

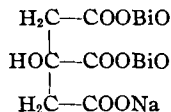
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## ON THE PHYSICO-CHEMICAL PROPERTIES OF SOLUTIONS OF DIBISMUTHYL MONOSODIUM CITRATE IN ETHYLENEGLYCOL.\*

BY W. F. VON OETTINGEN.

P. Hanzlik recently advocated the use of ethyleneglycol as a solvent and vehicle for bismuth compounds, and for this reason it was attempted to use also as a solvent for dibismuthyl monosodium citrate. This compound is prepared as an anhydride of the formula



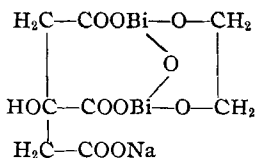
which, as such, is insoluble in water and in ethyleneglycol. The hydrate is, however, soluble in both solvents and can be diluted ad libidum. Because it is known that bismuth salts may form compounds with glycerol and different sugars, it appeared possible that a similar compound was also formed with ethyleneglycol.

The freshly precipitated moist hydrate of dibismuthyl monosodium citrate was therefore divided in two portions, one (a) was dried as usual, the other (b) was dissolved in ethyleneglycol, and the bismuth compound precipitated by means of acetone. After settling (preferably in the icebox), the precipitate was filtered off, washed with acetone, alcohol and ether and dried. The dried material represents a white amorphous powder, freely soluble in water. It does not dissolve in ethyleneglycol directly, but does so freely after hydration. Both samples were analyzed, and showed the same bismuth content:

- (a) Substance: 0.4763 Bi<sub>2</sub>S<sub>3</sub> 0.3772 64.3 per cent Bi  
(b) Substance: 0.4697 Bi<sub>2</sub>S<sub>3</sub> 0.3711 64.1 per cent Bi

The theoretical bismuth content for dibismuthyl monosodium citrate is 63.0 per cent bismuth, while the hypothetical compound of the type

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should contain 59.9 per cent bismuth. From the comparison of these two analyses it appears that both preparations are identical, and that ethylene glycol does not form a compound with the bismuth sodium citrate.

Next, the effect of temperature, hydrogen-ion concentration, and of cations and anions was studied, using 2.5 per cent solution of dibismuthyl monosodium citrate in water and in ethyleneglycol. The  $p_{\text{H}}$  of the aqueous solution was 7.6, that of the solution in ethyleneglycol was 8.2.

(a) *Effect of Heat.*—Ten cubic centimeters of both solutions, with addition of 0.5 cc. of phenol red solution (0.04 per cent) were placed in test-tubes, which were then sealed. Three tubes of each solution were placed in a beaker and heated for one-half, one and one and a half hour to 50, 100 and 150° C.

TABLE I.—EFFECT OF HEAT ON 2.5 PER CENT SOLUTIONS OF DIBISMUTHYL MONOSODIUM CITRATE IN ETHYLENEGLYCOL AND WATER.

Temp.	Time.	Aqueous Solution.		Ethyleneglycol.	
		$p_{\text{H}}$ .	Prec.	$p_{\text{H}}$ .	Prec.
50	30	7.6	No	8.2	No
	60	7.6	No	8.2	No
	90	7.6	No	8.2	No
100	30	7.3	Sl. turb.	8.2	No
	60	7.3	Sl. turb.	8.2	No
	90	7.3	Sl. turb.	8.2	No
150	30	7.2	Prec.	8.0	Prec.

Table I shows that the ethyleneglycol solution is somewhat more stable than the aqueous solution, remaining clear with heating to 100° C., for one and a half hour, under which conditions the aqueous solution shows a slight turbidity, and also a decrease of  $p_{\text{H}}$  from 7.6–7.3.

(b) *Effect of the Hydrogen-Ion Concentration.*—Ten cubic centimeters of the 2.5 per cent solutions of bismuth sodium citrate in water and in ethyleneglycol, with 0.5 cc. of phenol red solution were placed in test-tubes, and the  $p_{\text{H}}$  was ad-

TABLE II.—EFFECT OF HYDROGEN-ION CONCENTRATION ON 2.5 PER CENT SOLUTION OF DIBISMUTHYL MONOSODIUM CITRATE IN WATER AND IN ETHYLENEGLYCOL.

$p_{\text{H}}$ .	Aqueous Solution.		Ethyleneglycol.	
	Immed.	Forty-eight hours.	Immed.	Forty-eight hours.
9.24	Prec.	Solid gel.	Clear	Clear
8.2	Prec.	Prec.	Clear	Clear
8.0	Turb.	Prec.	Clear	Clear
7.9	Sl. turb.	Turb.	Clear	Clear
7.6	Clear	Clear	Clear	Clear
7.0	Clear	Clear	Clear	Clear
6.4	Clear	Clear	Clear	Clear
6.0	Clear	Clear	Sl. turb.	Clear
5.4	Clear	Sl. prec.	Sl. turb.	Clear
5.0	Sl. turb.	Sl. prec.	Turb.	Sl. turb.

justed to different levels by the addition of *N*/10 hydrochloric acid or *N*/10 sodium hydroxide. Observations were made immediately, and after forty-eight hours.

Table II shows that changes of the  $p_H$  produce a more marked effect in the aqueous solution than in the ethyleneglycol solution, the latter being only slightly affected in the lower range of our experiment. It may also be mentioned that with the ethyleneglycol solution considerably more acid or alkali (up to twice the amount) was required to produce a certain change of the  $p_H$ , which indicates that in the latter solution, the ionization was considerably reduced.

(c) *Effect of Cathions and Anions.*—9.7 cubic centimeters of both solutions, 0.5 cc. of phenol red solution were placed in test-tubes, and 0.3 cc. of the concentrated solution of the different salts were added to give the percentage stated in the following table. Observations were made immediately, after forty-eight and after sixty-two hours.

TABLE III.—EFFECT OF CATHIONS AND ANIONS ON 2.5 PER CENT SOLUTIONS OF DIBISMUTHYL MONOSODIUM CITRATE IN WATER AND IN ETHYLENE GLYCOL.

Conc. of salts %.	Aqueous Solution.						Ethyleneglycol.					
	Immed.		Forty-eight hours.		Sixty-two hours.		Immed.		Forty-eight hours.		Sixty-two hours.	
	$p_H$ .	Prec.	$p_H$ .	Prec.	$p_H$ .	Prec.	$p_H$ .	Prec.	$p_H$ .	Prec.	$p_H$ .	Prec.
0.92% NaCl	7.6	None	7.6	None	7.5	None	8.2	None	8.2	None	8.2	None
0.042% KCl	7.6	None	7.6	None	7.6	None	8.2	None	8.2	None	8.2	None
0.024% CaCl + 2H <sub>2</sub> O	7.6	None	7.6	None	7.6	None	8.2	None	8.2	None	8.2	None
0.003% NaHCO <sub>3</sub>	7.6	None	7.6	None	7.6	None	8.2	None	8.2	None	8.2	None
2.16% NaBr	7.6	None	7.6	None	7.5	None	8.2	None	8.2	None	8.2	None
2.32% NaJ	7.6	None	7.6	None	7.5	None	8.2	None	8.2	None	8.2	None
1.32% NaNO <sub>3</sub>	7.6	None	7.6	None	7.5	None	8.2	None	8.2	None	8.2	None
2.14% Na Acet.	7.6	None	7.6	None	7.6	None	8.2	None	8.2	None	8.2	None
1.17% KCl	7.6	None	7.6	None	7.6	None	8.2	None	8.2	None	8.2	None
1.59% KNO <sub>3</sub>	7.6	None	7.6	None	7.6	None	8.2	None	8.2	None	8.2	None
2.17% K <sub>2</sub> CO <sub>3</sub>	< 8.2	Prec.	< 8.2	Prec.	< 8.2	Prec.	< 8.2	Sl. prec.	< 8.2	Dis.	< 8.2	Prec.

Table III shows that both solutions behave exactly alike toward different cathions and anions. In a former study, in which a 10 per cent aqueous solution of dibismuthyl monosodium citrate was used, it was found that 0.024 per cent calcium chloride formed a white precipitate, which was partly redissolved; with more diluted solutions of the bismuth salt (2.5 per cent), this precipitation does not occur.

From these experiments it may be concluded that dibismuthyl monosodium citrate in ethyleneglycol solution is less dissociated, and, therefore, more resistant toward the influence of heat and hydrogen-ion concentration, but both solutions behave alike toward the cathions and anions that were tried.

TABLE IV.—PRECIPITANT ACTION OF 2.5 PER CENT SOLUTIONS OF DIBISMUTHYL MONOSODIUM CITRATE IN WATER AND IN ETHYLENE GLYCOL IN SERUM.

Cc. serum.	Cc. citrate.	In Water.			In Ethyleneglycol.		
		Immed.	Twenty-four hours.	Forty-eight hours.	Immed.	Twenty-four hours.	Forty-eight hours.
5	0.25	Sl. turb.	Prec.	Prec.	Clear	Prec.	Prec.
5	0.5	Sl. turb.	Prec.	Prec.	Clear	Prec.	Prec.
5	1.0	Clear	Prec.	++	Clear	Prec.	Sl. prec.
5	2.0	Clear	Prec.	+++	Clear	Sl. prec.	Sl. prec.
5	3.0	Clear	Prec.	+++	Clear	Clear	Clear
5	4.0	Clear	Prec.	+++	Clear	Clear	Clear

Next, a comparative study on the precipitant action of these solutions on serum, and a 10 per cent aqueous solution of egg albumin was made. In these

experiments various quantities of a 2.5 per cent solution of dibismuthyl monosodium citrate in water and in ethyleneglycol were added to 5 cc. of beef serum and 10 per cent egg albumin, respectively, and the observations were made immediately after twenty-four and forty-eight hours.

TABLE V.—PRECIPITANT ACTION OF 2.5 PER CENT SOLUTIONS OF DIBISMUTHYL MONOSODIUM CITRATE IN WATER AND IN ETHYLENEGLYCOL ON 10 PER CENT EGG ALBUMIN.

Cc. albumin.	Cc. citrate.	Immed.	In Water.		Immed.	In Ethyleneglycol.	
			Twenty-four hours.	Forty-eight hours.		Twenty-four hours.	Forty-eight hours.
5.5	0.25	Clear	Sl. turb.	Sl. turb.	Clear	Clear	Sl. turb.
5	0.5	Clear	Sl. turb.	Sl. turb.	Clear	Clear	Sl. turb.
5	1.0	Clear	Sl. turb.	Sl. turb.	Clear	Clear	Sl. turb.
5	2.0	Clear	Sl. turb.	Clear	Clear	Clear	Clear
5	3.0	Clear	Clear	Clear	Clear	Clear	Clear
5	4.0	Clear	Clear	Clear	Clear	Clear	Clear

As may be seen from Table IV, both solutions show nearly the same precipitant action, immediately after the addition to the serum, but after twenty-four and forty-eight hours, the precipitation is distinctly less marked in the ethyleneglycol solution. The same holds true for the egg-albumin solution, as illustrated in Table V. This difference may also be explained by a smaller degree of ionization of the bismuth compound in the ethyleneglycol solution.

Since ethyleneglycol is freely soluble in water, its concentrated solutions should act like hypertonic solutions, and this might influence the diffusibility of dibismuthyl monosodium citrate through membranes. For this reason a series of experiments on the diffusibility of 2.5 per cent solutions of the bismuth compound in water and ethyleneglycol were made. In these experiments, 10 cc. of the two solutions were placed in collodion bags, and dialysed against distilled water. The amount of bismuth left in the bags was determined after one, two, three and four days.

TABLE VI.—DIFFUSIBILITY OF DIBISMUTHYL MONOSODIUM CITRATE IN WATER AND IN ETHYLENE GLYCOL SOLUTION THROUGH COLLODION MEMBRANES.

Time, days.	In water.	In ethyleneglycol.
0	0.1998	0.1844
1	0.1962	0.1612
2	0.1919	0.1576
3	0.1902	0.1339
4	0.1980	0.0948

Table VI shows that with the ethyleneglycol, the diffusion is distinctly faster than with the aqueous solution. Similar results were obtained in using frog skin instead of collodion membranes. No attempt was made to determine the cause of this difference, since comparative studies on the rate of absorption from the site of the injection in animals showed that in the living organism the conditions are quite different.

#### SUMMARY.

Dibismuthyl monosodium citrate anhydride is insoluble in ethyleneglycol; the hydrate, however, is easily soluble, and the resulting solution may be diluted with water ad libidum.

A comparative study on the effect of heat, hydrogen-ion concentration, cations and anions, on 2.5 per cent solutions of bismuth sodium citrate in water and in ethyleneglycol indicates that in the ethyleneglycol solution, the bismuth sodium citrate is less dissociated, and, therefore, more stable.

The precipitant action of these solutions on serum and egg-albumin solutions indicates the same fact.

Ethyleneglycol solutions have the properties of hypertonic solutions, and from ethyleneglycol solutions, the bismuth diffuses more rapidly than from aqueous solutions.

## STUDIES ON ALKALI BISMUTH TARTRATES FROM THE CHEMICAL AND BIOLOGICAL STANDPOINT.\*

BY A. E. JURIST AND W. G. CHRISTIANSEN.

Although many publications have appeared concerning the preparation of alkali bismuth tartrates and the clinical value of them in the treatment of syphilis, little information is available regarding the behavior of alkali bismuth tartrates in aqueous solutions containing various stabilizing substances, such as buffers, sugars of different types, salts intended to aid absorption, protective colloids, etc. In addition to the results of this series of stability studies, a rather extensive set of experiments will be presented relating to the toxicity, absorption and local action (irritation at site of injection or other local reactions) of alkali bismuth tartrates when aqueous solutions of the latter are injected intramuscularly; particular reference will be made to the type of solution used. Also, the results of some rough  $p_H$  determinations using an indicator will be shown to have a direct relation to the stability of these solutions.

It was found that a very good estimate of the stability of a solution could be made by heating sealed ampuls of the solution at 105° C. and making periodic observations thereon. For the most part any solution which survived the heat-test for one-half hour or more was sufficiently stable to remain unchanged for the length of time required to make the biological studies desired. Also it was found that the sterilized and unsterilized solutions were on a par as regards stability; solutions used for the biological tests were sterilized by passage through a Berkefeld filter prior to ampuling. All solutions were made up to contain approximately 0.05 Gm. of bismuth metal per cc. or about 7% of the alkali bismuth tartrate. The data given in the following table describes most of the solutions prepared and the stability tests run on them. Unless otherwise stated the compound used was potassium tribismuth tartrate. As will be shown the difference between sodium tribismuth tartrate and potassium tribismuth tartrate was negligible.

TABLE I.—BISMUTH TARTRATE SOLUTIONS AND THEIR STABILITY.

Number.	Material added to the solution.	Stability at 105° C.	Stability in storage at room temperature.
1	5% Sucrose	Opalescent in 120 minutes	Clear light brown color
2	5% Sucrose and 2% benzyl alcohol	Opalescent in 120 minutes	Unchanged six mos.
3	10% Sucrose	Opalescent in 120 minutes	Clear light brown color
4	10% Sucrose and benzyl alcohol 2%	Opalescent in 120 minutes	Unchanged six mos.

\* Scientific Section, A. Ph. A., Baltimore meeting 1930.