Typical results obtained with the use of this method are given in the following table:

TABLE IV.—TITRATION OF TOTAL AMMONIA.

Cc. of Spirit.	Cc. of Alcohol Used.	Cc. of 0.1 H_2SO_4 Required.	Equivalent Weight of NH_3 Gm.	Theoretical Weight of NH_3 Gm.
2	15	22.57	0.0384	0.0386
2	15	22.55	0.0383	0.0386
2	20	22.65	0.0385	0.0386
2	20	22.22	0.0380	0.0386

Calculation of Theoretical Weight of Ammonia.—The ammonia water used in the preparation of the spirit assayed 10.06 p. c. of ammonia with a specific gravity of 0.9593, which is equal to 9.65 Gm. of ammonia in 100 cc. of ammonia water. Anisated Spirit of Ammonia contains 20 p. c. by volume of ammonia water or 1.93 Gm. of ammonia in 100 cc. of the spirit or 0.0386 in 2 cc. The standard proposed was similarly calculated using the percentage strength variations and specific gravity value stated for ammonia water in the U. S. P. X.

A PHYSICOCHEMICAL STUDY OF SOLUTION OF MAGNESIUM CITRATE.*

BY MARGARETHE OAKLEY AND JOHN C. KRANTZ, JR.

INTRODUCTION.

The recognition of a solution of magnesium citrate in the United States Pharmacopœia of 1850 heralded the appearance of scores of papers concerned with various ramifications of this galenical over the last eight decades. An interesting bibliography of this work has been compiled by Professor Langenhan (1). The increasing of the quantity of citric acid per bottle (350 cc.) from 33 Gm. to 35 Gm. precipitated anew the discussion of this product. The pivots around which most of the discussion revolved were the increased acidic taste of the solution and the relative therapeutic efficacy of acid magnesium citrate and the normal salt. Among other writers the new formula for solution of magnesium citrate was defended ardently by Seltzer (2) in 1927 and vehemently maligned by Neimeth (3) in 1929.

It is not the purpose of this investigation to promulgate the adoption of either formula, but to study certain interesting physicochemical aspects involved in the preparation.

ACIDITY AND ACID TASTE.

Much work has been conducted to determine the relationship existing between acid taste, hydrogen-ion concentration and titratable acidity. In 1898 Kastle (4) found a relationship existing between the acid taste and the affinity constants of nineteen different acids in $N/50$ concentration. The threshold concentrations at which various acids exhibited an acidic taste has been studied by Schreiber (5). For citric acid the threshold concentration was found to be about 0.0025 per cent. Harvy (6) made a comprehensive study of the subject and found that total acid concentration and hydrogen-ion concentration were factors in determining acid taste. Through these investigations the influence of buffer salts

---

* Scientific Section and Section on Practical Pharmacy, Miami meeting, 1931.

upon the acid taste of solutions was studied. In general it was found that the presence of buffer salts decreased perceptibly the hydrogen-ion concentration at which the threshold acid taste was detected.

EXPERIMENTAL.

Solutions of magnesium citrate were prepared using 33 Gm. and 35 Gm. per 350 cc., respectively. The sodium bicarbonate was included. The hydrogen-ion concentration of each solution was determined electrometrically using a Wilson (7) type hydrogen electrode. The results are given in Table I.

TABLE I.

Solution of magnesium citrate	33 Gm. citric acid	p_H 3.92
Solution of magnesium citrate	35 Gm. citric acid	p_H 3.82

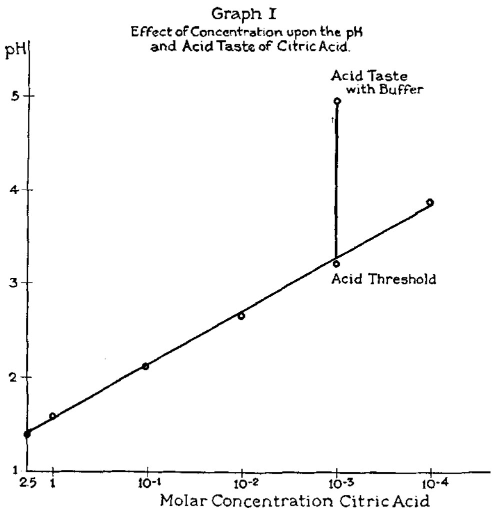
To form the acid salt $MgHC_6H_5O_7$ requires 32.4 Gm. of citric acid including the acid neutralized by the sodium bicarbonate. Therefore, the formula requiring 35 Gm. has present in it about 2.6 Gm. of free citric acid: The change in hydrogen-ion concentration is very slight, which is what one would expect in system of a high buffer capacity.

Solutions of citric acid in various molar concentrations were prepared and their hydrogen-ion concentrations determined. These data are given in Table II.

TABLE II.

Molar Conc. Citric Acid.	p_H.
2.5	1.39
1.0	1.61
0.1	2.14
0.01	2.63
0.001	3.16
0.00001	3.92

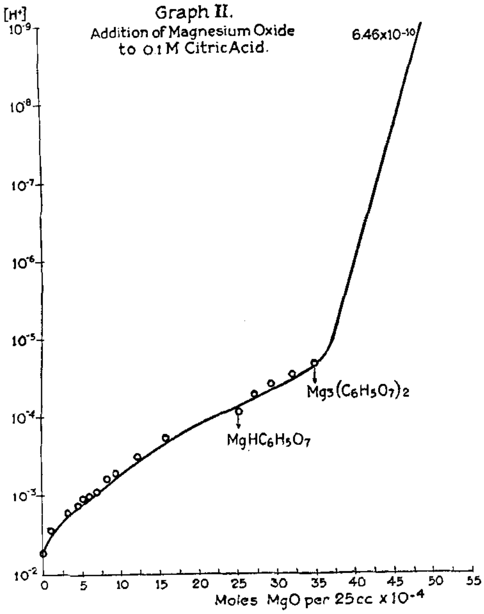
These data are plotted in Graph I. The graph indicates that the threshold acid taste for citric acid is 0.001 molar concentration or about 0.02 per cent. This value is approximately ten times the threshold concentration observed by Schreiber (5). The p_H of this solution is 3.16. When, however, about 0.5 cc. of tenth-normal magnesium citrate solution is added to 10 cc. of 0.001 molar citric acid solution, the p_H is changed to about 4.7 but the acid taste is very markedly accentuated. Thus in the preparation, the acid taste of the free acid is likely accentuated by the buffer salts present.



Graph I

Effect of Concentration upon the pH and Acid Taste of Citric Acid.

The pharmaceutical literature has contained many papers discussing the



nature of the magnesium salt present in the solution. Possibly the most recent of these investigations was conducted by Rees (8). He showed that the deposit found in the bottom of solution of magnesium citrate bottles was tribasic magnesium citrate. By studying the velocity of inversion of the sucrose present, this investigator arrived at the conclusion that the tribasic citrate was present in the solution dissolved in citric acid solution. It is doubtful that the evidence produced justified this conclusion. As matter of general interest the present authors studied the changes in hydrogen-ion concentration which occur when pure magnesium oxide is added to a citric acid solution. Various amounts of pure magnesium oxide were dissolved in 25-cc. portions of 0.1 molar citric acid solution and the hydrogen-ion concentration determined as described previously. These data are shown in Table III.

TABLE III.

Number.	Moles MgO.	*p*H.	[H⁺].
0	0	2.14	7.25×10^{-3}
1	1.24×10^{-4}	2.32	4.79×10^{-3}
2	2.48×10^{-4}	2.50	3.16×10^{-3}
3	3.72×10^{-4}	2.61	2.46×10^{-3}
4	4.96×10^{-4}	2.73	1.86×10^{-3}
5	5.45×10^{-4}	2.77	1.70×10^{-3}
6	6.20×10^{-4}	2.83	1.48×10^{-3}
7	7.20×10^{-4}	2.90	1.26×10^{-3}
8	8.45×10^{-4}	3.07	8.51×10^{-4}
9	9.93×10^{-4}	3.15	7.08×10^{-4}
10	12.4×10^{-4}	3.31	4.90×10^{-4}
11	16.7×10^{-4}	3.59	2.57×10^{-4}
12	25.5×10^{-4}	3.99	0.102×10^{-4}
13	27.3×10^{-4}	4.09	8.13×10^{-5}
14	29.8×10^{-4}	4.22	6.03×10^{-5}
15	32.3×10^{-4}	4.37	4.27×10^{-5}
16	34.8×10^{-4}	4.55	2.82×10^{-5}
17	37.4×10^{-4}	4.70	2.00×10^{-5}
18	50.1×10^{-4}	9.19	6.46×10^{-10}
19	100×10^{-4}	9.63	2.35×10^{-10}

When these data are plotted as shown in Graph II, an interesting relationship may be observed.

DISCUSSION OF RESULTS.

There are two interesting and pertinent observations that may be gleaned from a study of the graph.

First, when one equivalent of magnesium oxide has been added for one equivalent of citric acid as occurs in determination No. 12, the hydrogen-ion concentration is very close to that found in the solution when 33 Gm. of citric acid is used per bottle. The 15 Gm. of official magnesium carbonate consumes about 32.4 Gm. of citric acid. This would seem to point to the existence of large quantities of the compound $MgHC_6H_5O_7$ in the solution.

Second, until determination No. 17 there are no inflexions in the curve. Here the presence of an excess of magnesium oxide is responsible for the tremendous increase in hydroxyl-ion concentration. One would anticipate this type of neutralization curve from the relative magnitudes of the dissociation constants (9) of citric acid. The primary constant is 1.0×10^{-3}, the secondary is 2.5×10^{-5}, and the tertiary is 1.5×10^{-6}. Slightly different values are given by other authors for the secondary and tertiary constants. With a polybasic acid, having dissociation constants relatively so close to each other, the neutralization of the tertiary hydrogen-ions would occur before all of those ions arising from the primary and secondary dissociation are neutralized. Thus a gradual slope rather than an inflexion on the curve is in accordance with theoretical considerations. Thus when a chemical equivalent of magnesium oxide is added to an equivalent of citric acid, in addition to the formation of $MgHC_6H_5O_7$: undoubtedly there exists also in equilibrium with this compound some $Mg_3(C_6H_5O_7)_2$. The conversion of a considerable quantity of the acid salt into the normal salt, with which it is in equilibrium, is probably responsible for precipitation. Hence, the presence of an excessive quantity of citric acid would tend to shift the equilibrium in the direction of the acid salt and thus favor stability. Referring again to the curve, the secondary and tertiary constants differ from each other in magnitude about sixteen fold. Based upon an approximate mathematical analysis of titration curves Auerbach and Smolezyk (10) showed that unless the dissociation constants differed by more than sixteen fold no inflexion in the neutralization curve would exist and the curve would resemble that of a monobasic acid. The findings of the authors, although involving the variation of a divalent base seem to substantiate this assumption with citric acid.

SUMMARY.

1. The relation between hydrogen-ion concentration and total acidity for citric acid has been studied. Its application to the acid taste of solution of magnesium citrate has been emphasized.

2. The nature of the salt presence in the solution has been studied from a physicochemical standpoint.

BIBLIOGRAPHY.

(1) H. A. Langenhan, *U. S. P. Bull. Subcommittee 12* (1930), 18.
(2) L. A. Seltzer, *Drug. Circ.* (May 1927). (3) E. Neimeth, *The Messenger* (1929), 189.
(4) J. H. Kastle, *J. Am. Chem. Soc.*, 20 (1898), 97.
(5) Schreiber, "Studien über den geschmackssin through Bio-Assays," J. C. Munch.
(6) R. B. Harvy, *J. Am. Chem. Soc.*, 42 (1920), 712.
(7) J. Wilson, *Ind. Eng. Chem.*, 17 (1925), 74.
(8) E. W. Rees, *Am. J. Pharm.*, 102 (1930), 496.
(9) "Hydrogen Ions," Britton, page 135, D. Van Nostrand Co., N. Y., 1929.
(10) "Hydrogen Ions," Britton, page 155, D. Van Nostrand Co., N. Y., 1929.

BUREAU OF CHEMISTRY, MARYLAND STATE DEPARTMENT OF HEALTH.