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THE REACTION OF CHLORO-ACETIC ACID WITH AMMONIA AND THE PREPARATION OF GLYCINE

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The classical synthesis of glycine[1] from chloro-acetic acid and ammonia has never given entire satisfaction despite various claims in the literature. Although the cost of materials is low, it is significant that Clarke and Taylor[2] have rejected the method in favor of a two-stage cyanide process involving some expensive reagents. While the latter method is probably the best one now in ordinary use, it affords only 20 to 27% yield, calculated on the basis of the original starting material.

Clarke and Taylor have made valid objection to the Kraut process on account of the trouble in separating the glycine as the copper salt and displacing the copper by hydrogen sulfide. Equally valid is their criticism that the product is contaminated with ammonia, evidently in some form not readily volatilized. It is known, however, that glycine is too weak to form a stable salt with ammonia and can be recrystallized in the free state from ammonium hydroxide. Ammonium chloride is not necessarily the offending impurity, as we have shown in this Laboratory by the preparation of chlorine-free glycine which was seriously contaminated with ammonia.

In the chloro-acetic process the reaction does not stop with glycine but proceeds[3] in part to form iminodiacetic acid, $NH(CH_2COOH)_2$ and trimethylene-aminetricarboxylic acid $[N(CH_2COOH)_3]$ compounds obscurely named "glycollamic acids" in the literature. For brevity they are designated below as "di-acid" and "tri-acid." These acids bearing carboxyl groups in excess of amine nitrogen are strong enough to make fairly stable ammonium salts and thus may furnish the undesired ammonia contamination in a glycine preparation.

It seems reasonable also that either the di-acid or the tri-acid might make a mixed salt or amide with both glycine and ammonia, thus making the impurity persistent in material of low solubility. Several possibilities of cross combination appear in this way and may well account for the fact that in an actual synthesis of glycine the mother liquor, presumably including salts of the di-acid and tri-acid, is an almost uncrystallizable sirup and probably a complex mixture. The sirup does not necessarily contain either chloro-acetic acid or glycolic acid. It has a high content of organic ammonium salts and some residual glycine. Rough Kjeldahl analyses

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[1] Kraut, *Ann.*, **266**, 292 (1891).

[2] Clarke and Taylor, "Organic Syntheses," John Wiley and Sons, New York, **4**, 31 (1924).

[3] (a) Heintz, *Ann.*, **122**, 257 (1862); (b) **145**, 49 (1868).

showed that it contains nitrogen in excess of that accounted for as primary amine and ammonia. Its principal role is that of interfering with the crystallization of glycine and of contaminating the product.

The present investigation was first a study of the course of the chloro-acetic acid-ammonia reaction in the interest of increased production of the desired glycine in the original reacting solution. Secondly, the problem was to eliminate the ammonium chloride and organic by-products, thus isolating the crystalline product without resorting to copper compounds.

The first of these plans was tried with the realization that even a moderate increase in the content of glycine would eliminate a corresponding amount of sirupy by-products, particularly the most undesirable tri-acid. If this could be accomplished, there should be a sharp rise in the practical yield of crystalline glycine and a product of much higher purity.

In the second phase of the work, silver oxide was adopted as a reagent to eliminate the normal by-product of ammonium chloride. It was then an easy matter to isolate glycine as the one crystallizable substance remaining. In view of the cost of the silver oxide, a method is described for the easy recovery of the reagent.

The accompanying graph shows the rate of accumulation of glycine in comparison with that of ammonium chloride when a mixture of chloro-acetic acid and ammonia is made in proportions similar to those described in the literature. The period was three hours, with a final determination five days later when the reaction was complete. Production of chloride ion is obviously equivalent to transformation of chloro-acetic acid, and in an ideal case should equal production of glycine if no subsequent reaction took place.

Chloro-acetic acid, twice fractionally distilled and then once recrystallized from an excess of its own melt, was weighed into 15 molar equivalents of chilled conc. ammonium hydroxide (sp. gr. 0.90). The flask containing the mixture was fitted with a wired-in stopper carrying a stopcock and a thermometer. The outfit was immediately placed in a thermostat at 40°. Automatic shaking prevented temperature rise from the heat of the reaction. At intervals portions of the mixture were withdrawn, immediately diluted ten-fold and placed in an ice-bath.

The diluted solution was analyzed at once by the Volhard method for chloride ion, advantage being taken of the fact that unchanged chloro-acetic acid does not react with silver ion. As time permitted, an aliquot of each reaction sample was rapidly boiled with a moderate excess of sodium hydroxide until ammonia fumes could not be detected for a final ten minutes. The content of primary amine (glycine) was now estimated in each by the standard van Slyke de-amination method. The macro-apparatus was used with the customary corrections. From each numerical result 3%[4] was deducted, to allow approximately for the abnormal evolution of gas in the de-amination of glycine. Finally, Volhard titrations repeated several hours after the samples went on ice showed no appreciable change.

While ammonia is being expelled from the analytical samples, two slight errors enter. A small amount of new glycine is formed before the ammonia

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[4] Van Slyke, *Ber.*, **44**, 1684 (1911).

is gone and a small amount of glycine is eliminated by reaction with the excess chloro-acetic acid before the latter is all transformed by the alkali into sodium glycolate. Since these errors tend to compensate, as sodium hydroxide in boiling dilute solution does not hydrolyze glycine, and since the traces of residual ammonia would not vitiate the de-amination data to a significant extent, it is thought that the nitrogen values are reasonably accurate for the use in question.

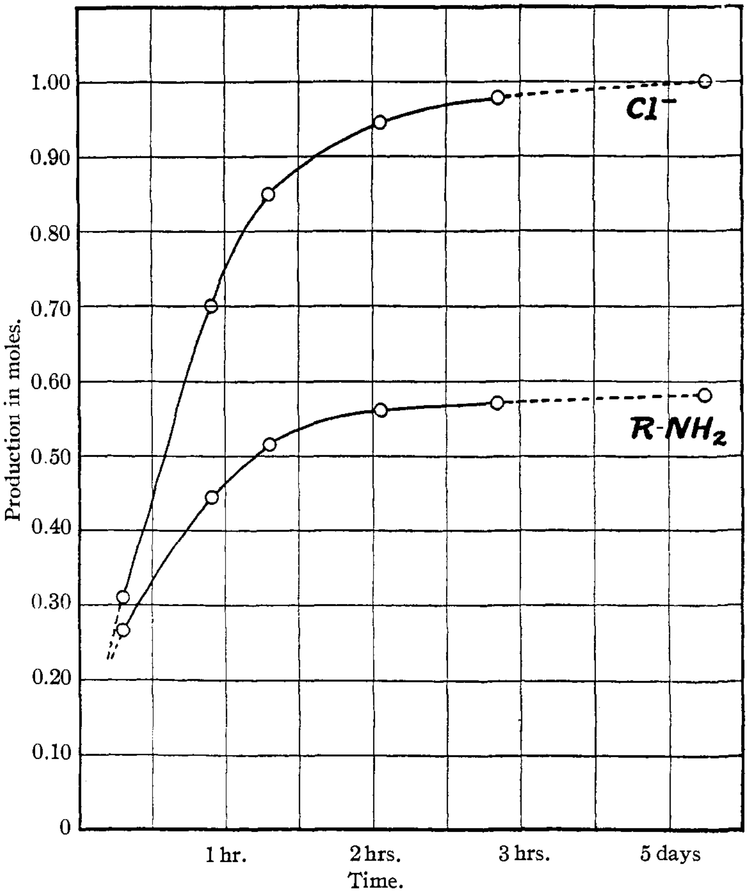

Fig. 1.—Transformation of one mole of chloro-acetic acid into ammonium chloride and glycine.

Apparently glycine and chloride ion are produced at nearly the same rate as long as ammonia is in gross excess over glycine. After about 25% production is attained, the accumulated glycine goes astray so rapidly that nearly two-thirds of the subsequent product is lost before the final exhaustion of the chloro-acetic acid is accomplished.

When the above procedure was continued through the silver oxide process described below, only about 20 to 25% yields of glycine were obtained in a fair degree of purity. This material was still decidedly contaminated with ammonium salts.

The obvious moral of the rate experiment was to multiply the ammonia-chloro-acetic acid ratio by about four, thus making the final ratio of chloride ion to glycine more like that at the time of the first analysis (that is, at the 18-minute reaction period of the graph). When this change was made, the final accumulation of glycine at once rose to 86%, and of this 63% was isolated in crystalline form as described later.

Several mixtures of widely variant proportions were analyzed, after two days' standing, by the de-amination method.

Molar ratio, ammonia to chloro-acetic acid	2:1	4:1	6:1	15:1	24:1	60:1	220:1
Primary amine produced, % of theoretical	29	32	37	58	65	86	95

The 220:1 mixture was carried through the full process, yielding 3.0 g. of glycine, or 75% of theoretical. The amount of ammonium hydroxide required in this case is, however, excessive for practical work. As in other cases, the actual yield always falls 20% or more below the potential yield, probably on account of decomposition as well as loss in crystallization and filtration.

Experiments at high temperatures and runs made with 40% ammonia under pressure gave no promise of significant improvement except that derived from raising the ammonia-acid ratio. Experiments with dilute mixtures, those with alcohol as solvent and those with ammonium carbonate[5] instead of ammonium hydroxide gave inferior results. With reduced-pressure evaporation of the reaction mixture, there were slightly improved yields but the improvement was not worth the trouble. Finally, the 60:1 ammonia ratio was chosen as the best compromise between two evils, namely, excessive volumes of ammonium hydroxide and excessive production of undesired salts.

Preparation of Glycine.—One mole of chloro-acetic acid (94.5 g.) is dissolved in 4 liters of ammonium hydroxide (sp. gr. 0.90) and set aside in a stoppered vessel for twenty-four hours in surroundings at about 30°, or for two or more days at about 20°, no attention being paid to the heat of the reaction. The mixture is then heated to recover the excess ammonia, which is received in a flask of distilled water cooled in running water.

One mole of silver nitrate (170 g.) is dissolved in about 500 cc. of water and converted into flocculent silver oxide by the addition of a slight excess of clear, technical sodium hydroxide solution. The oxide is washed by decantation, collected on a Büchner filter and washed free of sodium compounds.

The glycine reaction mixture is evaporated to about 500 cc., during which time nearly all free ammonia escapes. The silver oxide is then stirred into the solution until no lumps of unchanged reagent can be detected, all residual solid being in the form of

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[5] Nencki, *Ber.*, **16**, 2827 (1883).

silver chloride. This excess silver chloride is at once removed on the Büchner funnel. The filtrate is placed in a wide-mouthed flask equipped with a mechanical stirrer to prevent bumping, and is concentrated by boiling. This operation must not be interrupted while ammonia is still present, lest undesirable silver compounds be formed.

When the volume of the solution is reduced to about 200 cc., the silver-ammonia complex is completely decomposed and the rest of the silver chloride precipitated. More water is added and evaporated should there still be traces of silver in solution. The end-point is reached when a drop of aqueous hydrobromic acid, added to the clear supernatant liquid, no longer gives a localized turbidity. The silver chloride is collected on the funnel, and along with the original mass is placed in a 25% solution of technical sodium hydroxide for recovery later.

The glycine solution (vol., 190 cc.) is treated with 1 to 2 g. of Norit, filtered carefully by suction through retentive paper and treated with an equal volume of 95% ethyl alcohol. Pure-white glycine promptly crystallizes but the mixture is allowed to stand for an hour or more on ice. After filtration, washing with alcohol and drying in a desiccator, 43 g. of crystals are obtained. Another like volume of alcohol precipitates an additional 4 g., not quite so pure. It is isolated in like manner after an hour's cooling. Taken as a whole, the glycine contains nearly 0.1 mole per cent. of ammonium salts, judged by Nessler colorimetry.

The total yield of 47 g. is 63% of theoretical, or 0.63 mole. Primary amine left in the mother liquor in one run was 0.09 mole (by de-amination analysis). Total glycine thus accounted for, 0.72 mole. Total glycine originally estimated in solution, 0.86 mole, loss in manipulation, 0.14 mole.

If an ammonia-free product is desired, the glycine is dissolved in 200 cc. of water and shaken for a few minutes with 10 g. of granular permutite (after Folin). The mixture is filtered and 250 cc. of 95% ethyl alcohol slowly stirred into the filtrate. The precipitated glycine, a voluminous crystalline mass of snow-white appearance, is washed on the Büchner funnel with 95% alcohol and dried in a desiccator; yield, 37.5 g., or 50% of the theoretical for the whole process.

PURITY TESTS.—When heated to 230° (corr.) the final product starts to turn brown; it becomes almost black by 238°. In 0.1 *M* solution it shows no appreciable ammonia by Nessler colorimetry. In *M* solution a barely detectable coloration lies between that shown by 10^{-5} *M* ammonium chloride and that of the distilled water blank; chloride test, negative.

When permutite was omitted, but no other change made in the procedure, a *M* solution of the product gave Nessler coloration nearly as great as that of 10^{-4} *M* ammonium chloride. All tests were made in alkaline solution with allowance for acidity of the glycine. Observations were made immediately on mixing, as glycine soon reacts with Nessler's reagent to vitiate results.

Recovery of Silver.—The following modification of a well-known method[6] is convenient here.

The moist silver chloride (1 mole) from the glycine process is suspended in about 400 cc. of boiling 25% sodium hydroxide solution contained in a liter beaker. An excess of corn sugar or glucose sirup is cautiously stirred in at a rate slow enough to avoid a sudden violent reaction causing overflow. After a few minutes of boiling the chloride is transformed entirely into a crumb-like mass of finely divided silver.

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[6] Gmelin-Kraut, "Handbuch anorganischen Chemie," Carl Winter's Universitätsbuchhandlung, Heidelberg, **1914**, Band V, Abt. 2, p. 8.

By repeated decantations, rapidly made, and copious washing on the Büchner funnel with hot water, soluble matter is removed. A trace of chloride persists, however, but this need not be eliminated if the product is to be used again in the synthesis of glycine.

The silver, still wet, is treated in a liter Pyrex beaker with a slight excess of concd. nitric acid (sp. gr. 1.42). The silver, being very finely divided, is at once converted into silver nitrate, sufficiently pure for use again with glycine.

If the silver nitrate is desired as a laboratory reagent, the acid solution is simply heated until its temperature reaches about 240°, by which time the excess nitric acid is expelled. There is no trouble from bumping as the nitrate is extremely soluble at high temperatures.

The crude silver nitrate is then dissolved in cold water and diluted to 0.75 *M*, whereupon practically all dissolved silver chloride is precipitated. As would be expected, silver chloride is extremely insoluble in silver nitrate of concentrations below molal, but in nitrate solutions of more than molal concentration a considerable quantity of the halide either dissolves or is peptized.

The colloidal silver chloride, usually not in sufficient quantity to warrant salvage, is removed by filtration with the aid of decolorizing carbon. The resulting filtrate upon further dilution does not show the slightest turbidity and is perfectly serviceable as an ordinary reagent.

It is probably not worth while to attempt to make really pure silver nitrate from this recovered solution. It is possible, of course, to fuse the reduced silver and carry out the slow reaction of the compact ingot material with pure nitric acid and thus obtain a pure product.

Incidentally, the above process is very convenient for working up laboratory residues of silver chloride and thiocyanate. With iodide and bromide the process is also satisfactory, but more time should be taken to insure complete reduction with sugar.

Summary

An experimental study of the velocity and course of the reaction between aqueous chloro-acetic acid and ammonia shows that the product, glycine, goes astray seriously into by-products if its concentration is allowed to rise much over 1 mole per cent. of that of the ammonia present.

A method of preparation of glycine is given in which the ratio of ammonia to chloro-acetic acid is 60:1. Ammonium chloride is eliminated by means of silver oxide and a 50% yield of pure glycine obtained.

A simple method is given for recovery of silver oxide with the aid of glucose.

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