[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION, LAKESIDE LABORATORIES, INC.]

Mercurial Diuretics. VI. Ionization of Organic Mercurials

BY R. L. ROWLAND*

RECEIVED JUNE 23, 1952

As a result of interest in the proposed relationship of toxicity and ionization of organic mercurials, ionization constants were determined for 3-chloromercuri-2-methoxypropylurea and 3-chloromercuri-2-methoxy-2-methylpropylurea and equilibrium constants were determined for the reaction with water of the anhydrides of 3-hydroxymercuri-2-methoxypropylurea and of 3-hydroxymercuri-2-methoxy-2-methylpropylurea. Equilibrium constants were also considered for the reaction of a variety of organic halomercurials with water. The results indicate that the toxicity, as measured by death in rats within 14 days, is not a direct function of the degree of ionization. The values of the equilibrium constants agree with the concept that the solubility in alkali of organic halomercurials is the result of conversion to a more soluble, less ionized base.

The solubility in alkali of chloromercurials, RHgCl, has been considered as the result of conversion to the less ionized but more soluble hydroxymercurial, RHgOH. This interpretation is based, among the mercurials formed by addition to olefins, upon the observation that solution of 2,5-dichloromercurimethyldioxane resulted with an equivalent of alkali.[1] The fact that ionization constants have not been reported for the chloromercurials or hydroxymercurials, combined with the uniqueness of organic mercurials among organometallic compounds in stability to water, prompted an investigation of the course of alkali titration of chloromercurials and of acid titration of hydroxymercurials.

Titration of a variety of chloromercurials, prepared in a study of mercurial diuretics,[2] indicated that the equilibrium constant, $K = [RHgOH][H^+][Cl^-]/[RHgCl]$, for the reaction

$$R'CONHCH_2CR''(OCH_3)CH_2HgCl + H_2O \rightleftarrows R'CONHCH_2CR''(OCH_3)CH_2HgOH + H^+ + Cl^- \quad (1)$$

is *ca.* 1×10^{-10} (Table I). The value of the equilibrium constant for the similar reaction of the bromomercurial

$$NH_2CONHCH_2CH(OCH_3)CH_2HgBr + H_2O \rightleftarrows NH_2CONHCH_2CH(OCH_3)CH_2HgOH + H^+ + Br^- \quad (2)$$

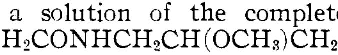
was 5×10^{-12}, indicative of the lower degree of ionization of the organic bromomercurials. The lack of a definite end-point in the titration of the bromomercurials is shown in Fig. 1, in which the titration curves are illustrated. The titration curves of N-(3-chloromercuri-2-methoxypropylcarbamyl)-succinamic acid and N-(3-bromomercuri-2-methoxypropylcarbamyl)-succinamic acid[3] were also observed; following the solution of these latter mercurials by the addition of slightly more than one equivalent of alkali, the titrations with the second equivalent of alkali were very similar to these shown in Fig. 1.

TABLE I

$K = [RHgOH][H^+][X^-]/[RHgX]$

R	X	pK
$CH_3CONHCH_2CH(OCH_3)CH_2$	Cl	9.8
$C_2H_5CONHCH_2CH(OCH_3)CH_2$	Cl	9.8
$C_4H_9CONHCH_2CH(OCH_3)CH_2$	Cl	9.9
$NH_2CONHCH_2CH(OCH_3)CH_2$	Cl	10.0
$NH_2CONHCH_2C(CH_3)(OCH_3)CH_2$	Cl	9.9
$C_2H_5NHCONHCH_2CH(OCH_3)CH_2$	Cl	9.9
$C_3H_7NHCONHCH_2CH(OCH_3)CH_2$	Cl	10.0
$C_6H_5NHCONHCH_2CH(OCH_3)CH_2$	Cl	10.1
$NaOOCCH_2CH_2CONHCONHCH_2CH(OCH_3)CH_2$	Cl	10.0
$NH_2CONHCH_2CH(OCH_3)CH_2$	Br	11.3
$NaOOCH_2CH_2CONHCONHCH_2CH(OCH_3)CH_2$	Br	11.2

The product from the reaction of the halomercurials with water or alkali has been represented in equations 1 and 2 as a hydroxymercurial. In the cases observed by us, however, the mercurial was precipitated from methanolic solution or from a concentrated aqueous solution as an anhydride of RHgOH. Thus from the solution of 3-chloromercuri-2-methoxypropylurea in concentrated sodium hydroxide the anhydride of 3-hydroxymercuri-2-methoxypropylurea (I) precipitated slowly over a period of 10 days in an amount which, after allowance for the solubility of the anhydride in water, approached the theoretical. Whether the solution of the anhydride is considered to contain RHgOH or the anhydride, presumably of a structure



$$\begin{array}{l} NH{=}C{-}NH{-}CH_2{-}CHOCH_3 \\ \quad | \qquad\qquad\qquad\quad | \\ \quad O{-}Hg{-}{-}{-}{-}{-}CH_2 \end{array}$$

it should be possible to determine the equilibrium constant for the reaction with water by observing the titration of its solution with acid.

Titrations of the solution of the anhydride of $NH_2CONHCH_2CH(OCH_3)CH_2HgOH$ (I) are presented in Fig. 2. Upon reaction with perchloric acid the solution of the anhydride should be converted to a solution of the completely ionized salt $NH_2CONHCH_2CH(OCH_3)CH_2Hg^+ClO_4^-$. From the pH of 4.2 at the mid-point of the titration with perchloric acid, the hydrolysis constant, K_{hyd}.

$$[I][H^+]/[NH_2CONHCH_2CH(OCH_3)CH_2Hg^+]$$

was found to be 6×10^{-5}. The ionization constant of the chloromercurial, K_{ion}, may be calculated to be 2×10^{-6} since $K_{ion} = K/K_{hyd}$. The equilibrium constant for the reaction of I with water, *i.e.*, the dissociation constant of the hydrated form of I

$$K_b = \frac{[NH_2CONHCH_2CH(OCH_3)CH_2Hg^+][OH^-]}{[I]} = \frac{10^{-14}}{K_{hyd}}$$

is consequently 1.6×10^{-10}. Similarly the ionization constant of the bromomercurial would be calculated to be 8×10^{-8}. Thus, it is apparent that the alkali solubilities of the chloromercurial

---

* R. J. Reynolds Tobacco Co., Winston-Salem, N. C.

[1] J. Sand and K. A. Hofmann, *Ber.*, **33**, 1358 (1900); J. Chatt, *Chem. Revs.*, **48**, 19 (1951).

[2] R. L. Rowland, W. L. Perry, E. L. Foreman and H. L. Friedman, THIS JOURNAL, **72**, 3595 (1950); R. L. Rowland, W. L. Perry and S. Gerstein, *ibid.*, **73**, 91 (1951); R. L. Rowland, W. L. Perry and S. Gerstein, *ibid.*, **73**, 3691 (1951).

[3] D. E. Pearson and M. V. Sigal, Jr., *J. Org. Chem.*, **15**, 1055 (1950).

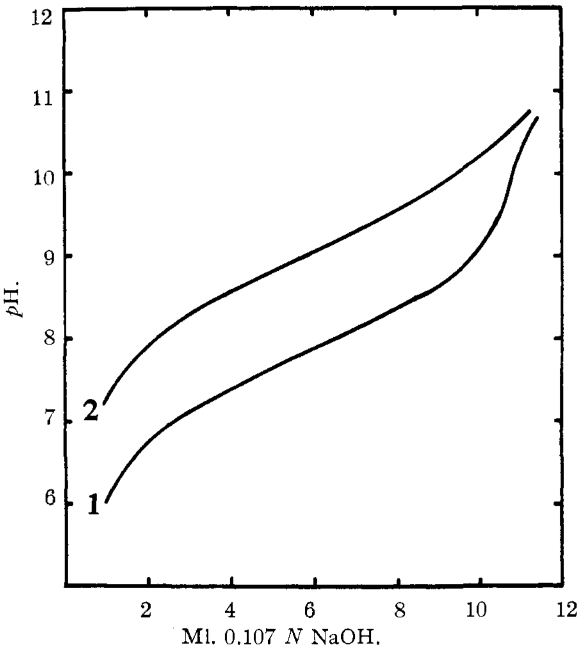


Fig. 1.—Titration of: 1, 0.4 g. of $NH_2CONHCH_2CH(OCH_3)CH_2HgCl$ in 100 ml. of water; 2, 0.45 g. of $NH_2CONHCH_2CH(OCH_3)CH_2HgBr$ in 150 ml. of water.

and of the bromomercurial are the result of conversion to the less ionized, more soluble hydroxymercurial or its anhydride.

A definite end-point was noted in the titration of I with hydrochloric acid (Fig. 2, curve 2). Addition of sodium chloride to a solution of I elevated the *p*H above 10; subsequent titration of the mixture of I and sodium chloride with perchloric acid or with hydrochloric acid gave the definite end-point change in *p*H as shown in Fig. 2, curve 3. The improvement in the titration by acid resulting from addition of chloride has been noted previously in the titration of phenylmercuric hydroxide by perchloric acid.[4] These effects of the presence of chloride upon the titration of I by acid are obviously what would be expected on the basis of the values of $K_{ion} = 2 \times 10^{-6}$ and $K_b = 2 \times 10^{-10}$.

The determination of K_b or K_{ion} was of interest since there would appear to be a general acceptance of the concept that the toxicity of mercurials increases with the degree or rate of ionization.[5] In those studies in which conclusions have been drawn concerning the relationship of ionization to toxicity, the ionization was approached by two methods. In the first, the ionization was considered relative to the rate or degree of reaction with ammonium sulfide or hydrogen sulfide.[6] The well-known reaction of organic mercurials with sulfides to form compounds of the structure $(RHg)_2S$ which generally decompose to form mercuric sulfide[7] would

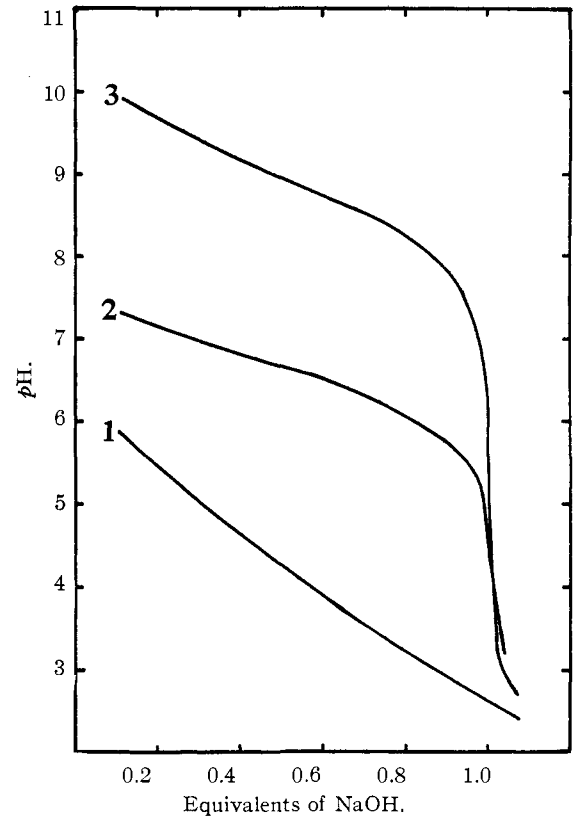


Fig. 2.—Titration of 100 ml. of a 0.03 *M* solution of the anhydride of $NH_2CONHCH_2CH(OCH_3)CH_2HgOH$: 1, with 0.1 *N* $HClO_4$; 2, with 0.1 *N* HCl; 3, with 0.1 *N* $HClO_4$ after addition of 0.5 g. of NaCl.

indicate that the reaction with sulfide is a measure of stability of the R–Hg–S compounds. A second approach to the determination of ionization was by the study of the toxicity of the mercurial to yeast, those mercurials which inhibited yeast in the smallest concentration being considered as the most highly ionized.[8] It is not too unexpected then that those compounds which are most toxic to yeast would be most toxic in higher organisms.

In the course of this investigation of mercurial diuretics[2] no mercurials were observed which possessed a significantly greater LD_{50}, 14 days in rats, than $NH_2CONHCH_2CH(OCH_3)CH_2HgOH$ (I) while the most toxic compound observed was $NH_2CONHCH_2C(CH_3)(OCH_3)CH_2HgX$ (II). This great toxicity, 8 times that of I, was observed in a solution prepared from II, where X is chlorine; the method of solution, addition of close to an equivalent of alkali, undoubtedly converted the major portion of the chloromercurial to the corresponding hydroxymercurial or its anhydride. Accordingly, determinations of K_{hyd} for $NH_2CONHCH_2C(CH_3)(OCH_3)CH_2Hg^+$ and of K_{ion} for $NH_2CONHCH_2C(CH_3)(OCH_3)CH_2HgCl$ were considered. The titration of II with sulfuric acid was similar to that of I; values of equilibrium constants were found of $K_{hyd} = 6 \times 10^{-5}$, $K_{ion} = 2 \times 10^{-6}$ and K_b of 1.6×10^{-10}. The lack of distinction in degree of ionization between I and

---

[4] R. M. Schramm, THIS JOURNAL, **69**, 1831 (1947).

[5] A. Burger, "Medicinal Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1951, p. 254; T. Sollmann, "A Manual of Pharmacology," 7th Ed., W. B. Saunders Co., Philadelphia, Pa., 1948, p. 957.

[6] (a) F. Muller, W. Schoeller and W. Schrauth, *Biochem. Z.*, **33**, 381 (1911); (b) T. Sollmann, "A Manual of Pharmacology," 7th Ed., W. B. Saunders Co., Philadelphia, Pa., 1948, p. 957.

[7] J. Chatt, *Chem. Revs.*, **48**, 21 (1951).

[8] J. B. Peterson, *J. Am. Med. Assoc.*, **87**, 223 (1926); also see footnote 6b.

II, as evidenced in these values for the equilibrium constants, would indicate that there is no basis for the concept of direct relationship of toxicity and degree of ionization. Such a conclusion is also indicated by the realization that the ionization constant for $NH_2CONHCH_2CH(OCH_3)CH_2HgCl$, 2×10^{-6}, is hardly less than the ionization constant, 3.3×10^{-7},[9] for mercuric chloride.

Experimental

Preparation of the Organic Mercurials.—The halomercurials were prepared by the methods previously reported[2] and were purified by crystallization to constant melting point.

Anhydride of 3-Hydroxymercuri-2-methoxypropylurea. a. In Methyl Alcohol.—To 138 g. of 3-chloromercuri-2-methoxypropylurea in 750 ml. of refluxing methyl alcohol was added a solution of 15.0 g. of sodium hydroxide in 300 ml. of methyl alcohol. The mixture was heated shortly after which the sodium chloride was removed by filtration. After the filtrate had remained one day at room temperature, the solid was collected by filtration and washed with methyl alcohol. The anhydride of 3-hydroxymercuri-2-methoxypropylurea weighed 103.5 g. (82%) and decomposed at 186–187° (cor.). It was possible to crystallize very small amounts of the product from absolute ethyl alcohol or methyl alcohol.

b. In Water.—Although the solubility of 3-chloromercuri-2-methoxypropylurea amounts to only 1.3 g. in 100 ml. of water at 25°, 41.5 g. of this mercurial dissolved in 125 ml. of 7% sodium hydroxide. The anhydride of the hydroxymercurial precipitated slowly on standing at room temperature. After 10 days the precipitate weighed 22 g. and decomposed at 184–185° (cor.) with no depression of decomposition temperature upon mixture with the product prepared utilizing methyl alcohol as the solvent. The concentration of mercury in the filtrate, 72 mg./cc., was only slightly greater than that noted for a saturated solution of the anhydride of the hydroxymercurial in distilled water, 70 mg. mercury/cc. corresponding to 116 mg. of organic mercurial/cc.[10]

Anhydride of 3-Hydroxymercuri-2-methoxy-2-methylpropylurea.—The anhydride of 3-hydroxymercuri-2-methoxy-2-methylpropylurea was prepared by treatment of the reaction mixture from the methoxymercuration of methallylurea[2] with two equivalents of sodium hydroxide. Partial concentration of the mixture at room temperature allowed the isolation of a solid which, after extraction with isopropyl alcohol and with ethyl alcohol, decomposed at 188–190° (cor.). *Anal.* Calcd. for $C_6H_{12}N_2O_2Hg$: Hg, 58.18. Found: Hg, 57.98.

Acid–Base Titrations.—The observation of *p*H during the titrations of the solutions of the organic mercurials was made with a Beckman *p*H meter, model G. Calculations of the constants were based on the values of the *p*H at the half-way point of the titrations which were carried out at 25°. In the titration of the halomercurials with sodium hydroxide, the concentrations were such that, at the half-way point, $[RHgX] + [RHgOH]$ was 0.009 ± 0.002 with the exception of the titrations of the N′-propyl-, N′-phenyl- and N′-β-carboxypropionylureas. Titrations of N-(3-chloromercuri-2-methoxypropylcarbamyl)-succinamic acid and of N-(3-bromomercuri-2-methoxypropylcarbamyl)-succinamic acid were conducted such that the total concentration of mercurial at the point at which [RHgX] was considered equal to [RHgOH], the half-way point, was 0.0055; this concentration, *ca.* one-half that of the 0.009 ± 0.002 mentioned previously, was utilized since prior to the titration of these substituted succinamic acids it was necessary to add an equivalent of alkali to neutralize the carboxyl group. The total concentration of mercurial was 0.006 *M* at the half-way point in the titration of N-(3-chloromercuri-2-methoxypropyl)-N′-propylurea and 0.002 *M* at the half-way point in titration of N-(3-chloromercuri-2-methoxypropyl)-N′-phenylurea; these lowered concentrations were the result of lesser solubility of the latter two mercurials in water. Titrations of the anhydrides of the hydroxymercurials with perchloric or sulfuric acid were run at concentrations 30 to 50% greater than the concentrations in the titration by alkali of the halomercurials. It may be noted, however, that the titrations illustrated in Fig. 2 are at yet higher concentrations.

All of the values of *pK* for the chloromercurials as listed in Table I are considered to be equivalent; errors inherent in these determinations are presumed to be greater than the differences between the *pK*'s.

Acknowledgment.—We wish to express our indebtedness to Dr. R. S. Justice and Mr. Gerold Patek for the results of preliminary titrations of the anhydride of 3-hydroxymercuri-2-methoxypropylurea, to Miss Jewell M. Hipke for performing several titrations and to Drs. H. L. Daiell and H. L. Friedman for their interest and encouragement.

MILWAUKEE 1, WISCONSIN

---

[9] B. Lindgren, A. Jonsson and L. G. Sillén, *Acta Chem. Scand.*, **1**, 479 (1947).

[10] The determinations of mercury by precipitation of mercuric sulfide from the acid solution were performed through the courtesy of Mr. H. Krahnke of these laboratories.