ON THE PHYSICAL AND CHEMICAL PROPERTIES OF BISMUTH SODIUM CITRATE AND BISMUTH SODIUM TARTRATE.*

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The use of the water-soluble bismuth sodium citrate and bismuth sodium tartrate for intramuscular injections gives interest to the precipitation reactions of these salts by physiological salt solutions and serum, and to their diffusibility. These were investigated on five and ten per cent solutions of the dibismuthyl monosodium citrate and the bismuthyl bismutho sodium tartrate, described in previous papers (1, 2).

Effect of Hydrogen-Ion Concentration.—While the 10% solution of the bismuth sodium citrate is practically neutral, having a p_H of 7.2 to 7.4, the bismuth sodium tartrate solution of the same concentration is decidedly alkaline, the p_H being 8.2 to 8.4. This alkalinity is probably due to the bismutho group which has basic qualities, as indicated by its tendency to form salts with a number of alkali salts of strong mineral acids. The effects of alteration of the p_H, produced by the addition of $N/10$ HCl or NaOH, also reveal a striking difference between the two preparations, as shown in Table I:

TABLE I.—THE EFFECTS OF p_H ON THE BISMUTH SOLUTIONS.

p_H of solution.	Precipitant effect on 5 per cent of Bi Na citrate.	Precipitant effect on 5 per cent solution of Bi Na tartrate.
9.8	+++	0
8.2	+	0
7.9	0	0
7.6	0	+
7.0	0	++
6.4	+	++
6.0	++	+++
5.4	++	+++
5.0	++	+++

The citrate remains in solution through the whole range of the physiological p_H, between 7.9 and 7 0, but is precipitated beyond this range, by alkali as well as by acid. The tartrate, on the other hand, is not precipitated by alkali as high as p_H 9.8, but is precipitated by decrease of the alkalinity within the physiological range, at 7.6. This precipitation of the tartrate occurs also when changes of the p_H at the same range are produced by the addition of adequate amounts of acetic acid, so that the precipitation is due to the change of the hydrogen-ion concentration, and not to the chloride ion; for the acetates in the physiological range have no precipitant action on bismuth sodium tartrate in aqueous solutions.

Effects of Physiologically Important Cathions and Anions.—In the following experiments the physiologic salts were added to 15 cc. of 10% solution of the two bismuth compounds in quantities that would occur in the serum and in physiological salt solutions; other salts were added in isomolecular ratio.

Table II shows that only the calcium salt precipitates the bismuth sodium citrate. The precipitate contained 64.2 per cent of bismuth and 3.4 per cent of calcium,

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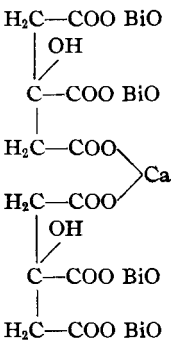
TABLE II.—THE EFFECTS OF PHYSIOLOGIC CATHIONS AND ANIONS ON THE BISMUTH SOLUTIONS.

Concentration of salt in per cent.	Dibismuthyl monosodium citrate.	Bismuthyl bismutho monosodium tartrate.
0.92 NaCl	No precipitate	Precipitate
0.042 KCl	No precipitate	Slight precipitate
0.024 $CaCl_2.2H_2O$	White precipitate (partly redissolved)	Precipitate
0.03 $NaHCO_3$	No precipitate	No precipitate
2.16 NaBr	No precipitate	Precipitate
2.32 NaI	No precipitate	Precipitate
1.32 $NaNO_3$	No precipitate	Slight precipitate
2.14 Na acetate	No precipitate	No precipitate
1.17 KCl	No precipitate	Precipitate
1.59 KNO_3	No precipitate	Slight precipitate
2.17 K_2CO_3	No precipitate	No precipitate

corresponding closely to the 63.8 per cent of Bi and 3.0 per cent of calcium required for tetrabismuthyl monocalcium dicitrate.



This precipitation can be prevented by the addition of sodium citrate; 0.2 to 0.4 Gm. or more of sodium citrate added to 10 cc. of the bismuth sodium citrate solution prevent immediate precipitation by 2 cc. of 10 per cent calcium chloride solution. Partial precipitation occurred on standing for fourteen hours, the amount of the precipitate decreasing with the quantity of the citrate.

Since the inhibiting action of sodium citrate on the precipitation of bismuth sodium citrate by calcium salts is probably due to reduction of the ionization of calcium, the effect of changes of the hydrogen-ion concentration was studied as these may be expected to act in the same direction. Mixtures of 5 cc. of 5 per cent bismuth sodium citrate were adjusted by the addition of $N/10$ NaOH or HCl to various levels of p_H between 8.0 and 6.5, the range in which the bismuth sodium citrate is soluble; and 2 cc. of 10 per cent calcium chloride solution were added. It was found that the calcium precipitated through this entire range, but the quantity of the precipitate increased with the hydrogen-ion concentration, *i. e.*, inverse of the p_H; corresponding to the increased ionization of the calcium salts in the more acid medium. This supports the assumption that the addition of sodium citrate interferes with the precipitation of bismuth sodium citrate by reducing the ionization of the calcium salt.

Bismuth sodium tartrate, as shown in Table II, is precipitated not only by calcium chloride, but also by sodium or potassium chloride, bromide, iodide and somewhat less by nitrate. This is probably due to the reactivity of the bismutho

group, *i. e.*, the BiO group connected with the hydroxyl group of the tartaric acid radicle. The acetate, bicarbonate and carbonate ions are not precipitant, nor are the sodium and potassium ions.

Effects of Locke Solution.—These were studied for the ordinary Locke solution, containing per cent: 0.9 NaCl; 0.042 KCl; 0.024 $CaCl_2.2H_2O$; and 0.03 $NaHCO_3$. The experiments were made by adding 1, 2, 3, 4 and 5 cc. of this solution to 5 cc. of 5 per cent solution of bismuth sodium citrate and bismuth sodium tartrate. The Locke solution was found to precipitate the bismuth sodium tartrate through its p_H and through its calcium and chloride ions. The sodium bismuth citrate is not precipitated by the Locke solution, for even the calcium chloride is non-precipitant in these dilutions.

Effects of Serum.—These were tried by mixing 5 cc. of cattle serum with increasing quantities of a 10 per cent solution of bismuth sodium citrate and bismuth sodium tartrate. Table III shows that bismuth sodium citrate gives slight

TABLE III.—THE EFFECT OF SERUM ON THE BISMUTH SOLUTIONS.

Cc. of cattle serum.	Cc. of Bi Na citrate.	Immediate effect.	Effect fourteen hours later.	Cc. of Bi Na tartrate.	Immediate effect.	Effect fourteen hours later.
5	0.25	Slight turbidity	Slight ppt.	0.25	Strong turbidity	Ppt.
5	0.5	Slight turbidity	Slight ppt.	0.5	Ppt.	More ppt.
5	1.0	Slight turbidity	Slight ppt.	1.0	Ppt.	Strong ppt.
5	2.0	No ppt.	Slight turbidity	2.0	Ppt.	Strong ppt.
5	3.0	No ppt.	No ppt.	3.0	Ppt.	Strong ppt.
5	4.0	No ppt.	No ppt.	4.0	Strong turbidity	Strong ppt.

turbidity and later slight precipitates when added in small quantities to serum. Higher ratio of the bismuth sodium citrate solution prevents the precipitation, presumably by diluting the calcium content. With the bismuth sodium tartrate the precipitation is distinctly greater, corresponding to the precipitant action of the p_H and calcium and chloride ions. That the precipitation is not due to protein may be seen from the fact that both preparations form only a slight turbidity with 10 per cent egg-albumen solution. The precipitation of these bismuth compounds by serum suggests that the immediate toxic effects of intravenous injections are due to flocculation rather than to the toxic action of the bismuth radicle.

The Relative Diffusibility of Bismuth Sodium Citrate and Bismuth Sodium Tartrate.—This was tried with collodion sacs in the presence of egg-albumen, so as to approach more closely to the conditions in the tissues. The sacs were filled with 8 cc. of a mixture of 5 cc. of a 10 per cent solution of the bismuth compounds and 20 cc. of a 10 per cent egg-albumen solution. Each sac was then placed in 91 cc. of distilled water for forty-eight hours, and the bismuth content of the inner and outer solution was determined as bismuth sulphide, after the destruction of the organic matter by digestion with sulphuric acid and hydrogen peroxide. The dialysates contained on the average 21.8 per cent of the bismuth in the case of the citrate, and 32.8 per cent for the tartrate. Three series of experiments with each, agreed closely in the average values, but the difference between the two salts is not considered significant.

Effects of Boiling.—While a bismuth sodium citrate solution can be boiled for five to ten minutes without acquiring more than a slight opalescence, bismuth sodium tartrate forms a more or less abundant precipitate under the same con-

ditions, so that the latter cannot be sterilized by heat. As phenol and tricresol do not precipitate either compound, solutions of bismuth sodium citrate and of bismuth sodium tartrate can be rendered sterile by the addition of 0.4 per cent tricresol. For intramuscular injections this is advisable, since neither preparation is in itself antiseptic.

CONCLUSIONS.

Ten per cent solutions of bismuth sodium citrate are practically neutral, the p_H being 7.2 to 7.4; 10 per cent solutions of bismuth sodium tartrate are distinctly alkaline, having a p_H of 8.2 to 8.4. Changes of the p_H within physiological limits, *i. e.*, from 7.0 to 7.9, do not precipitate the bismuth sodium citrate, while the precipitation of the bismuth sodium tartrate begins at a p_H of 7.6 and increases with increasing acidity.

Bismuth sodium citrate is precipitated by calcium chloride, while the tartrate precipitates with a great number of alkali salts of strong mineral acids, including chlorides.

The precipitation of bismuth sodium citrate by calcium chloride can be prevented by the addition of sodium citrate, which tends to reduce the ionization of the calcium chloride. Changes of the p_H within physiological limits of the solution in the alkaline direction act in the same way.

The addition of Locke solution to 5 per cent solutions of the bismuth sodium tartrate produces precipitation; 5 per cent bismuth sodium citrate solution is not precipitated.

The preparations do not precipitate proteins. The citrate may form a slight precipitate with the calcium of serum; the bismuth sodium tartrate is precipitated also by the other mineral salts.

The diffusibility of the citrate and of the tartrate is about the same, that of the latter being somewhat greater.

Aqueous solutions of bismuth sodium citrate can be sterilized by boiling, whereas the tartrate is precipitated by heat. Both solutions can be rendered sterile by the addition of 0.4 per cent tricresol.

BIBLIOGRAPHY.

(1) W. F. von Oettingen, Y. Ishikawa and T. Sollmann, *J. Pharmacol.*, XXXI (1927), 353.

(2) W. F. von Oettingen and Y. Ishikawa, JOUR. A. PH. A., XVII (1928), 124.

CUBIC DECIMETERS AND LITER DEFINED.

The new or redefined unit of volume, which by definition was made equal to the volume of a kilogram of pure water at the temperature of its maximum density, was given the same name as that formerly applied to the cube of the tenth of the meter; that is, it was called the liter, although by the new definition it had no direct relation to the unit of length.

As a result of the redefining of the liter in terms of the unit of mass, we now have two distinct units of volume, the cubic decimeter defined in terms of the meter, and the liter defined in terms of the kilogram.

The cubic decimeter and its one-thousandth part, the cubic centimeter, are used in measurements of volume derived from measurements of length, while the liter and its one-thousandth part, the milliliter, are used in measurements of volume and density of liquids based on determinations of mass.