[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Effect of Structure on Reactivity. VIII. Aminolysis of Methyl Acetate with Some β-Phenylethylamines

BY S. LUP JUNG, JOHN G. MILLER AND ALLAN R. DAY

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The order of the relative reactivities of some β-phenylethylamines with methyl acetate in dioxane–water solution is 3,4-dimethoxy-β-phenylethylamine > β-phenylethylamine > α-methyl-β-phenylethylamine and N-methyl-β-phenylethylamine > α-methyl-N-methyl-β-phenylethylamine and N-ethyl-β-phenylethylamine > N-propyl-β-phenylethylamine. Secondary solvent effects of the so-called inert diluents have been shown to have a marked effect upon the reaction rates. In a system containing β-phenylethylamine, methyl acetate, methanol and "inert" diluent, the relative rates with the following diluents were: saturated hydrocarbons > benzene > dioxane. Aminolysis under various solvent conditions has been shown to be subject to acid catalysis.

The sympathomimetic amines, which contain the carbon nucleus of β-phenylethylamine, are primary or secondary amines. In general when these amines are converted to tertiary amines, their characteristic physiological actions are lost or are markedly altered. This suggests a possible correlation between the N–H bond reactivity and physiological activity. It was thought that a study of the order of relative reactivities of some β-phenylethylamines in the aminolysis of an ester under standard conditions, to form the corresponding amides, would contribute to the understanding of sympathomimetic activity. Methyl acetate was chosen as the reference ester, dioxane was selected as the standard "inert" diluent and water was used as the catalytic solvent. The standard conditions finally adopted for most of the experimental work involved the use of 2 M amine, 1 M methyl acetate, 10 M water, with dioxane as the diluent. In the few cases tested it was noted that the rates were increased when the dioxane was replaced with benzene, n-hexane or cyclohexane.

Experimental

The experimental method was essentially that employed in earlier work,[1] but some changes were made to increase the accuracy and ease of measuring volumes and to exclude carbon dioxide. An ampoule filler which delivered exactly a 10-ml. aliquot from a 150-ml. reservoir was used to secure identical volumes and the solutions containing amines were protected with ascarite tubes at all times. The aminolysis reactions were carried out at 30 ± 0.002°. The Meeker–Wagner boric acid method was used to titrate the amines.[2] A Beckman pH meter, Model M, was employed for this purpose. The following reagents were used during the course of this work.

Reagent	B.p., °C.	n^{20}D
Methyl acetate	56.2–56.6	1.3614
β-Phenylethylamine	46.1–46.3 (1 mm.)	1.5332
N-Methyl-β-phenylethylamine	39 (1 mm.)	1.5166
N-Ethyl-β-phenylethylamine	49 (1 mm.)	1.5086
N-n-Propyl-β-phenylethylamine	62.5 (1.3 mm.)	1.5032
3,4-Dimethoxy-β-phenylethylamine	99.3–101.3 (0.5 mm.)	1.5460
α-Methyl-β-phenylethylamine	41 (1.5 mm.)	1.5188
Racemic N-methyl-α-methyl-β-phenylethylamine	48.8–50.2 (1 mm.)	1.5097
D(−)-N-Methyl-α-methyl-β-phenylethylamine	39.3–40.2 (0.8 mm.)	1.5097
Dioxane	99.8–100.2	1.4222
Benzene	79.3–79.4	1.5007
Cyclohexane	80.0	1.4220
n-Hexane	67.7	1.3781

The primary amines used were commercially available. They were dried over sodium hydroxide pellets and distilled in vacuum. The amines were then stored under nitrogen.

The secondary amines were prepared from the primary amines by the method of Guest and Johnson.[3] The remaining reagents were purified by standard procedures.

Sources of Error.—The major sources of error have been adequately discussed in the previous papers.[1] Some additional sources will be considered.

Amine carbonates have been shown to exert a positive catalytic effect on the rates. To reduce this effect, precautions such as flushing all apparatus with nitrogen, transferring under nitrogen and protecting with tubes filled with ascarite were observed.

Earlier work on ammonolysis[1a] has shown that the presence of five to ten moles of water in the reaction mixture did not lead to any appreciable hydrolysis of a series of esters. In the present work with primary amines, it was found that the extent of hydrolysis could not have been very large and certainly not large enough to materially affect the specific and relative rate constants shown in Table I. For example, when methyl acetate was treated with β-phenylethylamine in the presence of 15 M water and the solution kept at 30° until the reaction was practically complete, a 90% yield of pure amide was isolated. In the experiments where secondary amines were used a buffering action appeared at the end-point, indicating the presence of ammonium salts. In these cases, the rates were extremely slow and it is probable that the relative amounts of hydrolysis were larger.

Relative Reactivity and Solvent Effects.—The second-order rate constants and the relative reaction rate constants for a number of β-phenylethylamines are given in Table I.

TABLE I

SPECIFIC AND RELATIVE REACTION RATE CONSTANTS AT 30°

Amine	$K \times 10^{3a}$	Relative K values
β-3,4-Dimethoxyphenylethyl	3.87^b	1.22
β-Phenylethyl	3.18^b	1.00
α-Methyl-β-phenylethyl	0.142^b	0.045
N-Methyl-β-phenylethyl	.129^b	.041
N-Ethyl-β-phenylethyl	.0706^c	.022
D(−)-α-Methyl-N-methylphenylethyl	.0689^c	.021
Racemic α-methyl-N-methylphenylethyl	.0596^c	.019
N-n-Propyl-β-phenylethyl	.0353^c	.011

[a] Units = liter/mole hour. [b] 20% aminolysis. [c] 5% aminolysis.

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[1] (a) M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **70**, 1946 (1948); **71**, 1245 (1949); (b) E. McC. Arnett, J. G. Miller and A. R. Day, *ibid.*, **72**, 5635 (1950); **73**, 5393 (1951).

[2] E. W. Meeker and E. C. Wagner, *Ind. Eng. Chem., Anal. Ed.*, **5**, 396 (1933).

[3] B. Guest and H. H. Johnson, *Am. Chem. J.*, **42**, 340 (1909).

The values at or near 20% ammonolysis were selected in the case of the primary amines. For the secondary amines the values for about 5% aminolysis were chosen in most cases. The last four amines listed in Table I reacted so slowly with methyl acetate that the rate constants are reported for only 5% aminolysis. Although there was a small downward drift in the rate constant values, it is believed that the values reported are reasonably comparable with those reported for 20% aminolysis.

It will be noted that an α-methyl group reduces the activity almost as much as a N-methyl group. These marked decreases in reactivity must be due, in greater part, to steric effects. The difference in reactivity between the D(–)- and racemic forms of α-methyl-N-methylphenylethylamine is so small that it must be assumed their reactivities are the same.

Although dioxane had been chosen as the so-called "inert" diluent, for the experiments discussed above, it was realized that it was inert in a relative sense only. It seemed desirable to compare dioxane with other "inert" solvents such as benzene, *n*-hexane and cyclohexane. To make such a comparison, it was necessary to replace the ten moles of water with ten moles of methanol to ensure solubility of all of the components. All diluent effects were determined by using 1 *M* methyl acetate, 10 *M* methanol, 2, 1 and 0.5 *M* β-phenylethylamine, including the diluent. The three concentrations of the amine were employed to determine the generality of the drift of the rate constants with the per cent. of aminolysis in different diluents. The results of this investigation are shown in Table II.

TABLE II

AMINOLYSIS IN MIXED SOLVENTS OF METHANOL AND "INERT" DILUENT AT 30°[a]

Dioxane		Benzene		*n*-Hexane		Cyclohexane	
k	Aminolysis, %	*k*	Aminolysis, %	*k*	Aminolysis, %	*k*	Aminolysis, %
			2 *M* Amine				
1.42	11.7	1.95	10.6	3.11	24.5	3.26	25.7
1.42	26.7	1.87	24.1	3.18	33.6	3.22	34.5
1.40	34.5	1.85	34.4	3.05	57.0	3.08	57.6
			1 *M* Amine				
0.569	7.7	0.818	7.6	1.94	8.4	2.01	8.7
.557	14.1	.786	13.3	1.94	14.9	1.98	16.6
.557	15.7	.762	15.6	1.82	32.5	1.85	32.7
			0.5 *M* Amine				
0.240	3.4	0.424	4.1	1.15	9.4	1.15	10.7
.273	5.1	.389	5.5	1.12	20.0	1.11	20.5
.264	7.3	.376	10.1	1.08	28.2	1.07	26.9

[a] *k* = *k* × 10³; units = liter/mole hour.

At approximately 25% aminolysis with 2 *M* β-phenylethylamine, the rate increased about 32% when the dioxane was replaced with benzene, 119% with *n*-hexane and 130% with cyclohexane. These data suggest that very weak forces have important effects upon the rates observed. It had been assumed in earlier studies[1] that since ammonolysis reactions in dioxane gave such slow rates, its use as a diluent with hydroxylated solvents would have little or no effect upon the rates. Since aminolysis required hydroxylated solvents for measurable rates, it was thought necessary to consider only the amount of the hydroxylated substance.

It has been demonstrated that methanol forms hydrogen bonds with amines, esters and ethers.[4] The amines formed the strongest H-bonds. Jones and Badger[5] from their work on the absorption spectra of methanol in various solvents, concluded that aromatic hydrocarbons do give weak H-bonding with methanol but that solvents of the type *n*-hexane and cyclohexane do not. There is evidence also for hydrogen bonding between amines and dioxane as well as between amines and methanol although the former are weaker. It is probable that dioxane, since it is present in relatively large amounts, reduces the concentration of free methanol and ammonia molecules by hydrogen bonding with them. Thus the concentration of the complex,

$\overset{H}{CH_3O}\cdots H\text{-}NH_2$, which is believed to promote the ammonolysis reaction, would be decreased and lead to a slower reaction.

Acid Catalysis.—Although it is well established that bases catalyze aminolysis, the case for acid catalysis has not been equally well established. Because of this scarcity of evidence, the effects of β-phenylethylammonium carbonate and β-phenylethylammonium chloride on the aminolysis of methyl acetate with β-phenylethylamine were determined. One molar methyl acetate was used in all of the experiments. The sum of the concentrations of the amine and amine salt was kept at approximately 2 *M*. The results from different solvent systems are shown in Table III.

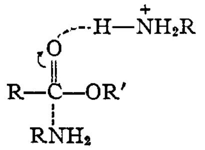
TABLE III

EFFECTS OF AMINE SALTS ON RATES OF AMINOLYSIS AT 30°[a]

10 *M* Water–Dioxane		10 *M* H_2O–Dioxane	
k	Aminolysis, %	*k*	Aminolysis, %
0.0372 *M* Carbonate		0.191 *M* Carbonate	
3.87	28.8	4.64	28.4
3.64	46.4	4.27	43.7
3.42	59.7	4.01	54.0
0.0979 *M* Hydrochloride		0.153 *M* Hydrochloride	
4.63	21.0	5.17	21.8
4.28	38.9	4.77	39.5
4.05	47.7	4.53	47.8
10 *M* Methanol–Dioxane		10 *M* Methanol–Cyclohexane	
0.0950 *M* Hydrochloride		0.1007 *M* Hydrochloride	
1.82	15.4	4.05	17.5
1.84	21.6	3.88	27.9
1.82	35.9	3.56	53.2

[a] *k* = *k* × 10³; units = liter/mole hour.

These data show that ammonium salts (acids) exert a small but definite catalytic effect on aminolysis. This may be shown as



This pictures a simultaneous attack on the carbonyl group by the ammonium ion and by the amine.

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[4] W. Gordy, *J. Chem. Phys.*, **7**, 93 (1939); W. Gordy and S. C. Stanford, *ibid.*, **9**, 204 (1941); W. Gordy, *ibid.*, **9**, 215 (1941).

[5] L. H. Jones and R. M. Badger, THIS JOURNAL, **73**, 3132 (1951).