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

Effect of Structure on Reactivity. VI. Catalysis in the Ammonolysis and Hydrolysis of Methyl Acetate

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The relative catalytic effects of a number of hydroxy compounds on the rates of ammonolysis in water–dioxane solutions under conditions of equimolar concentration of the hydroxyl group have been determined. The catalytic effects of sorbitol and inositol were the same and were greater than those of ethylene glycol and *cis*- and *trans*-1,2-cyclohexandiol. It was found that these compounds exhibited a similar catalytic effect on the rates of hydrolysis. Thus the studies of catalysis by 1,2-diols have been extended. In addition, it has been shown that the 1-amino-2-ol grouping exerts similar catalytic effects. The compound used in this case was β-dimethylaminoethanol.

Previous work in this series[1] has shown a special catalysis in the ammonolysis of esters in the presence of vicinal diols and related compounds containing a –O–C–C–O– group.

In the present investigation, water, methyl alcohol, ethylene glycol, *cis*- and *trans*-1,2-cyclohexandiols, sorbitol and inositol were studied at equimolar concentrations of the hydroxyl group. Solubility factors made a predominantly aqueous system a necessity.[2] The presence of higher concentrations of water than were used in previous work made hydrolysis a competing reaction and made necessary the determination not only of ammonia but also of ammonium acetate and acetamide as well.

Experimental

Reagents.—The dioxane was refluxed with 1 *N* hydrochloric acid for 7 hours in a nitrogen atmosphere. It was then washed and dried over potassium hydroxide. Finally it was refluxed with sodium for 4 hours and distilled; b.p. 101–101.5° at 760 mm., $n^{20}D$ 1.4223.

Methyl acetate after drying over anhydrous magnesium sulfate was fractionally distilled; b.p. 56.7–57.2° at 760 mm., $n^{20}D$ 1.3614.

Methyl alcohol was dried by refluxing with 10 g. of magnesium and 0.5 g. of iodine per liter of alcohol followed by fractional distillation; b.p. 64.7–65.2° at 760 mm., $n^{20}D$ 1.3286.

Ethylene glycol was distilled at 1 mm. and the fraction boiling at 60–68° was dried over anhydrous magnesium sulfate and finally fractionally distilled at 1 mm.; b.p. 70–71°, $n^{20}D$ 1.4274.

The *trans*-1,2-cyclohexandiol was prepared by the performic acid oxidation of cyclohexane[3]; b.p. 120–125° at 4 mm., m.p. 102–103°.

The *cis*-1,2-cyclohexandiol was prepared by the method of Criegee and Stanger[4] and by the method of Milas and Sussman[5]; b.p. 117° at 14 mm., m.p. 98°.

Commercial *i*-inositol was purified by several recrystallizations from water and vacuum drying, m.p. 225°.

Commercial sorbitol was recrystallized several times from a 50% alcohol–water solution and obtained as the pure hemihydrate, m.p. 89–93°. Anhydrous sorbitol was obtained by fusing the hydrate and storing over anhydrous magnesium sulfate, m.p. 110–111°.

β-Dimethylaminoethanol was dried over potassium hydroxide and fractionally distilled; b.p. 134.5–135.5° at 760 mm., $n^{20}D$ 1.4362.

Procedure.—The catalyst was measured into a 100-ml. volumetric flask, a calculated amount of water was added and then enough dioxane to give a total volume of 75–85 ml. The solution was cooled to 5–10° and sufficient dry ammonia introduced through a sintered glass dispersion tube to give a 2 *M* solution. The flow of ammonia was controlled by a diaphragm pressure gage and needle valve and metered by means of an aluminum float flow-rater. Only those solutions having a 2–2.05 molar concentration of ammonia were used. After the solution had come to room temperature, 0.1 mole of methyl acetate was added and sufficient dioxane to bring the total volume to 100 ml. Ten-ml. portions of the solution were delivered from a reservoir-type pipet into alkali-free glass ampoules. The latter were capped with gelatin capsules, cooled in ice and then sealed. The sealed samples were placed in a thermostat at 30 ± 0.005°, reserving portions two and nine for zero-time concentration of ammonia. The latter two were analyzed immediately.

Analysis.—Unused ammonia was determined by releasing the sample under excess hydrochloric acid and back titrating with a standard sodium hydroxide solution using a Beckman model M *p*H meter. The ammonium ion concentration in the same sample was determined by the procedure developed by Marcali and Reiman,[6] for the titration of ammonium salts with sodium hydroxide in the presence of formaldehyde. The total ammonia consumed was determined in the first titration. The difference between the total ammonia consumed and the total ammonium ion determined in the second titration gives the amount of ammonia used as the result of hydrolysis. The amount of ammonolysis, then, is the difference between the total ammonia reacted and that consumed by the hydrolysis.

Calculations

The ammonolysis of esters is a pseudo-second-order reaction and the alkaline hydrolysis of esters is a second-order reaction of the ester and hydroxyl ion. The following equations represent the essential reactions and equilibria.

$$CH_3COOCH_3 + NH_3 \longrightarrow CH_3OH + CH_3CONH_2 \quad (1)$$

$$CH_3COOCH_3 + \overset{-}{O}H \longrightarrow CH_3OH + CH_3CO\overset{-}{O} \quad (2)$$

$$CH_3CO\overset{-}{O} + H_2O \rightleftharpoons CH_3COOH + \overset{-}{O}H \quad (3)$$

$$NH_3 + H_2O \rightleftharpoons NH_4^+ + \overset{-}{O}H \quad (4)$$

It is not possible to write an exact and simple expression for the concentration of the hydroxyl ion. The treatment of such competitive second-order reactions, even without the added complications of the system used in the present investigation, is difficult.[7] In the present study we choose to write $OH^- = c[NH_3]$ where c is an undetermined constant which relates the hydroxyl ion concentration in the reaction medium to the ammonia concentration. The rate equation for the second-order reactions may then be written as

$$-\frac{d(MeOAc)}{dt} = k_1[MeOAc][NH_3] + k_2'[MeOAc][OH]^-$$
$$= k_1[MeOAc][NH_3] + k_2[MeOAc][NH_3]$$

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[1] M. Gordon, J. G. Miller and A. R. Day, THIS JOURNAL, **70**, 1946 (1948); **71**, 1245 (1949).

[2] Since the workers in this Laboratory have held the opinion since 1948 that the catalysis shown by the type compounds mentioned above may be quite similar to that shown by certain enzymes, the choice of a medium containing water was a most fortunate one.

[3] A. Roebuck and H. Adkins, *Org. Syntheses*, **28**, 35 (1948).

[4] R. Criegee and H. Stanger, *Ber.*, **69B**, 2753 (1936).

[5] N. Milas and S. Sussman, THIS JOURNAL, **59**, 2345 (1937).

[6] K. Marcali and W. Reiman, *Ind. Eng. Chem., Anal. Ed.*, **18**, 709 (1946); **20**, 381 (1948).

[7] A. A. Frost and W. C. Schwemer, THIS JOURNAL, **74**, 1268 (1952).

TABLE I

SPECIFIC AND RELATIVE REACTION RATE CONSTANTS AT 50% METHYL ACETATE REACTED

		Ammonolysis		Hydrolysis	
	System	$K \times 10^2$, l./mole-hr.	Relative K values	$K \times 10^2$, l./mole-hr.	Relative K values
1	10 M water-1.5 M ethylene glycol	0.24	0.11	0.05	0.056
2	20 M water-1.5 M ethylene glycol	1.00	0.47	0.28	0.31
3	30 M water-1.5 M ethylene glycol	3.34	1.58	1.50	1.67
4	3 M water-total 33 M water	3.02	1.43	1.28	1.42
5	3 M methyl alchol-30 M water	2.36	1.12	1.04	1.16
6	30 M water	2.11	1.00	0.90	1.00
7	$^1/_2$ M sorbitol-30 M water	4.38	2.08	1.96	2.18
8	$^1/_6$ M inositol or sorbitol-30 M water	2.72	1.29	1.12	1.24
9	1.5 M *cis* or *trans*-1,2-cyclohexanediol-30 M water	3.22	1.53	1.50	1.67
10	1.5 M β-Dimethylaminoethanol-30 M water	3.88	1.84	2.48	2.76

This may be integrated to give

$$k_1 + k_2 = \frac{2.303}{t(a - b)} \log \frac{b(a - x)}{a(b - x)}$$

By application of the Wegscheider principle[8] we may write

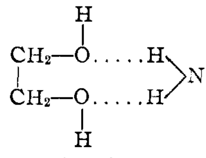
$$k_1/k_2 = CH_3CONH_2/CH_3CO\bar{O}$$

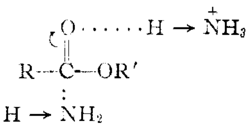
This term may be evaluated if it is assumed that $[CH_3CO\bar{O}] = [NH_4^+]$. Since both the sum and the ratio of k_1 and k_2 are measured, the individual values of k_1 and k_2 may be determined. The rate constants are expressed in units of liters per mole-hour.

Discussion

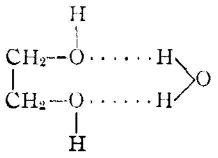
The data in Table I (1–4) indicate the effect of water on the rates of ammonolysis and hydrolysis and show that the role of the hydroxylated solvent is more significant than any effects due to dioxane, since the change in the concentration of water is the major change. A drift of the specific reaction rate constant as the reaction nears completion was found in all cases where the initial concentration of water was thirty molar. The postulated mechanism for the activation of ammonia by water,[2] $H_2N\text{-}H\cdots OH_2$, is substantiated by these data.

The fact that methyl alcohol (Table I, 5) is a weaker catalyst is undoubtedly due to the lower electron density on the oxygen atom of the alcohol. The superior catalysis of ethylene glycol, compared to water or methyl alcohol at equimolar concentration of the hydroxyl group, indicates that a somewhat different activation process must be in operation. A cyclic hydrogen bond structure had been previously postulated as the activating complex to account for the unusual activity of ethylene glycol. Although under the conditions used in the present study, the differences in the specific reaction rate constants were not so large as those previously reported, the differences were significant under conditions that rigorously tested the catalysis by having equimolar concentrations of the hydroxyl group.[9]





The effects of the catalytic solvent on the rates of ammonolysis and hydrolysis are in constant proportion in all cases. The rate of hydrolysis depends on the concentration of the hydroxyl ion. Since all other factors are constant, the rate of hydrolysis is a measure of the basicity of the catalyst. That water should be a better catalyst than methyl alcohol would be predicted, but the superior catalysis of ethylene glycol suggests a somewhat different process. A glycol–water complex of the type similar to the glycol–ammonia hydrogen-bonded structure, would serve to simulate the hydroxyl ion by increasing the electron density on the oxygen atom.



Inositol and sorbitol were found to have almost identical activity in promoting ammonolysis and hydrolysis of the ester (Table I, 7 and 8). That sorbitol and inositol are superior to ethylene glycol as catalysts for the ammonolysis and hydrolysis of esters may be attributed to the fact that regardless of the direction of approach of the ammonia molecule or water molecule to the polyhydroxy molecule, a pair of vicinal hydroxy groups is available. Due to its low solubility, inositol could not be tested at a concentration of 0.5 M. At 1/6 molar concentrations inositol and sorbitol had identical activities (Table I, 8). Table I summarizes the specific reaction rate constants for the various catalysts used at 50% methyl acetate reacted. The relative rate values are based on the system where thirty moles of water were present as the only hydroxylated catalyst.

The activity of *cis*- and *trans*-1,2-cyclohexandiol (Table I, 9) in promoting ammonolysis and hydrolysis was found to be almost identical with that of ethylene glycol. Consideration of the steric relationships of the hydroxyl groups, with reference to the oxygen–oxygen distance, shows that this is

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[8] R. Wegscheider, *Z. physik. Chem.*, **30**, 593 (1899).

[9] It has been found in this Laboratory that ammonium ions also catalyze ammonolysis. The effect is small and probably introduces little or no error in the basic rate equation used in the present study. It may be that ammonolysis involves both a nucleophilic (base) and an electrophilic (acid) attack on the carbonyl group of the ester.

not inconsistent with the cyclic hydrogen-bonded complexes shown above.

It has been shown that systems containing the grouping N–C–C–O exert a similar catalytic effect on the ammonolysis and hydrolysis of methyl acetate (Table I, 10). Only β-dimethylaminoethanol is reported here.[10]

[10] The work is being extended to other systems containing this grouping including compounds containing peptide linkages.

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[CONTRIBUTION FROM THE INORGANIC CHEMISTRY BRANCH, CHEMISTRY DIVISION, RESEARCH DEPARTMENT, U. S. NAVAL ORDNANCE TEST STATION]

The Hydrazinolysis of Nitroguanidine in Alcoholic Systems. Preparation and Reactions of 1,6-Dinitrobiguanidine[1a,b]

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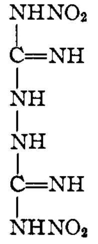
The hydrazinolysis of nitroguanidine in methanol or ethanol gives aminoguanidine in 50–70% yield; small amounts of nitroaminoguanidine (*ca.* 10%) and diaminoguanidine are formed. 1,6-Dinitrobiguanidine, $NO_2NHC(NH)NHNHC(NH)NHNO_2$, and 1,6-dinitro-2-(aminoguanyl)-biguanidine have also been isolated as their di-(aminoguanidinium) salts; the structure of each of these compounds has been elucidated and an extensive interrelationship between them has been established. 1,6-Dinitrobiguanidine can be prepared in 20–25% yield by the reaction of nitroaminoguanidine and 1-methyl-1-nitroso-3-nitroguanidine or in 55% yield by the hydrogen sulfide reduction of azobisnitroformamidine. When 1,6-dinitro-2-(aminoguanyl)-biguanidine is diazotized, 5-aminotetrazole is eliminated in a ring closure which yields 3,5-di-(nitramino)-1,2,4-triazole (isolated as its monopotassium or ammonium salt).

The hydrazinolysis of nitroguanidine in aqueous systems has been shown to yield nitroaminoguanidine,[2] as the principal product and amino- and diaminoguanidine,[3] as the by-products. In methanol or ethanol, however, the results are significantly different. In the first place, free nitroaminoguanidine can only be isolated with difficulty in small yields (10%), and in the second place, aminoguanidine is produced to the extent of 50–70% of theory. Small quantities of diaminoguanidine are also formed. Two new compounds, which are sparingly soluble in the alcohol, have also been isolated; the particular compound obtained depends on the alcohol employed for the solvent and on the other conditions of reaction.[4]

One of the compounds (IV) melts with decomposition at 146–147° and can be converted by refluxing in absolute methyl alcohol into the other compound (III), decomposing at 166–167°. Both of these compounds are readily soluble in water and give strongly basic solutions. Furthermore, they cannot be recovered or recrystallized from water because of extensive hydrolysis; from these aqueous solutions appreciable amounts of aminoguanidine can be isolated as suitable derivatives.

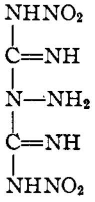
The chemical behavior and the elementary analyses of these compounds are in agreement with the idea that they are di-(aminoguanidinium) salts of closely related nitramino derivatives and that they possess the formulas: compound III, $(CH_6N_4)_2 \cdot C_2H_6N_8O_4$; compound IV, $(CH_6N_4)_2 \cdot C_3H_9N_{11}O_4$. The compound, $C_2H_6N_8O_4$ (I), gives a positive Franchimont test with α-naphthylamine and very slowly reduces potassium iodate in the Jamieson hydrazine nitrogen determination[5] which indicates the absence of a primary hydrazino group, but the presence of a protected hydrazino group which is liberated slowly through hydrolysis. Although this compound also reacts with both formaldehyde and glyoxal, the derivatives are not simple hydrazones; unlike nitroaminoguanidine, the compound does not yield a hydrazone with benzaldehyde.

Three probable structures, agreeing with the method of preparation and the empirical formula, $C_2H_6N_8O_4$, can be assigned



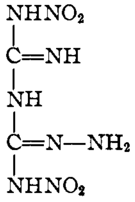
$NHNO_2-C(=NH)-NH-NH-C(=NH)-NHNO_2$

(A) 1,6-Dinitrobiguanidine



$NHNO_2-C(=NH)-N(NH_2)-C(=NH)-NHNO_2$

(B) 1,5-Dinitro-3-aminobiguanide



$NHNO_2-C(=NH)-NH-C(=N-NH_2)-NHNO_2$

(C) 1,5-Dinitro-2-aminobiguanide

Formula (C) can be excluded immediately since this compound with a primary hydrazino group would be expected to reduce potassium iodate solution rapidly and to form a hydrazone with ease. Either of the other two tentative structures is in agreement with the observation that potassium iodate is only reduced slowly in the Jamieson hydrazine titration. However, 1,5-dinitro-3-am-

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[1] (a) Presented at the 116th Meeting of the American Chemical Society, Atlantic City, N. J., September, 1949. This paper is published with the approval of the Office of Public Information, National Military Establishment. (b) For simplicity in naming and numbering certain of the derivatives in this paper, the parent compound $\underset{1}{NH_2}$-C($\underset{2}{NH}$)$\underset{3}{NH}\underset{4}{NH}$C($\underset{5}{NH}$)$\underset{6}{NH_2}$, is named "biguanidine" rather than hydrazobisformamidine or hydrazodicarbamidine. This is consistent with the nomenclature used in *Chemical Abstracts;* thus, $NH_2CONHNHCONH_2$, is biurea and HOOCNHNHCOOH is bicarbazic acid. Derivatives of $NH_2C(NH)N{=}NC(NH)NH_2$ are named as derivatives of azobisformamidine; this is again consistent with the usage of *Chemical Abstracts.*

[2] R. Phillips and J. F. Williams, THIS JOURNAL, **50**, 2465 (1928).

[3] R. A. Henry, H. D. Lewis and G. B. L. Smith, *ibid.*, **72**, 2015 (1950).

[4] When anhydrous hydrazine is used instead of the hydrate, insignificant amounts of these compounds are formed and the nitroguanidine is converted almost exclusively to aminoguanidine.

[5] G. S. Jamieson, *Am. J. Sci.*, **33**, 352 (1912); "Volumetric Iodate Methods," Chemical Catalog Co., (Reinhold Publ. Corp.). New York, N. Y., 1926, p. 36.