that method, depends upon the formation of cupric xanthate, the excess of copper being determined iodimetrically.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF STANFORD UNIVERSITY]

MIXED AQUO-AMMONOCARBONIC ACIDS. I. AMMONOLYSIS TO AMMONOCARBONIC ACID

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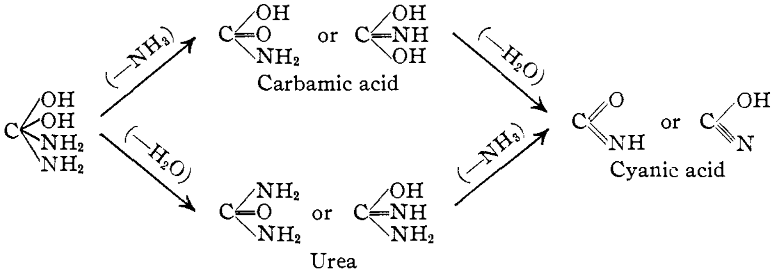
RECEIVED AUGUST 24, 1925 PUBLISHED JANUARY 8, 1926

Mixed aquo-ammonocarbonic acids may be defined as substances which are derivatives of both water and ammonia in the sense in which ordinary carbonic acid is a derivative of water, and in which the ammonocarbonic acids[2] are derivatives of ammonia. As such, they may be regarded as desolvation products (that is, formed by loss of water, or of ammonia, or of both) of one of three hypothetical mixed aquo-ammono-orthocarbonic acids: $C(OH)_3NH_2$, $C(OH)_2(NH_2)_2$, or $C(OH)(NH_2)_3$. This may be represented by a scheme such as the following.



Water or ammonia may, furthermore, be lost in such a way as to give rise to mixed aquo-ammonocarbonic acids containing two or more carbon atoms, as in the familiar formation of biuret and of cyanuric acid from urea, $2CO(NH_2)_2 = HN(CONH_2)_2 + NH_3$, and $3CO(NH_2)_2 = (HNCO)_3 + 3NH_3$.

The number of mixed aquo-ammonocarbonic acids which can be formally derived in this manner is very large. There are 65 mixed aquo-ammonocarbonic acids containing three carbon atoms or less, which should theoretically be capable of existence. Of this number 23 have actually been prepared either in the free state, as salts or, most commonly, in the form of esters.

Mixed aquo-ammonocarbonic acids may be conceived as being formed,

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[1] The material in this and the following paper is from a thesis submitted to the Department of Chemistry and the Committee on Graduate Study of Stanford University in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1924.

[2] Franklin, THIS JOURNAL, **44**, 486 (1922).

in general, from aquocarbonic acid by partial ammonolysis. Conversely, they may all be hydrolyzed back again to aquocarbonic acid with the liberation of ammonia. This generalization was made by Emich[3] who applied the name "carbon-amide" to these compounds. He offered the following general equation to represent their formation in this manner: $m\ H_2CO_3 + n\ NH_3 - p\ H_2O \rightleftharpoons H_{2m+3n-2p}C_mO_{3m-p}N_n$.

With the concept of ammonocarbonic acids in hand, one may carry Emich's generalization further, to represent the facts that mixed aquo-ammonocarbonic acids should not only be formed by the partial ammonolysis of aquocarbonic acid but also by the partial hydrolysis of ammonocarbonic acids. Furthermore, the mixed aquo-ammonocarbonic acids should not only all be capable of hydrolysis to aquocarbonic acid, as was experimentally shown by Emich, but they should all be capable of ammonolysis to an ammonocarbonic acid.

To express this, Emich's general equation may be extended as follows, using guanidine as a typical ammonocarbonic acid: $m\ H_2CO_3 + n\ NH_3 - p\ H_2O \rightleftharpoons H_{2m+3n-2p}C_mO_{3m-p}N_n \rightleftharpoons m\ H_5CN_3 + (3m - p)\ H_2O - (3m - n)\ NH_3$.

The complete equation, reading from right to left, represents the hydrolysis of an ammonocarbonic acid, through various mixed aquo-ammonocarbonic acids, to aquocarbonic acid. Reading from left to right, the equation represents the ammonolysis of aquocarbonic acid, through various mixed aquo-ammonocarbonic acids, to the ammonocarbonic acid.

The final step in the ammonolysis, to form an ammonocarbonic acid has not, however, previously been described in the literature and a description of the method of its accomplishment constitutes the experimental part of the present paper.

One generalization of some interest should not be omitted. The existence of only two aquocarbonic acids is a striking contrast to the fact that a very considerable number of ammonocarbonic acids is known. This contrast seems to be due to the instability of the linkage C—O—C in these compounds, so that aquocarbonic acids containing two or more carbon atoms are unknown, while the corresponding linkage C—NH—C in the ammonocarbonic acids seems to give rise to stable compounds.

The general difference in the stabilities of these two linkages is also valid in the case of the mixed aquo-ammonocarbonic acids, as may be illustrated by a comparison of the formula of biuret, $H_2NCO—NH—CONH_2$, with that of an unknown, hypothetical isomer, $H_2NC(NH)—O—CONH_2$. In fact, no compounds of this class containing the latter type of linkage are known, except that it has been postulated[4] that cyamelide, the somewhat obscure isomer of cyanuric acid, may contain such linkages. Fur-

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[3] Emich, *Monatsh.*, **9**, 378 (1888).

[4] Mulder, *Rec. trav. chim.*, **6**, 199 (1887). Hantzsch, *Ber.*, **38**, 1016 (1905).

thermore, a mixed aquothio-ammonocarbonic acid, prepared by Billeter,[5] was formulated by him as containing such linkages.

In considering the carbonic acids in the general sense, including therein aquo-, ammono- and mixed aquo-ammonocarbonic acids, it becomes apparent that there are four compounds, namely, carbonic acid proper, carbamic acid, urea and guanidine, which are distinct from all the others in that they are the most highly solvated acids.[6] By this it is meant that all of the other carbonic acids may be converted into one or more of these four compounds by the addition of solvent, that is, either water or ammonia. It might be anticipated, therefore, that an investigation of the ammonolysis of mixed aquo-ammonocarbonic acids would resolve itself into a consideration of the solvolytic relationships of these four acids, and such was in fact found to be the case.

It has been shown[7] that three of these four acids are mutually convertible one to another by reversible reactions, hydrolytic in one direction and ammonolytic in the other.

$$\mathrm{HOCOOH + NH_3 \rightleftharpoons H_2NCOOH + H_2O}$$
$$\mathrm{H_2NCOOH + NH_3 \rightleftharpoons H_2NCONH_2 + H_2O}$$

The last stage in the ammonolysis, however,

$$\mathrm{H_2NCONH_2 + NH_3 \rightleftharpoons H_2NC(NH)NH_2 + H_2O}$$

has never been shown to take place. Guanidine, it is true, has been hydrolyzed to urea, but the present paper is the first record of the ammonolysis of urea to guanidine.

The first part of the present work, carried out with urea, showed that in liquid ammonia solution the ammonolysis to guanidine does take place, and indicated qualitatively the factors which condition the reaction. Subsequent quantitative experiments showed that a condition of equilibrium was attained in the reaction. Finally, the ammonolysis to guanidine was experimentally shown to be a general reaction of all mixed aquo-ammonocarbonic acids. This was done by means of quantitative experiments with two, and qualitative experiments with 11 other mixed aquo-ammonocarbonic acids which are enumerated later in this paper.

Preliminary Qualitative Experiments

It was first attempted to carry out the ammonolysis of urea to guanidine with liquid ammonia in sealed glass tubes of the customary type. No guanidine was formed at temperatures up to 80°. At 250°, however, (attained in tubes of capillary dimensions) the formation of guanidine was demonstrated. The inhibiting effect of the presence of even traces

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[5] Billeter, *Ber.*, **20**, 1629 (1887).

[6] The orthocarbonic acids, hypothetical except for ortho-carbonic ester would, however, be still more highly solvated.

[7] Basaroff, *J. prakt. Chem.*, [2] 1, 283 (1870). Lewis and Burrows, THIS JOURNAL, **34,** 1515 (1912).

of water and the effect of ammonium chloride in facilitating the reaction were also demonstrated in this manner. The catalytic effect of ammonium chloride may be readily understood if its solution in liquid ammonia be considered as a solution of hydrochloric acid, the ammonium ion being an ammonated hydrogen ion in equilibrium with a certain concentration of non-ammonated hydrogen ion. Even in the absence of water and presence of ammonium chloride the ammonolytic reaction was found to be extremely slow.

A qualitative experiment was also carried out to ascertain the physical state of the reacting system at these high temperatures, well above the critical temperature of pure ammonia. A system consisting of 0.01 g. of urea, 0.01 g. of ammonium chloride, and about 0.8 cc. of liquid ammonia was sealed up in a tube of 1mm. bore. This tube was then heated in a glass air-bath so that the system could be visually observed. To all appearance little change took place up to 210° at which temperature the original liquid phase separated into two liquid phases. No further change occurred up to 245° at which temperature the tube burst. It is probable, then, that a three-phase system is under consideration in all of the work described in this paper.

Quantitative Experiments

General Procedure.—Although the qualitative experiments just described sufficed to establish the fact of the ammonolysis of urea to guanidine, the amount of guanidine formed was so very small that it seemed highly probable that the ammonolysis was far from complete. Considerable work was therefore done in a finally successful effort to carry out the reaction on a sufficiently large scale so that the extent of the ammonolysis under a given set of conditions could be quantitatively estimated.

Sealed tubes were used, about 15 mm. in internal diameter and 50 cm. long. These tubes, filled as described below, were placed in steel cylinders as shown in Fig. 1. Into these cylinders ammonia was introduced by distillation through the valve so that when they were heated the pressure developed inside the tubes was offset by an approximately equal pressure outside them.

The method by which the tubes were filled may be understood by reference to Fig. 2. The purpose of this apparatus was to render it possible to make up a system consisting of a measured volume of liquid ammonia and weighed quantities of solid materials, while ensuring the entire absence of moisture. For this purpose the tube was fitted with a side arm which was sealed to the apparatus at E. The system was then subjected to preliminary drying by drawing a current of dry air through a small tube (not shown in the figure) reaching to the bottom of the reaction tube. The path of the air was then through Stopcocks C and D to the pump.

The weighed quantities of the dry solid materials were then introduced through the open top of the reaction tube, which was then closed by a stopper carrying a short glass rod to serve as a handle during the next process, which was to seal off the tube above the side arm at Point 1 as shown in the figure. Stopcocks C and D were then opened to an efficient oil suction pump so that, Stopcock B being closed, the system was evacuated. During this evacuation the whole glass system was heated by means of a hand torch to ensure removal of all moisture from the walls. Stopcock D was then turned so as to shut off the system from the pump and open it to the drying tube, thereby filling the system with dry air. The evacuation, heating and washing with dry air was in every case repeated at least five times.

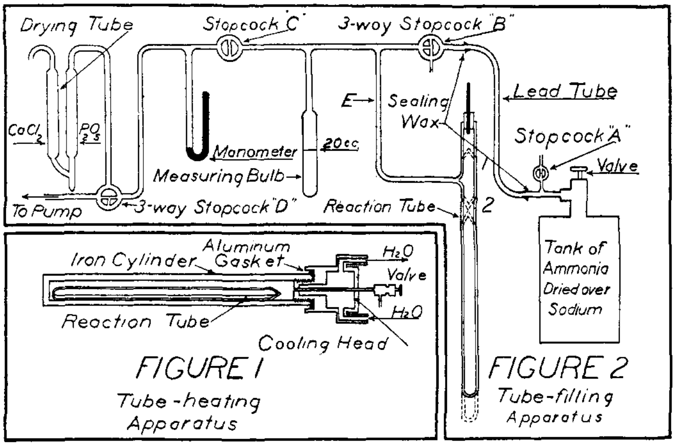

FIGURE 1
Tube-heating Apparatus

FIGURE 2
Tube-filling Apparatus

After the system was thus dried, it was evacuated and Stopcock C closed. A liquid-ammonia bath was then placed around the measuring bulb. The ammonia line up to Stopcock B having then been washed out with dry ammonia issuing into the air at B, this stopcock was turned so as to direct the stream of ammonia into the system. The ammonia thereupon condensed in the measuring bulb, which had been calibrated to hold 20 cc. When the desired quantity of ammonia had been thus obtained, Stopcock B was closed and the liquid-ammonia bath transferred from the measuring bulb to the bottom of the reaction tube, thus bringing about the distillation of the measured quantity of ammonia into the reaction tube.

The system was then opened through Stopcocks B and A to establish atmospheric pressure, while the entrance of air and atmospheric moisture was prevented by the simultaneous exit through A of a slow current of ammonia from the tank. The reaction tube, containing now all the reactant substances, was sealed off at point 2, just below the side arm. The finished tubes as a rule were about one-third filled with solution.

The heating, in all the experiments to be described, was carried out at 300° ± 5° for 120 hours. At the end of this time the cylinder containing the reaction tube was cooled as quickly as possible, usually within 15 or 20 minutes, although the sluggishness of the reaction, mentioned above, renders any serious change in the composition of the reacting system during this process unlikely.

The tube having been removed from the cylinder, its upper end was rubbed with a swab, wet with liquid ammonia. Since the lower end of the tube was warm, pure liquid ammonia was condensed on the interior walls of the upper part of the tube and, running down, washed them effectively. The lower part of the tube was then placed in a liquid-ammonia bath and the cooled tube opened at the tip. The opened end of the tube was then softened in a flame and drawn out to a long fine capillary. On removing the tube from the ammonia bath the solution boiled quietly, the ammonia escaping through the capillary at a sufficiently slow rate to prevent bumping.

The crystalline residue was dissolved in 2 cc. of water, the solution transferred to a calibrated 10cc. volumetric flask, and made up to volume with washings from the tube, using 2 cc. of water each time. The aqueous solutions were in all cases perfectly clear. Guanidine and urea were quantitatively estimated in this solution, using duplicate aliquot portions of 2 cc. each in each case.

Guanidine was determined by a slight modification of the Vozárik[8] method, which depends on the slight solubility of guanidinium picrate. It is necessary for good results that the concentration of guanidine be high in solutions in which it is to be determined, and it was for this reason that the products of the reaction were dissolved in no more than 10 cc. of water.

Urea was determined by the urease method, using the technique developed by Fox and Geldard.[9]

Results.—The facts that the reacting system did not consist of a single phase but of three, and that the results of analysis gave the composition of the system as a whole rather than of any single phase, preclude any attempt to calculate an equilibrium constant.

Nevertheless, it is possible to show, from the results of four experiments, as presented in Table I, that a condition of equilibrium is attained and that this equilibrium is independent of the particular mixed aquo-ammonocarbonic acid initially used.

In the first of these four experiments urea was used; in the second, cyanuric acid; in the third, ethyl allophanate; and in the fourth guanidine (guanidinium chloride) and water were the initial factors in the reaction.

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[8] Vozárik, *Z. angew. Chem.*, **15**, 670 (1902).

[9] Fox and Geldard, *Ind. Eng. Chem.*, **15**, 743 (1923).

The initial gram-equivalent concentrations of these substances were identical, and the compositions as a whole of the original solutions were so calculated that, were equilibrium to result, the compositions of the systems at the end of the reaction would be identical. The substantial identity found by experiment, as shown in Table I, then attests the truth of the two statements made above.

TABLE I

COMPOSITION OF ORIGINAL AND OF EQUILIBRIUM SOLUTIONS

	Composition of original solution gram equivalents[a]						Composition of system at equilibrium in moles		
Expt.	Ammonia[b]	Ammonium chloride	Urea	Cyanuric acid	Allophanic ethyl ester	Water and guanidine, each	Guanidine	Urea	Carbamic acid
1	0.740	0.009	0.00832	.....	.....	.....	0.0019	0.0053	0.0011
2	.748	.017	.....	0.00832	.....	.....	.0019	.0057	.0007
3	.748	.017	.....	.....	0.00832	.....	.0018	.0058	.0007
4	.732	.001	.....	.....	.....	0.00832	.0016	.0061	.0006

[a] One mole of cyanuric acid is three gram equivalents; of ethyl allophanate two gram equivalents.

[b] Including ammonia in ammonium chloride. In all four experiments, 0.731 mole of liquid ammonia was used.

In order that the compositions of the various systems at equilibrium might be identical it was necessary that the initial concentrations of ammonia be somewhat different in the four cases. Thus, if the cyanuric acid and the ethyl allophanate be thought of as taking part first in the formation of urea which is subsequently ammonolyzed to guanidine, then "extra" ammonia is required for the reactions represented by the following equations: $(HOCN)_3 + 3NH_3 = 3H_2NCONH_2$; $H_2NCONHCO\text{-}OC_2H_5 + 2NH_3 = 2H_2NCONH_2 + C_2H_5OH$.

When guanidinium chloride and water were used, however, the quantity of ammonia initially present had to be reduced by an equivalent amount since ammonia is formed, rather than consumed, in the attainment of equilibrium.

These small variations in the initial concentration of ammonia were taken care of, not by varying the quantity of liquid ammonia used, but by the more convenient and accurate method of varying the amount of ammonium chloride. The accompanying variation in the initial concentration of the catalyst, hydrogen chloride (or hydrogen ion) was, of course, inconsequential as regards equilibrium.

The introduction of a definite weight of water in the fourth experiment was effected by the use of a small bulb with a capillary tip such as is commonly used in the determination of the molecular weight of liquids by the Victor Meyer method. The sealed bulb was introduced into the system in the same manner as the solid materials, and withstood the operations used in making up the reacting system, but was crushed by the high pressure developed when the tube was heated, thus allowing the water to take part in the reaction.

The values given in Table I under the heading "Carbamic Acid" represent the failure of the guanidine and urea combined, at equilibrium, to account for all of the urea, cyanuric acid, ethyl allophanate, or guanidine, which were initially used. The evidence points to the conclusion that this is to be accounted for by a certain amount of hydrolysis of urea to carbamic acid and perhaps even to carbonic acid. It is remarkable that this hydrolysis should take place in spite of the overwhelming concentration of ammonia as compared with that of the water. The system is then in reality one of at least two coexistent equilibria rather than of the one which has been so far discussed. Unfortunately, no means was at hand for directly determining carbamic acid in a manner sufficiently accurate to be of value in these experiments. The values given, obtained by difference, are of course subject to several sources of experimental error, and the agreement among them is correspondingly poor.

Qualitative Examination of the Ammonolysis of Other Mixed Aquo-Ammonocarbonic Acids

Although the above quantitative work with three representatives of the mixed aquo-ammonocarbonic acids would seem to indicate that the ammonolysis to guanidine is a perfectly general reaction of this class of compounds, it nevertheless seemed desirable to establish this beyond any doubt by direct experiment, using as many other of these acids as were available.

It was found that ethyl carbamate (urethan), biuret, carbethoxycyanamide, ammeline, ammelide, *sym.*-dicarbethoxy-guanidine, methylurea, methyl allophanate, *sym.*-dicarbethoxy-urea (carbonyl-diurethan), carbethoxy-*N*-phenylbiuret, guanylurea hydrochloride, and triuret (carbonyl diurea), all gave, when heated at 300° with ammonium chloride in ammonia solution for 65 hours, considerable quantities of both urea and guanidine. In addition, ethyl carbonate was also found to give both guanidine and urea, while thio-ammeline, a mixed thio-ammonocarbonic acid, gave guanidine but, of course, no urea. The procedure in carrying out these experiments was the same as in those described above, except that no attempt was made to determine quantitatively the amounts of guanidine and of urea that were formed.[10]

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[10] In connection with the guanylurea experiment, since guanylurea forms a picrate having properties similar to those of guanidinium picrate, the test for guanidine might be thought to be inconclusive. It was, however, found by independent means that guanylurea was completely absent from the solution after ammonolysis. Guanylurea gives the same test with copper sulfate and sodium hydroxide that is given by biuret, except that this test is even more sensitive for guanylurea than for biuret. It was shown by this test that guanylurea was not present at the end of the reaction. There can therefore be no doubt as to the presence of guanidine being indicated by the formation of the insoluble picrate.

Discussion

The interpretation of the results of the present investigation has several points of interest. The results show that guanidine, cyanamide, or any other ammonocarbonic acid can exist in an environment containing more than very small amounts of water, only because of the sluggishness of the hydrolytic reaction. This sluggishness, indeed, is very marked so that, for example, it is possible to bring about the ammonation of cyanamide to guanidine in concentrated aqueous solutions of ammonium salts[11] before more than a very moderate degree of hydrolysis of either of them to ammonium carbonate has taken place. Nevertheless, the reason for the high yield of guanidine obtained by this procedure can only be that the heating is interrupted long before solvolytic equilibrium is reached.

Another point of interest is the bearing of the present work on the formation of guanidine derivatives as products of the metabolism of living organisms. It has been postulated[12] that one step in the synthesis of such derivatives is the ammonolysis of urea to guanidine. It can only be said that if living organisms, being essentially aqueous systems, can bring about this reaction, their ability to do so must be added to the list of unsolved problems in physiological chemistry.

The writer wishes to express his indebtedness to Dr. E. C. Franklin and the pleasure he has had in working under Dr. Franklin's kindly guidance. Thanks are also due to Dr. F. B. Dains of the University of Kansas and to Mr. L. A. Pinck of the Fixed Nitrogen Research Laboratory for some of the materials used in this investigation.

Summary

1. It is shown in this paper that a certain class of compounds, of which urea, carbamic acid, biuret, etc., are familiar examples, may be logically regarded as mixed aquo-ammonocarbonic acids, which are here defined.

2. Mixed aquo-ammonocarbonic acids, as a class, may be ammonolyzed to guanidine, an ammonocarbonic acid. This result is only attained, however, in systems from which water is carefully excluded. Anhydrous liquid ammonia solutions were used in the present investigation.

3. The ammonolytic reaction does not go to completion, but results in an equilibrium mixture of guanidine, urea and probably carbamic acid. The nature of this equilibrium at one temperature (300°) was approximately determined.

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[11] Blair and Braham, *Ind. Eng. Chem.*, **16**, 848 (1924).

[12] Mathews, "Physiological Chemistry," William Wood and Company, New York, 2nd ed., **1919**, p. 186.