Coulometric Titration of Various Organomercurials and Mercury Containing Compounds

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The feasibility of using constant current coulometry for the analysis of various pharmaceutical compounds containing mercury has been demonstrated. Electrolytically generated thioglycollic acid served as the titrant. No preliminary treatment of the mercury compound was necessary except for those substances in which the mercury is completely bound to carbon. These latter compounds were treated with concentrated hydrochloric acid to cleave the carbon to mercury bond. The mercury content was determined with samples in the milligram range with an indicated deviation of less than one per cent from the theoretical values.

COULOMETRIC titrations are rapidly taking an important place among the instrumental techniques. Applications and advantages of this technique have been recently reviewed (1). Coulometric methods are dependent on the stoichiometry existing between the quantity of electricity and the quantity of electroactive substance transformed at an electrode during the electrolysis. The amount of material that has reacted is computed using Faraday's law.

The internal generation of a reagent by constant current coulometry has made available many unstable but potentially useful reagents for chemical analysis. One of these, organically bound sulfhydryl, has been used by Miller and Hume for the quantitative determination of different metal ions; namely, mercury (II), copper (II), gold (III), and hexacyanoferrate (III) (2, 3). It was thought that their basic technique of generating the sulfhydryl group electrochemically should be of value in the determination of mercury, organically bound, in compounds of pharmaceutical interest.

The method of Miller and Hume employs mercury (II) thioglycollate, a soluble sulfhydryl compound, as the reagent precursor for the coulometric generation of free sulfhydryl. The mercury (II) thioglycollate-thioglycollic acid couple was found to be coulometrically suitable in terms of current efficiency and potentiometric reversibility, enabling efficient titration to proceed with accurate end point detection. The reaction which supplies the reagent sulfhydryl, occurs at the mercury-pool cathode. It may be expressed by the following equation

$$Hg(RS)_2 + 2H^+ + 2e^- = Hg^0 + 2RSH \quad \text{(Eq. 1)}$$

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and is completely reversible. This indicates that one sulfhydryl group per electron is made available by the deposition of mercury. Any free sulfhydryl may be reacted and, thus, effectively removed by reversing the current and generating mercury (II) from the mercury-pool anode according to the following equation (4)

$$Hg^0 = Hg^{++} + 2e^- \quad \text{(Eq. 2)}$$

The reactions that occur in the bulk of the solution may be described by the following equations

$$RSH + R'Hg^+ = R'HgSR + H^+ \quad \text{(Eq. 3)}$$

$$2RSH + Hg^{++} = Hg(RS)_2 + 2H^+ \quad \text{(Eq. 4)}$$

where $R'Hg^+$ represents the monoalkyl or monoaryl mercury (II) ion arising from the dissociation of the organomercurial in the untreated sample (e.g., chlormerodrin in aqueous solution). The mercury (II) in reaction (4) represents the mercury set free from organic combination by treating the sample with a strong mineral acid.

EXPERIMENTAL

Apparatus.—The constant current source described by W. N. Carson, Jr., was used (5). The circuit was so designed that a single switch synchronously controlled the flow of generating current through the cell and the timer. The electric timer[1] used is calibrated to one-tenth of a second. Potentials were measured with a pH meter[2] with a saturated calomel reference electrode and an amalgamated silver wire indicator electrode. The titration cell was a 50-ml. Pyrex beaker, to the bottom of which a side arm (glass tubing, O.D. 0.75 cm.) was fused. A platinum wire served as the electrical contact to the mercury pool through this side arm. A platinum wire helix served as the nonworking electrode. It was separated from the working solution by an agar plug containing sodium nitrate. A block diagram of the titration assembly is shown in Fig. 1.

Reagents and Solutions.—All chemicals used were reagent grade unless otherwise specified. Thiogly-

[1] A Precision Time-it, Precision Scientific Co., Chicago, Ill.
[2] Beckman model H-2.

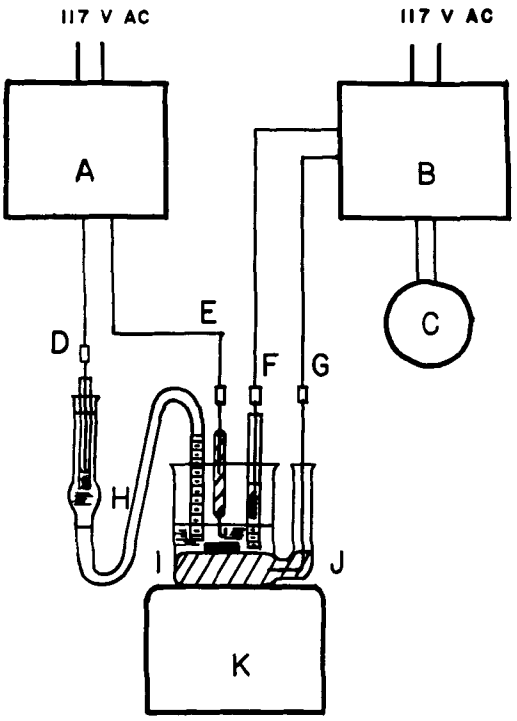

Fig. 1.—A block diagram of the titration apparatus. *A*, Beckman model H-2 pH meter; *B*, constant current source and integral milliameter; *C*, synchronous timer; *D*, saturated calomel reference electrode; *E*, mercury indicating electrode; *F*, platinum wire helix generating electrode; *G*, platinum wire contact to mercury pool electrode; *H*, saturated potassium chloride salt bridge; *I*, generating solution 5 to 7 ml.; *J*, side arm for mercury pool contact; *K*, magnetic stirrer.

collic acid (Eastman Kodak Co.), 70% practical grade and 80% analytical grade; phenylmercuric nitrate, phenylmercuric acetate, powder (The Matheson Co.); meralluride acid, powder;[3] meralluride, injectable solution; chlormerodrin, powder;[4] mercaptomerin sodium, crystals for injection[5] and injectable solution; mercury (II) salicylate powder U.S.P.; mercury (II) oxide (red) powder N.F.; ammoniated mercury powder U.S.P.

A solution of mercury (II) acetate, 0.1 *M* in acetic acid, was standardized against a standard disodium EDTA solution. The buffer used in this work (approximate pH = 5) was a solution 1.0 *M* in acetic acid and also 1.0 *M* in sodium acetate. The mercury (II) thioglycollate was prepared by mixing stoichiometric quantities of thioglycollic acid and mercury (II) chloride. The resulting precipitate was filtered and washed, and then treated with 6.0 *N* sodium hydroxide, dropwise, until completely dissolved (approximate pH = 5). This stock solution was then diluted with distilled water to 0.1 *M* with respect to mercury (II) thioglycollate.

Equal volumes of the buffer solution and the stock mercury (II) thioglycollate solution were mixed to produce the generating solution.

[3, 4] The authors wish to thank Lakeside Laboratories, Milwaukee, Wis., for the donation of these materials.

[5] The authors wish to thank Wyeth Laboratories, Philadelphia, Pa., for the donation of this material.

General Procedure.—The titration was carried out by placing about 5 to 7 ml. of the previously prepared supporting electrolyte-generating solution into the titration cell. Nitrogen was bubbled through this solution for about 5 minutes to remove any dissolved oxygen. A slow flow of gas was continued during the entire titration procedure in order to maintain an inert atmosphere. The point of maximum potential inflection was determined by generating an excess of mercury (II), then reversing the current and back titrating with sulfhydryl (Eqs. 2 and 1, respectively). Before the addition of the sample, the solution was pretitrated to the potentiometric inflection point to remove any slight excess of mercury (II) or sulfhydryl that might be present. The unknown sample was then introduced into the cell and the generating current maintained using appropriate time intervals until the original inflection point was passed (Eq. 1). After each generation period, the indicator potentials were read after equilibrium was reached. Equilibrium was attained quite rapidly, all cases requiring less than 1 minute. The end point time was then calculated from the point of maximum potential inflection. In all the titrations that were performed, the end point was necessarily overrun; and before a new sample was added, the excess sulfhydryl generated was back titrated to the potentiometric inflection point by reversing the current (Eq. 2).

Successive titrations are possible with a given portion of the supporting electrolyte-generating solution. However, the volume increase by the addition of the samples into the titration cell was found to limit the number of successive titrations that could be conducted. By maintaining a small volume in the cell, a sharper inflection point was obtained. In the case of the treated materials, the acidity of the samples added was also found to be a limiting factor. The titration curve shown in Fig. 2 is typical of all the titrations that were performed with the treated and untreated samples.

Samples Titratable without Preliminary Treatment.—The following solutions were prepared by dissolving the compounds in distilled water: phenylmercuric nitrate 0.5 Gm./L., phenylmercuric acetate 1.0 Gm./L., chlormerodrin 0.2 Gm./100 ml. A suitable sample of each solution, 1 to 2 ml., was then taken, pipetted directly into the cell, and titrated according to the procedure outlined.

Preliminary Treatment of the Samples.—The treatment of the various mercury-containing compounds varied only slightly depending on their nature. In preparing the mercury compounds, concentrated hydrochloric acid was used to cleave the mercury-carbon bond, thus releasing the mercury so that it could react with the generated sulfhydryl. The reaction that occurred with the acid for most of the alkyl and aryl salts investigated, of the type RHgOH, RHgX, and R_2Hg, is expressed by the following reaction (6)

$$R_2Hg \xrightarrow{HCl} RH + RHgCl \xrightarrow{HCl} RH + HgCl_2 \quad \text{(Eq. 5)}$$

Previous workers have accomplished similar bond cleavage by employing 50% sulfuric acid and then titrating with potassium thiocyanate (7). However,

TABLE I.—TITRATION DATA FOR CHLORMERODRIN, UNTREATED SOLUTION

No.	Current, ma.	Time, sec.	Taken, mg. Hg	Calcd. mg. Hg	Found, mg. Hg	Error, mg. × 10^{-3}
1	7.0	75.15	1.0926	0.5463	0.5469	+0.6
2	7.0	74.80	1.0926	0.5463	0.5443	−2.0
3	7.0	75.20	1.0926	0.5463	0.5472	+0.9
4	7.0	75.00	1.0926	0.5463	0.5457	−0.6
5	7.0	75.25	1.0926	0.5463	0.5476	+1.3
6	7.0	75.00	1.0926	0.5463	0.5457	−0.6
7	7.0	75.05	1.0926	0.5463	0.5461	−0.2
8	7.0	75.15	1.0926	0.5463	0.5469	+0.6

TABLE II.—TITRATION DATA FOR CHLORMERODRIN, TREATED SOLUTION

No.	Current, ma.	Time, sec.	Taken, mg. Hg	Calcd. mg. Hg	Found, mg. Hg	Error, mg. × 10^{-3}
1	7.0	149.50	1.0926	1.0926	1.0878	−4.8
2	7.0	149.60	1.0926	1.0926	1.0886	−4.0
3	7.0	150.45	1.0926	1.0926	1.0947	+2.1
4	7.0	150.50	1.0926	1.0926	1.0951	+2.5
5	7.0	149.50	1.0926	1.0926	1.0878	−4.8
6	7.0	149.80	1.0926	1.0926	1.0900	−2.6
7	7.0	150.30	1.0926	1.0926	1.0937	+1.1
8	7.0	150.35	1.0926	1.0926	1.0942	+1.6
9	7.0	150.10	1.0926	1.0926	1.0922	−0.4
10	7.0	149.75	1.0926	1.0926	1.0897	−2.9

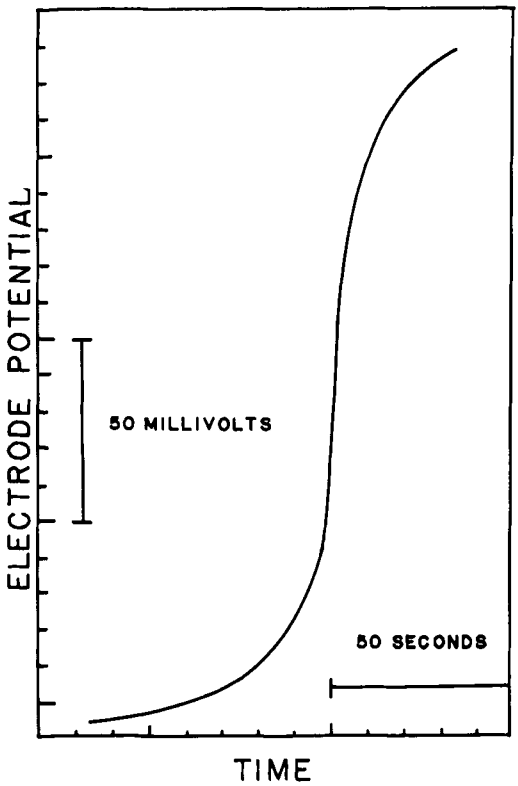

Fig. 2.—Typical titration curve obtained for chlormerodrin treated sample.

this earlier method is not applicable when hydrochloric acid or chloride ions are present.

With the following substances, it was necessary to vary the procedure as follows: 50 ml. of phenylmercuric nitrate solution (0.05%) and phenylmercuric acetate solution (0.10%) were pipetted into separate 100-ml. volumetric flasks. The solutions were boiled down to approximately 25 ml., and 5 ml. of concentrated hydrochloric acid was added, dropwise. After carefully boiling until complete solution was accomplished (usually 10 to 15 minutes), the solutions were neutralized with 6 *N* sodium hydroxide to a pH of approximately 5. Upon cooling, the solutions were diluted to the mark with distilled water.

Any loss of mercury (II) chloride, due to volatilization during the boiling procedure, was found to be negligible.

The two injectable solutions were sampled with a micrometer syringe.[6] Predetermined volumes (0.5 or 1.0 ml.) of these solutions were introduced into 50-ml. volumetric flasks containing 1 to 2 ml. of the concentrated acid. Distilled water, 10–15 ml., was added to the solutions before they were gently boiled. After solution was accomplished, they were cooled to room temperature and diluted to the mark with distilled water.

When solid materials were to be analyzed, appropriate samples (100 or 200 mg.) of the dry materials were weighed and then washed into a 100-ml. volumetric flask containing 2 ml. of the concentrated acid with 15 ml. of distilled water. In the case of mercury (II) salicylate, more distilled water was added and the heating time extended to dissolve the material completely. After cooling the solutions, they were diluted to the mark with distilled water. In the case of the samples of the injectable solutions and the dry materials, the neutralization step was found unnecessary since a minimum of acid was used.

Titration of Treated Samples.—The treated samples (1 to 2 ml.) were taken from the solutions, prepared as previously described, and pipetted directly into the titration cell.

[6] "Agla" brand micrometer syringe, Wellcome Research Laboratories, Beckenham, Kent, England (0.5-ml. capacity, with the precision of delivering 0.01 ml. to ±0.5%).

TABLE III.—SUMMARY OF ALL DATA OBTAINED IN TITRATING MERCURY COMPOUNDS

Sample Taken	No. Determinations Made	Sample, mg. Hg	Thoretical e.p., mg. Hg[b]	Found, Av. mg. Hg	Mean Dev.[c]	Std. Dev.[d]
Phenylmercuric acetate[a]	8	1.1914	0.5957	0.5933	0.0023	0.0035
Phenylmercuric acetate	9	0.5957	0.5957	0.5954	0.0034	0.0041
Phenylmercuric nitrate[a]	10	0.6100	0.3050	0.3055	0.0030	0.0041
Phenylmercuric nitrate	10	0.3050	0.3050	0.3050	0.0022	0.0011
Mercuhydrin acid	9	0.6378	0.6378	0.6407	0.0029	0.0036
Mercuhydrin injection	8	0.3900	0.3900	0.3885	0.0011	0.0012
Mercaptomerin sodium	15	1.3234	0.6617	0.6613	0.0011	0.0015
Mercaptomerin sodium injection	8	0.8270	0.4135	0.4154	0.0017	0.0022
Ammoniated mercury	10	0.7958	0.7958	0.7969	0.0020	0.0026
Mercury salicylate	8	0.5958	0.5958	0.5987	0.0020	0.0024
Mercuric oxide (red)	10	0.7408	0.7408	0.7406	0.0012	0.0015
Chlormerodrin[a]	8	1.0926	0.5463	0.5463	0.0009	0.0011
Chlormerodrin	10	1.0926	1.0926	1.0914	0.0026	0.0029

[a] Samples untreated; all others are treated as described.
[b] Calculated on the basis of available mercury to react with the sulfhydryl.

[c] $d = \frac{\Sigma|X_i - \bar{X}|}{n}$ [d] $s = \sqrt{\frac{\Sigma(X_i - \bar{X})^2}{(n-1)}}$

RESULTS AND DISCUSSION

Titration Data.—Tables I and II indicate typical data obtained in the titration of chlormerodin, untreated and treated samples, respectively. Table III is a summary of all the data obtained in titrating the various organomercurials.

Conclusions.—The experimental data indicated that electrolytically generated sulfhydryl can serve as a titrant in the determination of mercury (II) released from organic combination. In the samples treated with concentrated hydrochloric acid, the total mercury can be determined with the exception of mercaptomerin sodium. In the latter case, only half the total mercury content can be titrated. This indicates that the hydrochloric acid treatment is effective in cleaving the mercury-carbon bond, rendering the mercury available for reaction with the generated sulfhydryl, while insufficient to disrupt the mercury-sulfur bond.

A significant advantage to the general application of this method is the possibility of titrating the material directly without any preliminary treatment. The direct titration of the untreated solutions of chlormerodrin, phenylmercuric acetate, and phenylmercuric nitrate showed that this was possible. In these determinations, one-half the total mercury was titratable.

The chief difficulty with methods now generally available, involving direct titration with thiocyanate is the presence of chlorides. This drawback is overcome with the present procedure. In addition, the drastic heating usually necessary to decompose organic mercurials is eliminated since the hydrochloric acid treatment is effective in the carbon-mercury bond cleavage.

Although interferences by such ions as copper (II), gold (III), and hexacyanoferrate (III) are possible, their presence in the compounds studied is virtually nonexistent and, therefore, introduce no difficulty in the analyses.

The precision of the titrations is as good as, or better than, that with the methods ordinarily used for other mercury compounds.

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