

(C) The Effect of Refrigeration

Continuing our study of the factors influencing the deterioration of the commercially available sodium hypochlorite type chlorine preparations, we next investigated the effect of low temperatures on their stability. Low temperatures are considered stabilizers for most types of perishable chemicals and particularly so for those which are extremely unstable. It was presumed, therefore, that refrigeration would probably inhibit deterioration to a large degree, if not prevent it completely in our preparations. The work to be done, therefore, was looked upon as merely confirmatory.

EXPERIMENTAL

Samples of the ten preparations being investigated were refrigerated in an electric ice box of standard make and at the temperature usually used for food preservation in the home. The solutions were removed only long enough during each analysis to come to the standard temperature to be pipetted. The pipetted samples were then titrated with 0.1 *N* sodium thiosulfate in the usual way (1). Some of the data collected are shown in Table V. The solutions are identified in the first column. The original strengths of the preparations are given in the second column, and the final strengths, 260 days later, in the third column. In the last column are reported

the percentage deterioration of each solution. The percentage deterioration ranged from 1.06 to 22.03.

TABLE V.—PER CENT STRENGTHS OF THE SAMPLES UNDER THE CONDITIONS OF THE STUDY AND THEIR PER CENT DETERIORATIONS

Preparation	Initial Strength, Per Cent Available Chlorine, May 28,	Final Strength, Per Cent Available Chlorine, Feb. 12,	Per Cent Deterioration
	1940	1941	
C-9	4.71	4.66	1.06
C-7	2.64	2.59	1.89
C-3	4.76	4.64	2.52
C-4	3.52	3.43	2.56
C-1	1.00	0.97	3.00
C-2	4.60	4.31	6.30
C-8	4.55	3.90	14.29
C-5	4.73	3.97	16.07
C-6	5.77	4.72	18.20
C-10	4.72	3.68	22.03

There seems to be no correlation of the deterioration rates of the chlorine solutions under the various conditions of storage. For example, solution C-1 is the most stable of the solutions when stored under constant moderate heat (Table II), but this solution ranks eighth when stored in a dark room (Table IV) and fifth when held under refrigeration (Table V).

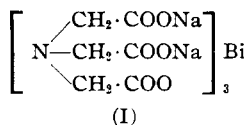
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Sodium Bismuth Triglycollamate*

By Robert A. Lehman and Reavis C. Sproull

In 1925 Hahl (1) disclosed a method for preparing a compound to which he gave the following structure:



Hahl's procedure consisted in warming together sodium carbonate, triglycollamic acid (*sym*-tricarboxytrimethylamine) and bismuth oxide until all were dissolved, and then evaporating to dryness. However, the quantities of reagents given do not agree even approximately with the structure suggested.

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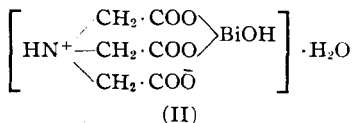
Furthermore, Michaelis and Schubert (2) have shown by potentiometric titration of triglycollamic acid that two of the carboxyl groups are highly ionized (*pK* 3) and indistinguishable, while the third carboxyl group exists as a "zwitterion" (*pK* 10). A solution of disodium triglycollamate is thus nearly neutral (*pH* 8), while the trisodium salt is quite alkaline (*pH* 11). In view of these properties of the acid, it seems improbable that a compound of structure (I) would give a stable and neutral aqueous solution as claimed by Hahl.

Preliminary experiments showed that sodium bismuth triglycollamate possesses pharmacological and chemical properties which, in certain respects, differentiate it

from other soluble bismuth compounds used in medicine. It therefore appeared desirable to reinvestigate the chemistry of the compound.

DISCUSSION AND RESULTS

When a hot aqueous solution of triglycollamic acid is boiled with one mol equivalent of bismuth (as Bi₂O₃), a clear solution results, which, upon cooling, throws down, in good yield, crystals whose structure may best be formulated as follows:



This substance can be readily recrystallized from water without hydrolysis of the bismuth. On drying to constant weight (II) loses two molecules of water probably giving (III):

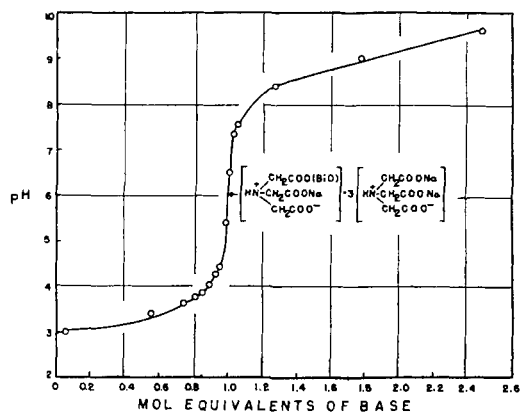
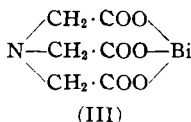
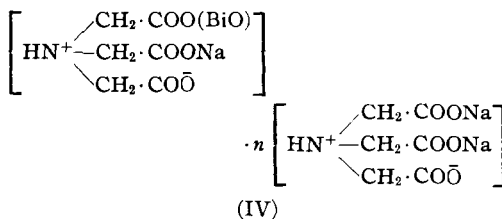


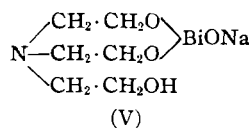
Fig. 1.—Titration of acid bismuth triglycollamate (II) in the presence of three mol equivalents of disodium triglycollamate.

A saturated aqueous solution of (II) is quite unstable with respect to chemical reagents, for hydroxyl, chloride or phosphate ions precipitate the appropriate insoluble bismuth salts. While only slightly soluble in cold water, (II) is very soluble in a solution of disodium triglycollamate, presumably forming a series of double salts or complex ions. A 0.05 M solution of (II) containing three mol equivalents of disodium triglycollamate has a pH of 3.0 and gives the titration curve shown in Fig. 1. It will be seen that one mol equivalent of base has been consumed at the inflection, at which point the solution is substantially neutral. Neutralization of one carboxyl group in (II) with sodium hydroxide in the presence of excess disodium triglycollamate might thus give solutions of the following series of compounds:



Moreover, the presence of the disodium triglycollamate greatly increases the stability of these solutions toward chemical reagents and in proportion to the amount present. Thus, when *n* is 3, and the resulting solution is 0.05 M with respect to bismuth, no precipitation occurs upon addition of phosphate or chloride ions, nor within the pH range 2.8 to 10.0. Such a solution is stable to light and when sterile can be stored indefinitely. It can be evaporated to dryness or greatly diluted without chemical change. A crystalline double salt corresponding to structure (IV) where *n* is 1 has been prepared and found to be less stable than when *n* is 2 or 3, but decidedly more stable than the sodium salt of (II). While nothing can be said as to the nature of the complexes whose formation is postulated, nevertheless their solutions are rather unique in the wide variation in conditions under which they show no chemical or physical change. The pharmacology of these compounds will be reported elsewhere; it may be mentioned, however, that they are of sufficiently low toxicity to make their therapeutic application feasible.

Recently Miller (3) has prepared unstable bismuth derivatives of triethanolamine and triisopropanolamine which he believed to be similar to the active principles present in Hanzlik's empirical mixture, Sobisinol (4). The structure advanced by Miller for one of these compounds is:



It has been pointed out that the initial reaction in the preparation of Sobisinol is a reduction of the sodium bismuthate. If this takes place at the expense of the triisopropanolamine, compounds of structures similar to (II) might possibly be obtained. However, the quantities of reactants used by Hanzlik would only account for the conversion of a portion of the bismuthate to a substance of this kind.

EXPERIMENTAL

Preparation of Triglycollamic Acid.—This was prepared as described by Michaelis and Schubert (2) except that the much less expensive chloroacetic instead of iodoacetic acid was used. Yield, 60%; m. p. (with decomposition), 234° C. (uncorr.). Anal. Calcd. for C₆H₉O₆N: C, 37.7; H, 4.71. Found. C, 37.7; H, 4.35. The disodium salt was prepared

by dissolving the acid in two mol equivalents of sodium hydroxide and evaporating to dryness.

Preparation of Acid Bismuth Triglycollamate (II).—Fourteen grams (0.03 mol) of bismuth oxide (calcd. for Bi_2O_3 : 89.7% Bi; found: 89.1%) were suspended in a solution of 11.5 Gm. (0.06 mol) of triglycollamic acid in four liters of boiling water. The suspension was boiled until a clear or only slightly turbid solution resulted. This required from 5 to 10 min. The solution was then filtered and chilled to 5° C. The fine, colorless needles were filtered off with suction, washed with ice water, alcohol and ether, and air dried. Yield, 20 Gm., 77%. The salt was recrystallized from water three times before analysis. Hydrolysis was prevented by dissolving the crystals directly in a just sufficient amount of distilled water, already at the boiling point, filtering and chilling rapidly. About 125 cc. of water is required per Gm. of salt. Solubility at room temperature is about 0.09 Gm. per 100 cc. The salt decomposes at 258–262° C. (uncorr.) when the temperature of the melting point bath is raised at the rate of 2 degrees per minute. Bismuth was determined by digestion with nitric, sulfuric and perchloric acids, double precipitation as basic carbonate and ignition to Bi_2O_3 . The water content was determined by drying to constant weight at 125° C.

Anal. Calcd. for $\text{C}_6\text{H}_{10}\text{O}_8\text{NBi}$: Bi, 48.3; N, 3.24; H_2O , 8.31. Found: Bi, 48.2; N, 3.10; H_2O , 8.25.

A solution of acid bismuth triglycollamate (II) was prepared by dissolving 4.33 Gm. (0.01 mol) of (II) and 7.05 Gm. (0.03 mol) of disodium triglycollamate in water and diluting to 100 cc. This 0.1 *M* solution was then titrated with 0.1 *M* sodium hydroxide using the glass electrode, and the titration curve is shown in the figure.

The structure of (II) is presumed to follow from the method of preparation, the titration curve and the analytical data. Structure (III) is the only one that could account for the loss of two molecules of water from (II) without anhydride formation. Since triglycollamic acid itself does not form an anhydride nor lose weight at 125° C., (III) is believed to be correct.

Preparation of Double Salt (IV) $\text{C}_4\text{H}_7\text{O}_2\text{N}(\text{COONa})\cdot(\text{COOBiO})\cdot\text{C}_4\text{H}_7\text{O}_2\text{N}(\text{COONa})_2\cdot 4\text{H}_2\text{O}$.—To 7.64 Gm.

(0.04 mol) of triglycollamic acid suspended in about 100 cc. of water was added 3.18 Gm. (0.03 mol) of anhydrous sodium carbonate dissolved in 50 cc. of water. The resulting solution was brought to boiling and 4.66 Gm. (0.01 mol) of bismuth oxide was added in small portions. It is preferable to triturate the oxide with water beforehand. The mixture was then boiled until clear, filtered and evaporated on the steam bath to about 35-cc. volume. Upon standing over night at room temperature, large colorless prisms were formed which were collected on a filter and washed with small portions of ice water. The material was recrystallized from a small volume of hot water in which case several days were required for the crystals to form. After filtering and washing as before, the double salt was dried quickly between filter paper. It was then suspended in alcohol, filtered, washed on the filter with ether and briefly air dried. The crystals must be preserved in a sealed container since they effloresce rapidly in dry air. Yield, 40%. Anal. Calcd. for $\text{C}_{12}\text{H}_{22}\text{O}_{17}\text{N}_2\text{BiNa}_3$: Bi, 28.1; N, 3.76; H_2O , 9.68. Found: Bi, 28.3; N, 3.70; H_2O , 9.69.

SUMMARY

Methods have been given for the preparation of a well-crystallized acid bismuth triglycollamate and a hydrated crystalline double salt of sodium bismuth triglycollamate with disodium triglycollamate. Structures have been suggested and properties described.

The authors wish to express their appreciation for the assistance of Miss Theis Aitken.

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