philadelphia, Pa., 1930, p. 94.

TABLE I

EXPERIMENTS WITH ESTER AND AMMONIA ALONE PRESENT

Initial concentration of ester, 0.2999 m./l.

Time, hours	0	766.7	1055.0	1511.1	1775.4	2139.3	2399.5
Concn. NH_3	0.0983	0.0883	0.0854	0.0836	0.0817	0.0796	0.0792
$k \times 10^5$		48.1	45.5	36.8	35.7	34.1	31.0

Initial concentration of ester, 0.3059 m./l.

Time, hours	0	765.6	1053.9	1510.0	1774.3	2138.1
Concn. NH_3	0.2110	0.1862	0.1802	0.1733	0.1681	0.1631
$k \times 10^5$		54.9	51.3	45.2	44.8	42.6

Initial concentration of ester, 0.3027 m./l.

Time, hours	0	744.5	888.5	1223.8	1489.1	1753.2
Concn. NH_3	0.4494	0.3805	0.3705	0.3523	0.3420	0.3287
$k \times 10^5$		83.9	83.5	79.8	75.4	76.4

Initial concentration of ester, 0.3051 m./l.

Time, hours	0	744.0	888.0	1223.2	1488.5	1583.2
Concn. NH_3	0.5716	0.4764	0.4649	0.4424	0.4262	0.4201
$k \times 10^5$		97.0	94.7	90.5	89.1	89.7

TABLE II

EXPERIMENTS WITH ADDED AMMONIUM CHLORIDE AND SUFFICIENT SODIUM CHLORIDE TO MAKE THE TOTAL SALT CONCENTRATION 0.1 MOLAR

Init. concn. ester, 0.2086 m./l. Concn. NH_4Cl, 0.1013 m./l.

Time, hours	0	911.3	1397.2	1560.5	1901.3	2256.7	2567.5
Concn. NH_3	0.3272	0.3102	0.2998	0.2971	0.2890	0.2769	0.2647
$k \times 10^5$		29.3	32.2	32.1	34.6	40.7	47.3

Init. concn. ester, 0.2224 m./l. Concn. NH_4Cl, 0.0402 m./l.

Time, hours	0	1103.2	1373.0	1708.6	2040.4	2520.0	3024.7	3457.3	3939.6
Concn. NH_3	0.2987	0.2749	0.2680	0.2597	0.2517	0.2402	0.2308	0.2210	0.2046
$k \times 10^5$		35.8	38.3	40.6	42.5	45.5	46.1	48.7	57.0

TABLE III

EXPERIMENTS WITH ADDED SODIUM METHYLATE

Init. concn. ester, 0.2073 m./l. Concn. $NaOCH_3$, 0.0209 m./l.

Time, hours	0	263.4	313.3	673.0	936.8
Concn. NH_3	0.3106	0.2503	0.2427	0.2018	0.1869
$k \times 10^5$		469	464	450	414

The only other reactions which might conceivably occur are formation of (1) double amides and (2) amines. A reaction of the first type[8] is improbable as double amides have only been obtained by rather drastic heat treatment of mixtures of nitriles and acids. In regard to the second type, Chattaway[9] found that certain alkyl esters of acetic acid, in which the alkyl groups possessed strong electronegative loadings, gave amines instead of the normal amide formation. Should this reaction occur with methyl esters, then primary amines should be products but qualitative tests for their presence were negative.

Analyses carried out in the usual manner on solutions of esters showed that free acid was less than the precision of measurement and similar analyses of amide solutions also gave negative results. That the error arising from loss of ammonia because of removal and insertion of stoppers during sampling is small, was demonstrated by making analyses on a blank run containing methanolic ammonia only at intervals over a period of two months, which indicated a total change of less than four parts per thousand. Error due to reversibility of the reaction is negligible, since the reaction of phenylacetamide with ammoniacal methanol occurs to less than 2% in three months.

Results

Detailed experimental results for a few typical runs made with methyl phenylacetate are given in the tables in which k is a bimolecular rate constant in moles per liter per hour.

Results obtained from experiments which were run at 100°, both on ammonolysis of phenylacetic ester and on the reverse reaction, the alcoholysis of the acid amide, are in agreement with

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(8) Colby and Dodge, *Am. Chem. J.*, **13**, 1 (1891).

(9) Chattaway, *J. Chem. Soc.*, 355 (1936).

the findings of Meyer.[10] They indicate that the rate of the latter reaction has the higher temperature coefficient and that the equilibrium condition is such as to be unfavorable to amide formation.

Discussion

From these results it follows that the reaction deviates considerably from the bimolecular course expected, that ammonium salts retard markedly and that sodium methylate accelerates. We have been unable to account entirely for the large drifts in the second order constants. The downward drift observed in the experiments with ammonia and ester alone (Table I) are perhaps due partly to the fact that the reaction under these conditions is, as we shall see (equation 7), of the 3/2 order in ammonia instead of the first order, and partly perhaps to the very great retarding effect that the production of even a small amount of ammonium ion by hydrolysis would have. Neither of these explanations can account for the drifts observed in the presence of ammonium salts or of sodium methylate.

We have therefore investigated the effect of varying concentrations of reagent upon the initial specific rate which was in every case obtained by plotting the quantity log $B(A - X)/A(B - X)$ against time and estimating graphically the initial slope of the curve which is equal to k multiplied by the quantity $2.303/(A - B)$. These calculations for the experiments with ammonia and ester alone present showed that the reaction under these conditions is rather erratic and not reproducible. Nevertheless it seemed certain that the rate increases more rapidly than in proportion to the ammonia concentration but less than proportionately to the ester concentration. It further appeared that phenylacetamide retards slightly. Sodium chloride increases the rate about 15% at 0.05 molar concentration. The effect produced by ammonium chloride, which is in the opposite direction and much larger, is certainly not a salt effect. None of these effects seem competent to account for the drifts in Tables II and III.

The effects of ammonium chloride and sodium methylate are in agreement with the hypothesis that the reaction is subject to a basic catalysis. The obvious mechanism for such a catalysis would involve amide ion as the actual reactant, and we shall discuss it in terms of this mechanism. The same conclusions[11] can however be obtained from other mechanisms. Thus the reaction might be a truly termolecular one involving ester, ammonia and methylate ion, or the initial equilibrium might involve the ester and methylate ion.

We shall consider the reactions

$$2NH_3 \rightleftarrows NH_4^+ + NH_2^- \qquad K_{Am} \quad (1)$$

$$NH_3 + CH_3OH \rightleftarrows NH_4^+ + CH_3O^- \qquad K_B \quad (2)$$

with the equilibrium constants noted. In the presence of ammonium salts the reaction of equation 1 will alone determine the amide ion concentration. Consequently, both amide ion concentration and rate of the catalyzed reaction should vary inversely as the concentration of ammonium ion. Actually the rate varies linearly with the reciprocal of the ammonium ion concentration but the extrapolated rate at infinite ammonium ion concentration is far from negligible. There is, therefore, an uncatalyzed reaction as well as the catalyzed one, and the total reaction is the sum of the two competing processes

$$RCOOCH_3 + NH_3 \longrightarrow RCONH_2 + CH_3OH \qquad k_1 \quad (3)$$

$$RCOOCH_3 + NH_2^- \longrightarrow RCONH_2 + CH_3O^- \qquad k_2 \quad (4)$$

with the rate constants noted. The total rate v is then given by

$$v = k_1[E][NH_3] + k_2K_{Am}[E][NH_3]^2/[NH_4^+] \quad (5)$$

and the specific rate k_0 by

$$k_0 = k_1 + k_2K_{Am}[NH_3]/[NH^+_4] \qquad (6)$$

As Fig. 1 shows, plots of k_0 against $1/[NH_4^+]$ are linear for the three esters studied, with the exception of one point for the nitro compound. From these plots we may read off values of the quantity k_2K_{Am}, which is equal to the slope divided by the ammonia concentration, and of the quantity k_1 which is equal to the intercept. The values obtained are listed in Table IV.

TABLE IV

	$k_1 \times 10^5$	$k_2K_{Am} \times 10^5$	k_h	$K_{ion} \times 10^5$
Phenylacetate	25.0	1.6	0.636	4.88
p-Chlorophenylacetate	45.0	3.33	1.62	6.45
p-Nitrophenylacetate	80.0	9.33	4.57	14.1

k_1 is the initial specific rate at an infinite concentration of ammonium ion, k_2K_{Am} is calculated from the slopes obtained from Fig. 1, K_{ion} is the ionization constant of the corresponding phenylacetic acid according to Dippy and Williams,[2] and k_h is the hydrolysis constant taken from Kindler.[3]

In the absence of added ammonium salt the reaction of equation (2) will determine the am-

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[10] L. Meyer, *Ber.*, **22**, 24 (1889).

[11] Brönsted, *Chem. Rev.*, **5**, 231 (1928).

monium ion concentration and through this the concentration of amide ion. Consequently we have

$$[NH_4^+] = [CH_3O^-]$$

and, to a reasonable precision, since the extent of reaction (2) is small, although much larger than that of equation (1)

$$[NH_4^+] = \sqrt{K_B[NH_3]}$$

From this we have

$$v = k_1[E][NH_3] + k_2K_{Am}[E][NH_3]^{3/2}/\sqrt{K_B} \quad (7)$$

and

$$k_0 = k_1 + k_2K_{Am}[NH_3]^{1/2}/\sqrt{K_B} \quad (8)$$

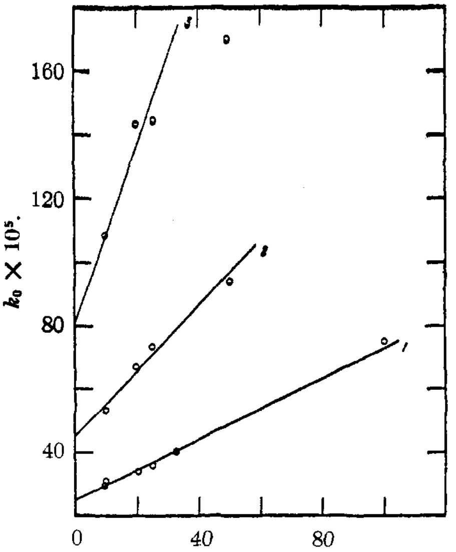

Fig. 1.—1, Phenylacetate; 2, *p*-chlorophenylacetate; 3, *p*-nitrophenylacetate.

In Fig. 2 the values of the specific rate k_0 from five experiments on methyl phenylacetate at constant ester concentration are plotted against the square root of the ammonia concentration. Four of the points lie on a straight line whose intercept leads to a value for k_1 of 27×10^{-5}, which is in satisfactory agreement with the value 25×10^{-5}, obtained from the experiments on the effect of ammonium chloride by the use of equation (6). We attribute the marked deviation of the single point to accidental contamination of the reaction solution with some acidic impurity to which these unbuffered solutions are especially sensitive.

A further check on the correctness of this interpretation of the reaction may be gained by comparison of the slope of the phenylacetate curve in Fig. 1 with the slope of the line in Fig. 2. According to equations (6) and (8), K_B can be calculated from the ratio of these slopes. Consequently we may derive from our experiments the value of 3.2×10^{-6} for K_B, the ionization constant of ammonia in methyl alcohol. This quantity has been measured by conductivity methods by Bjerrum, Unmack and Zechmeister[12] who obtained the value of 1.2×10^{-6} at 18°. Considering the uncertainties in both methods the agreement is not unsatisfactory. The considerable acceleration of the reaction produced by sodium methylate (Table III) is qualitatively in agreement with the hypothesis of a base catalyzed reaction, but there is a quantitative discrepancy which shows that some new factor enters in this case. It is easily shown from equations (1) and (2) that the specific rate in the presence of methylate ion should be given by

$$k_0 = k_1 + k_2K_{Am}[CH_3O^-]/K_B$$

From this we calculate by using the values of k_1 and k_2K_{Am} from Table IV a new value for K_B of 6.3×10^{-5}. The difference of more than an order of magnitude between this and the other values seems to be outside of the probable experimental error.

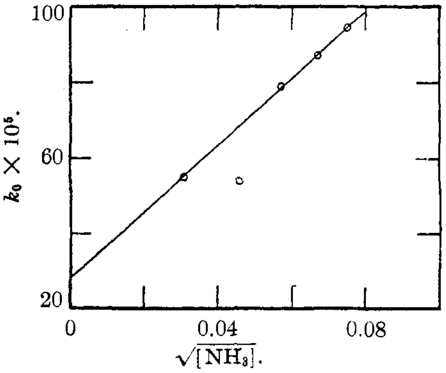

Fig. 2.

It has recently become apparent[13] that a linear relationship exists between the logarithms of the rate or the equilibrium constants of two reaction series whenever the series in question are closely related in mechanism. Such a similarity might be expected to exist between the reaction of an ester with amide ion or with ammonia and the reaction of the ester with hydroxyl ion. As Fig. 3 shows, the linear relation does appear when the rate of either amide ion or ammonia reaction is compared with

[12] Bjerrum, Unmack and Zechmeister, *Kgl. Danske Videnskab Selskab, Math.-fys. Medd.*, **5**, No. 11 (1925).

[13] Hammett and Pfluger, THIS JOURNAL, **55**, 4079 (1933); Hammett, *Chem. Rev.*, **17**, 125 (1935); Hammett, THIS JOURNAL, **59**, 96 (1937).

the rate of the alkaline hydrolysis. In this figure the abscissas are the logarithms of Kindler's[3] rate constants for the hydrolysis of the three phenylacetic esters. In curve 1 the ordinates are the logarithms of our k_1, in the curve 2 they are the logarithms of our k_2K_{Am}. It is especially worthy of note that the correlation exists for the reaction of electrically neutral ammonia (k_1) with the ester as well as for the reaction of negatively charged amide ion (k_2K_{Am}).

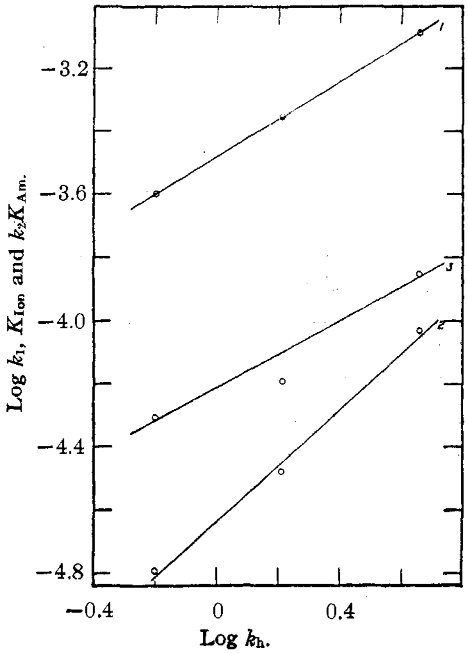

Fig. 3.

That the existence of this correlation may be taken as serious evidence for a similarity in mechanism is shown by curve 3 in Fig. 3 in which the ordinates are the ionization constants of the corresponding phenylacetic acids. The constants for this reaction, whose mechanism is of necessity fundamentally different from the others, do show a parallel trend with the other constants, but the deviations from linearity are unmistakably larger.

Summary

The rate of reaction of methyl phenylacetate and of its *p*-chloro and *p*-nitro derivatives with ammonia in methanol solution has been measured at 25°. The reaction shows considerable deviation from second order course, the source of which is not clear. It is markedly retarded by ammonium chloride and strongly accelerated by sodium methylate. The quantitative study of these effects indicates that there is an uncatalyzed reaction of ester with ammonia and a parallel base catalyzed reaction, presumably a reaction of ester with amide ion. There exist linear relationships between the logarithms of the rates of both catalyzed and uncatalyzed reactions and the rates of hydrolysis of the same esters.

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NOTES

Synthesis of 2,3-Cyclopentenophenanthrene

BY ERNST BERGMANN AND O. BLUM-BERGMANN

While the synthesis of 1,2-cyclopentenophenanthrenes can be effected by various methods, no way is known so far, leading to the series of 2,3-cyclopentenophenanthrene (V). In order to determine its physical properties (spectrum, formation of mixed crystals with similar phenanthrene derivatives, especially of the cyclopentenophenanthrene type), we prepared (V) by an unambiguous method.

The starting material for our synthesis was the anhydride of cyclopentane-1,2-dicarboxylic acid (I), which was reacted upon with α-naphthylmagnesium bromide, using the method of Weizmann and co-workers.[1] The resulting 1-(α-naphthoyl)-cyclopentane-2-carboxylic acid (II) was reduced with amalgamated zinc wool and gave 1-(α-naphthyl-methyl)-cyclopentane-2-carboxylic acid (III). Its cyclization to give 2,3-cyclopentano-1-keto-1,2,3,4-tetrahydrophenanthrene (IV) was effected with difficulty, the best reagent proving to be phosphoric oxide in boiling benzene. Clemmensen reduction of the ketone (IV) and dehydrogenation with selenium gave the desired hydrocarbon (V).

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[1] Weizmann and co-workers, *J. Chem. Soc.*, 1370 (1935).