

In the cases of the tetra- and pentamethyl derivatives, the method of synthesis was regarded as sufficient proof of their structures.

p-Bromo- and *p*-iodomandelic acids are well known, hence their melting points and neutral equivalents were considered to be sufficient to identify these compounds.

A summary of the bacteriological data is presented in Table II. These tests were made *in vitro* on three different organisms (*B. coli*). The activities are compared with mandelic acid as a standard.

TABLE II

Mandelic acid derivative	Activity
Mandelic	1
<i>p</i> - <i>n</i> -Propyl	1 or less
<i>p</i> - <i>n</i> -Butyl	1 or less
<i>p</i> - <i>n</i> -Amyl	1 or less
<i>p</i> -Isoamyl	1 or less
<i>p</i> - <i>t</i> -Amyl	1 or less
Pentamethyl	No activity
2,3,5,6-Tetramethyl	Less than 1
<i>p</i> -Bromo	2-4
<i>p</i> -Iodo	2-4

The first seven of the compounds listed in Table II are so costly to prepare and show so little activity that further experimentation with them would appear fruitless. The two halogen deriva-

tives possess sufficient activity to warrant animal tests to determine their efficacy as urinary tract antiseptics.

The authors are glad to acknowledge the cooperation of Dr. Robert S. Shelton of the Wm. S. Merrell Co., of Cincinnati, Ohio, who performed the bacteriological work, and wish to thank Dean William M. Blanchard of this department who was instrumental in securing financial aid from The National Research Council and from Mr. J. K. Lilly of Indianapolis, Indiana.

Summary

1. Nine substituted mandelic acids have been prepared and compared with mandelic acid with regard to bacteriological activity. Only the *p*-bromo- and *p*-iodomandelic acids show any promise as medicinals.

2. Ando's method for the synthesis of substituted mandelic acids has been extended for alkyl derivatives and has been shown to work poorly for halogen derivatives.

3. Boron trifluoride is not satisfactory to use in the place of anhydrous stannic chloride as the condensing agent.

GREENCASTLE, INDIANA

RECEIVED AUGUST 8, 1938

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF TRINITY COLLEGE]

Amide Hydrolysis with High Concentrations of Mineral Acids

BY VERNON K. KRIEBLE AND KARL AUGUST HOLST

The hydrolysis of amides in dilute acid solutions has been studied repeatedly. There are, however, few studies on record for acid concentrations greater than normal, and these have nearly all been made on acetamide.

Benrath¹ had some indications that the velocity of hydrolysis of acetamide reached a maximum by increasing the acid concentration. This was definitely shown by Taylor² for both hydrochloric and hydrobromic acids although he did not find such a maximum for sulfuric acid. As we have been interested in the hydrolysis of nitriles it seemed worth while to extend the study to amide hydrolysis.

Materials and Procedure

Amides.—These were bought from well-known manufacturers and further purified. We did not try to remove

all the water from formamide. This was allowed for in weighing out samples of this particular amide.

Formaldehyde.—Merck U. S. P. grade was used.

Calcium Hypochlorite.—The grade marked "H. T. H." and manufactured by the Mathieson Alkali Works was used. All other chemicals were of the blue label or reagent grade.

Procedure.—Exactly 200 cc. of acid, carefully standardized in terms of molality, was delivered to a glass-stoppered flask which was placed in a thermostat for one-half hour before the experiment was started. Enough amide was weighed out to make the solution contain from 0.5 to 0.8 mole of amide if the formol method of analysis was to be used and 0.05 mole if the oxidation method was to be used to follow the hydrolysis. The acid was poured on the amide which quickly dissolved. The solution after thorough mixing was poured into a series of Pyrex tubes. These were closed with rubber stoppers, wired down, and then put back in the thermostat. When a sample was to be taken, a tube was removed and a definite quantity pipetted into a titration beaker containing enough water to dilute the solution sufficiently to stop the reaction. This

(1) Benrath, *Z. anorg. allgem. Chem.*, **151**, 53 (1926).

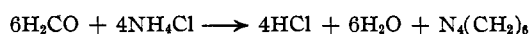
(2) Taylor, *J. Chem. Soc.*, 2741 (1930).

diluted solution was immediately cooled, neutralized, and analyzed for ammonia.

Method of Analysis.—When the amide is hydrolyzed the corresponding organic acid and ammonia are produced. Consequently, it is possible to follow the progress of the hydrolysis by estimating the ammonia present in the hydrolytic solution. This can be done in various ways, but in this investigation it was done by the oxidation of the ammonia with an hypochlorite or else by the Sørensen formol titration. In the oxidation method the ammonia reacts with a standard hypochlorite solution releasing nitrogen.



The excess hypochlorite is estimated by adding potassium iodide and titrating the liberated iodine with standard sodium thiosulfate. It was found that the procedure given by Kolthoff and Stenger,³ was to be preferred to others recorded in the literature. This method was used for most of the rates studied in connection with acetamide and with propionamide where sulfuric acid was the catalyst. It, however, could not be used in the hydrolysis of formamide, which was oxidized by the hypochlorite as well as the ammonia. So the Sørensen formol titration method following the directions given by Hawk and Bergeim⁴ was tried. Here formaldehyde reacts with ammonium salts in a neutral solution forming hexamethylenetetramine and liberating an equivalent of the mineral acid which then can be titrated with a standard base.



This proved to be an excellent method. In any given experiment the velocity constants for various time intervals were much more consistent than by the oxidation method. It was used exclusively with formamide and would have been used with the other amides had we been familiar with its accuracy when the research was started. The rates for acetamide with 1.5 and 3 molal hydrochloric acid were followed by this method and are in line with those determined by the oxidation method.

Order of the Reaction.—The velocity constants were calculated by the monomolecular formula

$$K = \frac{1}{t} \ln \frac{a}{a-x}$$

(3) Kolthoff and Stenger, *Ind. Eng. Chem., Anal. Ed.*, **7**, 79 (1935).

(4) Hawk and Bergeim, "Practical Physiological Chemistry," P. Blakiston's Son Co., Philadelphia, Penna., 1931, p. 830.

the time being taken in hours. For the same acid concentration equally good constants were obtained even though the amide concentration varied from 0.05 to 0.8 mole. Benrath also found that whenever the acid concentration exceeded that of the amide the monomolecular formula held. Taylor likewise used this formula in dealing with high concentration of mineral acids on acetamide. Table I illustrates two typical hydrolyses and shows that the velocity is well maintained to more than 85% of completion.

TABLE I

H ₂ SO ₄ , 2.0 molal HCONH ₂ , 0.52 mole			HCl, 9.5 molal HCONH ₂ , 0.8 mole		
t, hrs.	% hydrolyzed	K	t, hrs.	% hydrolyzed	K
0.166	16.9	1.11	0.26	27.2	1.23
.416	37.0	1.11	.42	39.4	1.20
.75	55.0	1.06	.58	51.8	1.25
1.18	70.4	1.02	.75	61.3	1.26
1.50	80.9	1.10	1.00	72.5	1.29
1.75	85.4	1.10	1.25	79.5	1.26
2.00	88.4	1.07	1.50	85.5	1.28

In any experiment the velocity constant recorded represents an average of at least six time intervals taken between 18 and 85% of complete hydrolysis. It was seldom that any points averaged varied more than 5% from the mean.

Experimental Results

Hydrolysis of Formamide

Table II		Table III	
Molality HCl	K	Molality H ₂ SO ₄	K
2	.82	2	1.08
4	1.59	2.9	1.51
5	1.74	3.5	1.62
6	1.84	4.5	1.72
7	1.78	5.0	1.73
8	1.62	6	1.54
9.5	1.27	8	1.12

Hydrolysis of Acetamide

Table IV		Table V	
Molality HCl	K	Molality H ₂ SO ₄	K
1.50	0.025	0.97	0.024
2.67	.038	2.00	.032
2.91	.039	2.50	.033
4.13	.035	3.00	.032
5.00	.026	4.14	.027

Hydrolysis of Propionamide

Table VI		Table VII	
Molality HCl	K	Molality H ₂ SO ₄	K
1.5	0.034	0.186	0.012
3.0	.050	.97	.041

Table VI

3.5	0.050
4.0	.048
5.0	.042

Table VII

1.75	0.053
3.07	.052
4.13	.045
5.29	.032
6.00	.026
7.51	.017
11.20	.006

Discussion

The results obtained for the hydrolyses of the different amides may be discussed from several angles. In every case there is a concentration in which the rate of hydrolysis of the amide is maximum. This concentration is not the same for different amides nor is it the same for hydrochloric acid and sulfuric acid. In each case the molality of the hydrochloric acid at its highest rate is greater than the molality of sulfuric acid for its highest rate.

This is the first time that maximum rates have been observed in the hydrolysis of formamide and propionamide and also for acetamide where sulfuric acid is the catalyst. It is, therefore, probably true for all amides. Benrath and Taylor investigated the hydrolysis of acetamide in concentrations up to 7 *N* sulfuric acid and found no indication of a maximum rate while both found maximum values for hydrochloric acid at approximately 3 *N* concentration. It should be pointed out that a comparison of rates of hydrolysis where high concentrations of acid are involved on a normality basis has little meaning. In the first place, the ratio of water molecules to acid molecules, for example, in a 7 *N* sulfuric acid and a 7 *N* hydrochloric acid solution is quite different and the activity of water in the higher concentrations cannot be ignored. In the second place, polybasic acids in these concentrations function only as monobasic acids. It is much better to make the comparison on a molality basis.

Comparing the effects of the same molal concentrations of the same acids on the different amides, it is apparent that the order of decreasing activity for these amides is formamide, propionamide and acetamide. It is interesting to note that propionamide is hydrolyzed faster than acetamide just as propionitrile is hydrolyzed faster than acetonitrile. This was noted by Crocker⁵ also. The reverse is the case when alkali is the catalyst, as Crocker and Lowe and Calvet have pointed out.⁶

(5) Crocker, *J. Chem. Soc.*, **91**, 593 (1907).

(6) Crocker and Lowe, *ibid.*, **91**, 952 (1907); Calvet, *J. Chem. Phys.*, **30**, 1, 140, 198 (1933).

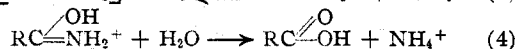
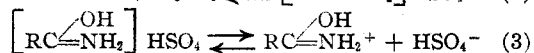
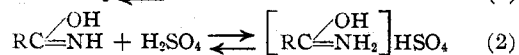
All the rates studied show that the velocity constant is not a simple function of the molality of the acid and consequently not of the acidity function of the acid. It is to be noted, however, that before the maximum velocity is reached sulfuric acid, which has a higher acidity than hydrochloric acid, is the better catalyst. After the maximum velocity hydrochloric acid is the better catalyst. In other words, acidity is an aid to the reaction up to the maximum velocity and after that a retarding influence. The maximum velocity is reached by both acids at approximately the same acidity as Table VIII shows.

TABLE VIII
MOLALITIES AND ACIDITIES OF SOLUTIONS AT MAXIMUM VELOCITIES

Amide	Acid	Molality	H_0
Formamide	HCl	6	-1.75
Formamide	H ₂ SO ₄	4.75	-1.70
Acetamide	HCl	3.25	-1.02
Acetamide	H ₂ SO ₄	2.5	-0.90
Propionamide	HCl	3.20	-1.00
Propionamide	H ₂ SO ₄	2.40	-0.88

While the velocity of amide hydrolysis, therefore, does not vary directly as the acidity, it is an important factor in the control of the velocity.

Mechanism of Reaction.—In amide hydrolysis, according to former investigators, we are possibly dealing with the following reactions



Hantzsch and Geidel⁷ conclude from their absorption experiments in the ultraviolet that at equilibrium the imino form is in large excess, particularly in the aromatic amides. Pauling and Sherman⁸ have calculated from the heats of formation that amides are resonating molecules and Kumlér⁹ that acetamide at least is largely a dimer held by hydrogen bonds. Hantzsch and Geidel also conclude that the salt formed when acid is added to the amide is the salt of the imino form because the absorption spectra agree with the salt of the imino ether. From freezing point measurements they show that the salt is highly ionized. Benrath, and Euler and Ölander,¹⁰ and others have

(7) Hantzsch and Geidel, *Ber.*, **64B**, 667 (1931).

(8) Pauling and Sherman, *J. Chem. Phys.*, **1**, 606 (1933).

(9) Kumlér, *THIS JOURNAL*, **57**, 600 (1935).

(10) Benrath, *Z. anorg. allgem. Chem.*, **151**, 53 (1926); Euler and Ölander, *Z. physik. Chem.*, **151**, 107 (1927).

come to the conclusion that it is the amide cation that hydrolyzes to the acid.

Even if all these reactions are in evidence when an amide is added to a mineral acid, it does not explain why the velocity of hydrolysis reaches a maximum and then falls off with increased acid concentration. Benrath came to the conclusion that the velocity was greatest when sufficient acid was added to convert all the amide into a cation. When the acid is increased beyond this point the cation combines with the anion to form an undissociated salt which does not react with water and hence the velocity of hydrolysis falls off. Taylor comes to a somewhat similar conclusion as he says that increased acid concentration caused the formation of an unhydrolyzable complex between the acid and the amide. If this were the true explanation, then the molality of the acid at maximum velocity should vary with the concentration of the amide, but this does not appear to be the case. Benrath used a concentration of 2.4 *N* acetamide while Taylor used 0.05 *N* and we used 0.05 to 0.8 *N*. Benrath had his maximum velocity at 3.18 molal hydrochloric acid and Taylor at 3.0 and we at 3.25.

There is another reaction of the amides which is apparently closely associated in mechanism with their hydrolysis, namely, their reaction with nitrous acid. Plimmer¹¹ showed that amides do not react with nitrous acid in acetic acid. We have confirmed this statement. They will not react until enough mineral acid has been added to make the solution 2 *N* according to Plimmer. Taylor¹² reports that an aqueous solution must be 4 *N* with respect to mineral acid before decomposition takes place. On the other hand, amines, amino acids and urea react with nitrous acid in acetic acid without addition of mineral acids. The alpha amino group in amino acids reacts completely in five to thirty minutes according to Van Slyke. In these compounds we have an amino group which apparently is lacking in the amides until a certain acidity is attained. It is for this reason that Plimmer concludes that the amide in solution is in the imino form, but when sufficient mineral acid is added the equilibrium is shifted in (1) to the left in favor of the true amide which then reacts with nitrous acid. If this is the true explanation for amide decomposition with nitrous acid, it also offers a plausible explanation for the maximum velocity phenomena for amide hydrolysis.

(11) Plimmer, *J. Chem. Soc.*, **127**, 2651 (1925).

(12) Taylor, *ibid.*, 2741 (1930).

From unpublished results in this Laboratory it is known that the maximum velocity for amide hydrolysis in acetic acid requires a much lower mineral acid concentration than in aqueous solutions just as it does for nitrous acid decomposition. It appears, therefore, that amide decomposition with nitrous acid and amide hydrolysis at maximum velocity are correlated with the same mineral acid concentration and perhaps with the amide imide equilibrium of reaction (1), the supposition being

that increased acidity favors the $\text{RC}=\overset{\text{O}}{\text{N}}\text{H}_2$ tautomer and thus lowers the cation $\text{RC}=\overset{\text{OH}}{\text{N}}\text{H}_2^+$ concentration and hence the rate of hydrolysis. It is equally plausible that, so far as the nitrous acid reaction is concerned, the reason that amines and amino acids react in acetic acid while amides do not is due to the fact that the former are much more basic and therefore form salts more readily and hence react while amides do not form salts and therefore do not react.

Dr. C. D. Coryell has suggested that the abnormal amide hydrolysis might depend on the activity of water. The activity of water drops to 0.51 in an 8 molal hydrochloric acid solution and to 0.48 in the same molal concentration of sulfuric acid. According to this idea, with increase in acid concentration the ratio of the velocity to the activity of water should increase so long as the concentration of the amide cation increases faster than the proper power of the activity of water de-

TABLE IX
HYDROCHLORIC ACID ON ACETAMIDE AT 50°

Mol. HCl	$K \times 10^{10}$	$\frac{K \times 10^4}{\text{Act. H}_2\text{O}}$	$\frac{K \times 10^4}{(\text{Act. H}_2\text{O})^2}$
2.5	32.4	36.2	40.0
3.19	34.1	40.0	47.5
3.87	30.0	40.7	47.0
4.56	26.5	35.0	45.5
5.27	23.0	32.5	45.0
6.75	16.9	27.5	45.0

^a Velocity constants taken from Benrath, ref. 1.

SULFURIC ACID ON PROPIONAMIDE AT 25°

Mol. H ₂ SO ₄	$K \times 10^3$	$\frac{K \times 10^3}{\text{Act. H}_2\text{O}}$	$\frac{K \times 10^3}{(\text{Act. H}_2\text{O})^2}$
0.18	12	12.1	12.2
.97	41	41.6	42.6
1.75	53	57.2	61.7
3.07	52	61.7	73.7
4.13	45	58.9	77.6
5.29	33	48.7	73.9
6.00	26	41.6	67.2
7.50	17	33.1	76.3
11.20	5	19.3	71.4

creases. When, however, the amide has all been converted into a cation the velocity should decrease at the same rate as the power of activity of water or the ratio of K to the activity function of water should remain a constant. Unfortunately, the data on velocities beyond the maximum are very meager. Benrath studied the action of hydrochloric acid on acetamide up to 6 N or 6.75 molal and we studied sulfuric acid on propionamide to 11.2 molal. Table IX shows the ratio of the velocity constants to the square of the activity of water.

The constancy of the ratio of the rate constant to the square of the activity of water is striking and indicates that there may be two molecules of water involved in the hydrolysis of the amide cation. It is necessary to have more experimental data to establish definitely this point of view.

We are extending the investigation to include: (1) the action of nitrous acid on amides with varying mineral acid concentrations; (2) the hydrolysis of disubstituted amides; (3) the hydrolysis of acetamide with varying activities of water.

Summary

A study has been made of the hydrolysis of formamide, acetamide and propionamide under the influence of high concentrations of hydrochloric acid and of sulfuric acid.

Each amide has a maximum velocity of hydrolysis at one particular acid concentration. This acid concentration is not the same for both hydrochloric acid and sulfuric acid nor is it the same for different amides. The molality of hydrochloric acid is higher at maximum velocity than for sulfuric acid.

The maximum velocity is reached at about the same acidity for both acids irrespective of the amide. Formamide, however, required a higher acidity than acetamide or propionamide.

Various explanations for the maximum velocity are discussed. A new suggestion has been put forward, namely, that the decrease in the activity of water accounts for the decrease in the velocity of hydrolysis at the higher acid concentration.

HARTFORD, CONN.

RECEIVED OCTOBER 17, 1938

[CONTRIBUTION FROM THE FOREST PRODUCTS LABORATORY,⁴ FOREST SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

The Microstructure and the Diffraction Pattern of Basswood Ash¹

BY E. A. PARKER,² W. E. PATZER³ AND GEO. J. RITTER³

In the burning of wood to ash it was found that an ash residue retaining the fine structure of the original wood could be obtained by carefully controlling a current of oxygen-ozone in the furnace.

Ash residues were prepared from basswood cross sections for determining the microstructure of the ash and the location of the ash-forming constituents. Ash retaining the structure of wood cubes was also made for comparison of its crystalline arrangement with that of ash from wood sawdust. Further, ash was prepared from acid-hydrolyzed wood sections to determine whether the hydrolysis affected the microstructure of the ash constituents.

Previous workers had made ash from thin wood sections in air at glowing furnace temperatures.

Brown⁵ believed the ash contained considerable siliceous material in the form of rodlike structures arranged parallel with the fibers. The ash structure was similar to that photographed by Ritter.⁶ Uber and Goodspeed^{7,8} concluded that the ash-forming constituents were distributed throughout the cell wall, but doubted their existence in the middle lamella.

Experimental

Microstructure of the Ash.—Wood specimens in the present study were burned carefully in a slow current of oxygen containing a small percentage of ozone which was generated by an ozonizer connected with the furnace (Fig. 1). The gas mixture was brought in direct contact with the specimen in the furnace, which was electrically heated to 300 to 325°. Excessive shrinkage of the thin wood sections during the burning was prevented by mounting each specimen on a glass object slide by means of a

(1) Presented before the Division of Cellulose Chemistry, American Chemical Society, Milwaukee, Wis., September 5-9, 1938.

(2) University of Illinois, Urbana, Illinois.

(3) Forest Products Laboratory, Madison, Wis.

(4) Maintained at Madison, Wis., in cooperation with the University of Wisconsin.

(5) F. Brown, *Bull. Torrey Bot. Club*, **47**, 407 (1920).

(6) Geo. J. Ritter, *Rayon and Melliland Textile Monthly*, **16**, [9] 98-100; [10] 58-60 (1935).

(7) F. M. Uber and T. H. Goodspeed, *Proc. Nat. Acad. Sci.*, **21**, 428 (1935).

(8) F. M. Uber and T. H. Goodspeed, *ibid.*, **22**, 463 (1936).