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Metal Complexes of Thiouracils I: Stability Constants by Potentiometric Titration Studies and Structures of Complexes

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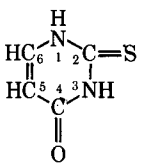
Abstract □ The divalent metals, Cu^{++}, Pb^{++}, Cd^{++}, Ni^{++}, and Zn^{++}, complex with the 5- and/or 6-alkyl-substituted thiouracils, HU. Significant concentrations of MU^+ and MU_2 complexes in homogeneous solution for all but Cu^{++} permitted estimation of the respective K_1 and K_2 stability constants by potentiometric titrations, where the log K_1 values were directly proportional to the pKa values of the parent thiouracils. Thus, the complex with 5,6-dimethyl-2-thiouracil (pKa′ 8.08) was the most stable, and the complex with 5-carboethoxy-2-thiouracil (pKa′ 6.43) was the least stable of those studied. The initial MU^+ complex is formed by the covalent bonding of the divalent cation at the anionic sulfur. When sulfhydryl formation in thiouracil is blocked by prohibiting tautomerization, as with 6-methyl-*N,N′*-diethyl-2-thiouracil, or by alkylation of the sulfur, as with 2-ethylmercapto-4-hydroxypyrimidine, no complexation with metal ions was observed. Pb^{++} and Cd^{++} ions have stability constants, K_1, for MU^+ formation with thiouracils that are 100 times greater than with Ni^{++} or Zn^{++}. No complexation of thiouracils with Fe^{+++}, Fe^{++}, Co^{++}, Ca^{++}, or Mn^{++} was observed. The MU_2 complex is formed by the covalent bonding of the divalent metal to two sulfur anions; this bis(6-*n*-propyl-2-thiouracil)-cadmium (II) is the first complex to precipitate from solution on the titration of cadmium ion and 6-*n*-propyl-2-thiouracil at 25 and 35°. The structure was confirmed by elemental analysis and IR spectra of synthesized compounds. In all other cases of studied complexation of Cd^{++} and Pb^{++} with 2-thiouracil, 6-methyl-2-thiouracil, 5-methyl-2-thiouracil, 5,6-dimethyl-2-thiouracil, 5-carboethoxy-2-thiouracil, and 6-*n*-propyl-2-thiouracil, the first complex that precipitated on potentiometric titration had a 1:1 stoichiometry and was most probably the cyclic dimer, M_2U_2, bis(thiouracil-metal) (II), although the polynuclear polymer, M_nU_n, was possible. The heightened acidity of the 4-OH of the initial MU^+ complex promoted dissociation at low pH values and subsequent covalent bonding of the divalent cation to the sulfur of one thiouracil and the oxygen of another. The resultant M_2U_2 or M_nU_n structure was confirmed by elemental analysis and IR spectra of synthesized complexes. The formed and precipitated complexes of Pb^{++} and Cd^{++} as MU^+, MU_2, and M_2U_2 were stable, at least in mildly alkaline solutions, whereas those of Ni^{++} and Zn^{++} were destroyed in mild alkali with the final precipitation of the metal hydroxides.

Keyphrases □ Thiouracils–metals—complexation □ Complexes, thiouracil–metal—stability constants □ Metal–thiouracil complexes —structure □ Solubility, aqueous—thiouracils □ Potentiometric titration—analysis □ IR spectrophotometry—structure □ UV spectrophotometry—structure

The antithyroid activities of 5-methyl-, 6-methyl-, and 5,6-dimethyl-substituted thiouracils have been claimed to be 0.7, 1.0, and 1.2 relative to 2-thiouracil (Structure I*a*) (1–3).



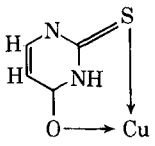
HU I*a*

The present antithyroid derivative of choice, because of its claimed maximal activity and low toxicity in the intact animal, is 6-*n*-propyl-2-thiouracil (1–5). Alkylation of thiouracil at the N-1, N-3, or sulfur positions greatly reduced (2), and substitution by electronegative groups at the 5- or 6-position practically eliminated, any antithyroid activity (1–3).

Cupric ion has been implicated in thyroid function (6). The copper content of the normal and pathologic thyroid has been determined (7) and verified by Kasanen and Viitanen (8) who found elevated copper levels in toxic and nontoxic goiters. The formation of diiodoty-

rosine and thyroxine is increased when cupric ion is added to homogenates of thyroid gland (9). Other evidence that cupric ion aids in the formation of thyroxine, by formation of iodine from iodide, has been presented (10–12).

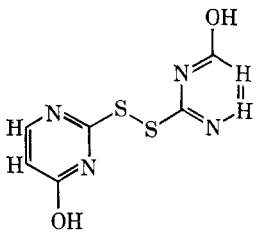
Since cupric ion and other heavy metals precipitate thiouracil and its derivatives from aqueous solution, Libermann (13, 14) conjectured that complexing ability and antithyroid activity may be correlated. He assumed that completeness of precipitation could be taken as a measure of the stability of the complex. However, this assumption is not necessarily valid. Some ethylenediaminetetraacetic acid (EDTA) complexes have high stability *and* high water solubility. Libermann (14) suggested the structure for the cupric–thiouracil complex (Structure I*b*), which assumed a 1:1 stoichiometry of



I*b*

metal to ligand and chelate binding of the cupric ion by the sulfur at the 2-position and the oxygen at the 4-position. Consideration of the stereochemistry of 2-thiouracil and the square-planar nature of cupric ion shows that the proposed structure is impossible because the phenolic oxygen and thionyl sulfur are coplanar and physically distant.

The oxidation of thiouracil by iodine has been shown to occur with ease at physiological pH values. The product is the disulfide (Structure I*c*) (15):



I*c*

The disodium salt of this disulfide is stable, but the free acid readily disproportionates to thiouracil and higher oxidation products (15).

This ease of the oxidation of 2-thiouracil by iodine suggests that thiouracil's antigoitrogenic mechanism of action may be the reduction of iodine to the ineffective iodide. However, since cupric ion has been implicated in thyroid function at the level of iodine production, the removal of cupric or cuprous ion by complexation with thiouracil could be an alternate explanation for its mode of action. If the complexation of cupric or cuprous copper is important in the mechanism of action of the thiouracils, then the stability constant of the complex may be larger for copper than with other physiological metal ions. Furthermore, it may be possible to correlate the stability constant of the copper complex or complexes of thiouracils and other metals with the biological activity of the particular thiouracil derivative. The correlation can only be expected under the conditions of equal concentrations at the site of action. Any differences in the *in vivo* solubility or stability of the thiouracil derivative should be considered.

The principal purpose of these studies was to provide quantitative information on the complexation of metal ions with thiouracils. The types of metal ions which complex, the effect of thiouracil substituents on the stability constants, and the structure of the complexes were to be determined. This first paper in the series applies the method of potentiometric titrations to the study of aqueous solutions of metal complexes of thiouracil that maintain homogeneous solutions for portions of the titrations. This excludes the study of solutions of mixtures of copper ions and thiouracils that give immediate precipitation by this method. The complexes of lead, cadmium, nickel, zinc, ferric, ferrous, manganese, calcium, and cobaltous ions with 2-thiouracil (TU). 6-*n*-Propyl-2-thiouracil (PTU), 6-methyl-2-thiouracil (6MTU), 5-methyl-2-thiouracil (5MTU), 5,6-dimethyl-2-thiouracil (5,6DMTU), 5 carboethoxy-2-thiouracil (5CETU), *N*,*N'*-diethyl-6-methyl-2-thiouracil, and 2-ethylmercapto-4-hydroxypyrimidine (2EM4HP) are to be considered, however.

EXPERIMENTAL

Purification of 2-Thiouracil (TU)—2-Thiouracil[1] was recrystallized from hot water. The product was washed with water and acetone and dried in a vacuum oven at 80°, m.p. 322–323° dec. (all melting points are uncorrected); literature value 310–312° dec. (16), about 340° (17). Equivalent weight 130.3; calculated for $C_4H_4N_2OS$ 128.1. IR spectrum (18), $\bar{\nu}$ in cm.$^{-1}$ (Nujol mull): 3020 (NH); 1680 (C=O); 1280, 1240, 1177. UV spectrum (16), (0.1 *M* $HClO_4$), $\lambda_{max.}$ 273 (ϵ 13,700), $\lambda_{max.}$ 212 (ϵ 16,600).

Purification of 6-*n*-Propyl-2-thiouracil (PTU)—The compound[2] was recrystallized from hot water and dried at 80°, m.p. 219–221°; literature value 219–221° (19). Equivalent weight 170.0; calculated for $C_7H_{10}N_2OS$ 170.2. IR spectrum, $\bar{\nu}$ in cm.$^{-1}$ (Nujol mull): 3100 (NH); 1650 (C=O); 1550, 1240, 1190. UV spectrum (0.1 *M* $HClO_4$), $\lambda_{max.}$ 272 (ϵ 15,840), $\lambda_{max.}$ 214 (ϵ 15,840).

Purification of 6-Methyl-2-thiouracil (6MTU)—The compound[3] was recrystallized from hot water and dried in a vacuum oven at 50°, m.p. 331–332° dec.; literature value >300° (1). Equivalent weight 142.1; calculated for $C_5H_6N_2OS$ 142.1. IR spectrum, $\bar{\nu}$ in cm.$^{-1}$ (Nujol mull): 3100 (NH); 1640 (C=O); 1195, 1165. UV spectrum (0.1 *M* $HClO_4$), $\lambda_{max.}$ 274 (ϵ 15,460), $\lambda_{max.}$ 213 (ϵ 15,760).

Purification of 5,6-Dimethyl-2-thiouracil (5,6DMTU)—This material[4] was recrystallized from hot water and dried at 50° in a vacuum oven, m.p. 286–287° dec.; literature value 283–285° (1). Equivalent weight 156.5; calculated for $C_6H_8N_2OS$ 156.2. IR spectrum, $\bar{\nu}$ in cm.$^{-1}$ (Nujol mull): 3210, 3110 (NH); 1660 (C=O); 1600, 1210, 1130. UV spectrum (0.1 *M* $HClO_4$), $\lambda_{max.}$ 276 (ϵ 17,340), $\lambda_{max.}$ 215 (ϵ 14,020).

Purification of 5-Methyl-2-thiouracil (5MTU)—5-Methyl-2-thiouracil[5] was recrystallized from hot water, washed with water, and dried at 50° in a vacuum oven, m.p. 334° dec; literature value not available (17). Equivalent weight 141.2; calculated for $C_5H_6N_2OS$ 142.1. IR spectrum, $\bar{\nu}$ in cm.$^{-1}$ (Nujol mull): 3090 (NH); 1640 (C=O); 1240, 1200, 1165. UV spectrum (0.1 *M* $HClO_4$), $\lambda_{max.}$ 274 (ϵ 15,450), $\lambda_{max.}$ 213 (ϵ 15,730).

Purification of 5-Carboethoxy-2-thiouracil (5CETU)—5-Carboethoxy-2-thiouracil[6] was used as received, m.p. 245–246°; literature value 245° (17). Equivalent weight 197.5; calculated for $C_7H_8N_2O_3S$

[1] Nutritional Biochemical Corp., Cleveland, Ohio.
[2] Nutritional Biochemical Corp., and K & K Laboratories, Plainview, N. Y.
[3] Nutritional Biochemical Corp. and K & K Laboratories.
[4] K & K Laboratories.
[5] Sigma Chemical Co., St. Louis, Mo.
[6] Cyclo Chemical Corp., Los Angeles, Calif.

200.2. UV spectrum (0.1 M $HClO_4$), $\lambda_{max.}$ 310 (ϵ 15,121), $\lambda_{max.}$ 269 (ϵ 18,991), $\lambda_{max.}$ 213 (ϵ 10,762).

Purification of 2-Thio-6-aminouracil—2-Thio-6-aminouracil was used as received, m.p. 330°; literature value 295° (17). UV spectrum (0.1 M $HClO_4$), $\lambda_{max.}$ 275 (ϵ 18,413), $\lambda_{max.}$ 202 (ϵ 5856).

Synthesis and Purification of 6-Methyl-*N*,*N*'-diethyl-2-thiouracil (X)—This material was synthesized by the procedure of Lacey (20). *N*,*N*'-Diethylthiourea[7] (3.2 g.) was added to 20 ml. of glacial acetic acid and brought to a boil in a round-bottom flask fitted with a reflux condenser and a dropping funnel containing 8.6 g. of diketene.[8] The diketene was added over a 0.5-hr. period, and the reaction was allowed to cool overnight. The reaction was further heated for 0.5 hr. and then cooled; the acetic acid was removed by vacuum evaporation. Twenty milliliters of water was added to the residue; the mixture was shaken to emulsify and put into a refrigerator overnight. The precipitated contents were recrystallized from hot water and dried in a vacuum oven at 50°, m.p. 97–98°; literature value 97–98° (20). IR spectrum, $\bar{\nu}$ in $cm.^{-1}$ (Nujol mull): 1680 (C=O); 1250, 1105. UV spectrum (H_2O), $\lambda_{max.}$ 278 (ϵ 13,100), $\lambda_{max.}$ 222 (ϵ 15,250). Potentiometric titration with 0.1 N NaOH indicated that no titratable acid function was present. The yield was 73%.

Synthesis and Purification of 2-Ethylmercapto-4-hydroxypyrimidine (2EM4HP) (IX)—Eight grams of 2-thiouracil (0.062 mole) was added to 2.49 g. NaOH (0.062 mole) in 100 ml. of water, and acetone was added; the solution was cooled overnight in a refrigerator. A precipitate of the sodium salt of 2-thiouracil formed (8.3 g., 0.055 mole), which was filtered and collected.

The sodium salt of 2-thiouracil (0.055 mole) and ethyl iodide (0.06 mole, 9.35 g.) were added to 120 ml. of 95% ethanol in a round-bottom flask and refluxed until the sodium thiouracil had gone into solution. It was necessary to add an additional 4 g. (0.026 mole) of ethyl iodide during the reaction to put the sodium thiouracil into solution. The reaction mixture was cooled and the ethanol removed by vacuum evaporation. A white residue was left, which was recrystallized from ethanol once and then finally purified by sublimation, m.p. 152–153°; literature value 152° (17). IR spectrum, $\bar{\nu}$ in $cm.^{-1}$ (Nujol mull): 1660 (C=O), 1270, 1170, 1540. UV spectrum (H_2O), $\lambda_{max.}$ 280 (ϵ 5500), $\lambda_{max.}$ 230 (ϵ 11,750). Equivalent weight 156.4; calculated for $C_6H_8N_2OS$ 156.2.

Anal.—Calcd. for $C_6H_8N_2OS$: C, 46.13; H, 5.16; N, 17.94; S, 20.52. Found: C, 46.40; H, 5.31; N, 18.04; S, 20.37.[9]

Potentiometric Titrations—All potentiometric titrations were performed using a Sargent model D automatic titrator equipped with a 2.5-ml. capacity syringe buret. The sample solutions were titrated under nitrogen in water-jacketed titration cells at constant temperature. A Beckman combination electrode with Ag–AgCl reference was used. The pH standardization at 4 and 7 was checked before and after each titration. In no case was the pH drift larger than 0.05 pH unit and usually was less than 0.02 unit.

The 0.1 N sodium hydroxide titrant was prepared and maintained carbonate-free. Sample solutions for titration were prepared with constant concentrations of thiouracil (2×10^{-3} M) and varying concentrations of metal ion, as listed in Table I. The ionic strength was maintained constant at 0.006 M by substituting 0.03 M sodium perchlorate for equal volumes of 0.01 M divalent metal nitrate, since the ratio of the molar concentrations of sodium perchlorate to divalent metal nitrate is 1:3 for equal ionic strengths.

The pKa' values of the various thiouracils (Table II) were determined by potentiometric titration with standard alkali, with an initial ionic strength of 0.006 M and estimated from the pH of half-neutralization. The pKa' values at 25.0° were the averages of at least three separate determinations and had standard deviations of less than 0.05. The pKa' values at 35.0 and 45.0° were usually single determinations made at the same time and under the same conditions as the titrations of the metal–thiouracil mixtures. The equivalent weights of the thiouracils have been given under the characterization of the individual compounds.

Standardization of Metal-Ion Solutions—Analytical grade nitrate salts of cupric, cadmium, lead, nickel, ferric, cobalt, calcium, zinc, and manganese were used to prepare stock solutions in distilled water. The stock solutions were standardized using the mercury, mercury-EDTA electrode[10] (21, 22). The general procedure was to titrate potentiometrically solutions containing 2-ml. aliquots of 0.01–0.04 M metal nitrate, 25.0 ml. of buffer (22), and 1 drop of 1.0×10^{-3} M Hg–EDTA solution (22) with 0.1000 M EDTA. The reference electrode was a saturated calomel electrode. In the case of cobalt, an excess of standard calcium was added, and the excess was determined by titration with EDTA according to the general procedure outlined. Since the procedure of Reilley *et al.* (22) cannot be used to standardize ferric ion, the procedure of Pribil *et al.* (23) was used. The procedure was to titrate a solution containing 5 ml. of 0.01 M ferric ion, 25.0 ml. of a pH 3 chloroacetic acid buffer (0.2 M), and 1 drop of a 0.01 M ferrous perchlorate solution. The titrant was 0.1000 M EDTA, and the electrode system consisted of a platinum indicator electrode and a calomel reference. Since ferrous ion is easily oxidized, fresh ferrous-ion stock solutions were prepared as needed from analytical grade $FeSO_4 \cdot 7H_2O$[11] and boiled, nitrogen-purged water.

Aqueous Solubility of Thiouracils—Saturated aqueous solutions (50 ml. of 0.1 M $HClO_4$ in 100-ml. sealed flasks) of 2-thiouracil, 6-*n*-propyl-2-thiouracil, 6-methyl-2-thiouracil, 5-methyl-2-thiouracil, 5,6-dimethyl-2-thiouracil, 5-carboethoxy-2-thiouracil, and 6-amino-2-thiouracil were equilibrated at 25.0° in a controlled temperature shaker bath. Filter sticks (Sargent No. S-30417) were used to remove samples from the equilibrated solutions. The first filtrate was discarded; 2.0-ml. aliquots of the filtered, equilibrated solution were taken, appropriately diluted with 0.1 M $HClO_4$, and read on the Cary spectrophotometer or the Beckman DU against a 0.1 M $HClO_4$ blank solution. Repetitive samples were taken with time to assure complete equilibration. Possible oxidation (15) of the equilibrating solutions of TU, PTU, 5MTU, and 6MTU were denied by the fact that the absorbances at several wavelengths were of the same ratio to similar absorbances for fresh solutions of these thiouracils. The calculated solubilities are listed in Table II.

Spectrophotometric Titrations of Thiouracils—Thirty milliliters of solutions, 0.921×10^{-4} and 1.00×10^{-4} M in 2-thiouracil and 8.00×10^{-3} M in sodium perchlorate, contained in a water-jacketed titration cell (25.0°), were titrated with 1.00 N NaOH and 0.0499 N NaOH, respectively. Nitrogen gas, free of carbon dioxide (passed through an Ascarite tube) and saturated with water (passed through a sparger tube immersed in water) at 25.0°, was passed into the cell for each run. The cell solution was stirred with a magnetic stirrer. A constant-rate buret (Sargent) equipped with a 2.5-ml. syringe buret was used to deliver the titrant to the cell. The volume delivered could be read to the nearest 0.5 μl. A microaperture flow cell (Beckman catalog No. 97290) was connected by polyethylene tubing (Clay-Adams Co., No. PE 200) to the titration cell and to a 5.0-ml. gastight syringe (Hamilton). After each addition of standard alkali, the gastight syringe was actuated by hand to draw the titration cell solution into the flow cell and the spectrum recorded *versus* a water blank. The gastight syringe was actuated several times before each spectrum was recorded to ensure thorough mixing of any solution that may have remained in the flow cell or tubing. The pH of the solution was read after mixing using a glass-calomel electrode system and a Radiometer pH meter (No. TTT 1). The total volume change during the titration of the sample solution was less than 2% and was considered negligible.

The absorbances at the $\lambda_{max.}$ and other wavelengths were plotted against pH. The pKa' values were determined from the intercept of plots of $\log [(A - A_{H^+})/(A_{OH^-} - A)]$ *versus* pH, where A is the absorbance at a given pH value, A_{H^+} is the absorbance in 0.10 M $HClO_4$, and A_{OH^-} is the absorbance at pH 9 in accordance with the expression (24):

$$\log \left(\frac{A - A_{H^+}}{A_{OH^-} - A} \right) = pKa' - pH \qquad \text{(Eq. 1)}$$

The pKa' values determined by spectrophotometric titrations are given in Table II.

Synthesis of Bis(2-thiouracil)cadmium (II) or $Cd(TU)_2$ (IV)—A solution containing 0.06 mole of 2-thiouracil in 2 l. of hot water was prepared. To the 2-thiouracil solution was added slowly, with stirring, a solution containing 0.03 mole of cadmium nitrate in about 200 ml. of water. The resulting mixture was allowed to stand 0.5 hr. on low heat (about 70°). It was then allowed to cool to room temperature, and the pH was adjusted to 6.5 with concentrated NaOH.

[7] Eastman Organic Chemical Co., Rochester, N. Y.
[8] K & K Laboratories, Plainview, N. Y.
[9] Huffman Laboratories Inc., Wheatridge, Colo.
[10] Sargent Co., Chicago, Ill.
[11] Matheson Coleman & Bell, Cincinnati, Ohio.

Table I—Composition of Solutions and Estimated Logarithmic Stability Constants of 1:1 (MU^+) and 1:2 (MU_2) Metal Complexes of Substituted Thiouracils from Potentiometric Titrations

Ligand[a]	Metal	$10^3[M^{++}]_0$	Temperature	Slope[b]	log K_1[c]	log K_2[c]
2TU	Pb^{++}	2.00	25.0°	1.00	4.68(4.68)[b]	3.07
		1.80	25.2°	1.15	4.69	3.69
		1.60	25.2°	1.15	4.70	3.54
		1.40	25.1°	1.11	4.72	3.47
		1.20	25.0°	1.11	4.73	3.42
		1.00	24.9°	1.08	4.76	3.37
		0.800	24.9°	1.12	4.76	3.49
		0.600	24.9°	1.10	4.84	3.47
		0.400	24.9°	1.08	4.83	3.41
		0.200	24.9°	1.07	4.75	3.49
					4.74 ± 0.05	3.44 ± 0.15
		2.00	34.95°	1.10	4.52(4.58)[b]	3.24
		0.800	34.85°	1.10	4.62	3.40
					4.67 ± 0.05	3.32 ± 0.08
		2.00	44.85°	1.00	4.52(4.54)[b]	2.62
		0.800	45.15°	1.16	4.49	3.37
					4.50 ± 0.01	2.99 ± 0.37
	Cd^{++}	2.00	25.1°	1.00	4.21(4.21)[b]	3.12
		1.80	25.3°	1.36	3.88	4.00
		1.60	24.9°	1.12	4.10	3.57
		1.40	25.3°	1.23	4.03	3.55
		1.20	25.1°	1.36	3.85	3.94
		1.00	25.1°	1.22	4.02	3.46
		0.800	25.1°	1.59	4.13	3.58
		0.600	25.1°	1.33	3.98	3.31
		0.400	25.0°	1.60	4.07	3.36
		0.200	25.0°	1.60	3.96	3.03
					4.02 ± 0.10	3.49 ± 0.29
		2.00	34.7°	1.31	4.07	3.68
		0.80	34.7°	1.26	4.10	3.86
					4.08 ± 0.01	3.77 ± 0.09
		2.00	45.0°	1.10	4.05	3.20
		0.800	45.0°	1.25	3.93	3.70
					3.99 ± 0.06	3.45 ± 0.25
	Ni^{++}	60.00	25.0°	1.13	2.46	3.78
		6.00	25.0°	1.11	2.59	3.57
		4.00	25.0°	1.01	2.38(2.43)[b]	1.69
		1.60	25.0°	1.08	2.60	2.12
		1.00	25.0°	1.20	2.40	2.84
					2.49 ± 0.09	2.66 ± 0.71
PTU	Pb^{++}	2.00	25.8°	1.00	4.79(4.82)[b]	3.34
		1.60	25.8°	1.00	4.76(4.77)[b]	—
		1.00	25.8°	1.12	4.84	3.48
		0.400	25.8°	1.24	4.67[d]	3.26
		0.200	25.8°	1.13	4.50[d]	—
					4.79 ± 0.03	3.36 ± 0.09
		2.00	34.80°	1.08	4.58(4.65)[b]	3.50
		0.800	34.80°	1.15	4.69	3.32
					4.63 ± 0.05	3.41 ± 0.09
		2.00	44.85°	1.00	4.43(4.47)[b]	3.32
		0.800	44.58°	1.05	4.45	3.32
					4.44 ± 0.01	3.27 ± 0.04
	Cd^{++}	2.00	25.0°	—	4.16	4.22
		1.60	25.3°	1.43	—	4.73
		1.00	25.3°	1.66	4.17	4.81
		0.400	25.3°	1.42	4.31[d]	4.20
		0.200	25.3°	2.06	—	—
					4.16 ± 0.005	4.49 ± 0.28
		2.00	35.1°	1.49	3.95	4.64
		0.800	34.9°	1.48	3.78	4.97
					3.86 ± 0.08	4.80 ± 0.17
		2.00	44.9°	1.58	4.01	4.35
		1.20	44.9°	1.42	3.65	4.19
					3.83 ± 0.18	4.27 ± 0.08
	Ni^{++}	2.00	25.9°	1.91	1.34	3.49
		1.60	25.9°	—	0.30[d]	4.46[d]
		1.00	25.9°	—	1.36	3.53
					1.35 ± 0.01	3.51 ± 0.02
	Zn^{++}	2.00	25.9°	—	2.16	3.62
6MTU	Pb^{++}	2.00	26.0°	1.00	4.63(4.66)[b]	3.29
		1.60	25.5°	1.00	4.73(4.80)[b]	3.33
		1.00	25.5°	1.22	4.68	3.45

(*Continued*)

Table I—(*Continued*)

Ligand[a]	Metal	$10^3[M^{++}]_0$	Temperature	Slope[b]	log K_1[c]	log K_2[c]
		0.400	25.0°	1.22	4.73	3.00
					4.69 ± 0.04	3.26 ± 0.16
		2.00	35.1°	1.00	4.70(4.74)[b]	3.51
		0.800	35.1°	1.10	4.80	3.59
					4.75 ± 0.05	3.55 ± 0.04
		2.00	44.9°	1.02	4.54	3.28
		0.80	44.95°	1.19	4.52	3.48
					4.53 ± 0.01	3.38 ± 0.10
	Cd^{++}	2.00	26.0°	1.25	4.15	3.43
		1.60	25.5°	1.33	4.16	3.59
		1.00	25.5°	1.32	4.09	3.70
		0.40	26.0°	1.96	3.67[d]	4.15[d]
					4.13 ± 0.03	3.57 ± 0.11
		2.00	35.2°	1.15	4.31	3.89
		0.800	35.2°	1.47	4.35	3.96
					4.33 ± 0.02	3.92 ± 0.03
		2.00	44.85°	1.00	4.26(4.33)[b]	3.82
		0.800	35.0°	1.46	4.18	3.80
					4.22 ± 0.0	3.81 ± 0.01
	Ni^{++}	2.00	26.0°	1.53	4.13	3.18
5MTU	Pb^{++}	2.00	25.0°	1.00	4.75(4.75)[b]	3.14
		1.60	25.3°	1.06	4.74	3.34
		1.00	24.5°	1.20	4.85	3.24
		0.400	24.5°	1.20	4.89	3.57
					4.80 ± 0.06	3.32 ± 0.16
		2.00	35.05°	1.00	4.65(4.66)[b]	3.25
		0.800	34.9°	1.08	4.73	3.12
					4.69 ± 0.04	3.18 ± 0.06
		2.00	44.85°	1.02	4.51(4.55)[b]	3.30
		0.800	44.85°	1.14	4.59	3.13
					4.55 ± 0.04	3.21 ± 0.08
	Cd^{++}	2.00	25.0°	1.07	4.28(4.36)[b]	3.47
		1.60	25.0°	1.32	4.27	3.75
		1.00	25.3°	1.42	4.22	3.92
		0.400	25.0°	1.93	3.79[b]	4.48[b]
					4.25 ± 0.03	3.71 ± 0.18
		2.00	34.85°	1.16	4.14	3.82
		0.800	34.9°	1.28	4.25	3.93
					4.19 ± 0.05	3.87 ± 0.07
		2.00	44.75°	1.14	3.97	3.23
		0.800	44.95°	1.44	4.11	3.85
					4.04 ± 0.07	3.54 ± 0.31
	Ni^{++}	2.00	26.0°	1.49	2.30[d]	2.84
		1.60	25.3°	1.21	2.72	2.74
		1.00	25.0°	1.31	2.61	1.63[d]
					2.66 ± 0.05	2.79 ± 0.05
5,6DMTU	Pb^{++}	2.00	25.8°	1.00	5.01(5.04)[b]	4.04
		1.60	25.0°	1.00	4.98(5.04)[b]	3.86
		1.00	25.3°	1.00	5.03(5.04)[b]	3.83
		0.400	25.3°	1.37	4.79[d]	3.92
					5.01 ± 0.02	3.91 ± 0.08
		2.00	34.85°	1.00	5.04(5.02)[b]	4.37
		0.800	34.85°	1.06	4.99	4.72
					5.01 ± 0.02	4.54 ± 0.17
		2.00	45.35°	1.00	4.81(4.86)[b]	4.23
		0.800	44.9°	1.32	4.82	4.13
					4.81 ± 0.00	4.18 ± 0.05
	Cd^{++}	2.00	25.5°	1.00	4.52[c](4.53)[b]	—
		1.60	25.5°	1.14	4.36	3.99
		1.00	25.3°	1.32	4.37	4.24
		0.400	25.5°	1.31	4.37	4.11
					4.37 ± 0.004	4.11 ± 0.10
		2.00	34.85°	1.11	4.50	4.23
		0.800	34.95°	1.33	4.40	4.40
					4.45 ± 0.05	4.31 ± 0.08
		2.00	44.85°	1.23	4.28	4.21
		0.800	45.0°	1.67	4.19	4.45
					4.23 ± 0.04	4.33 ± 0.12
	Ni^{++}	1.00	25.5°	1.38	3.03	2.99
5CETU	Pb^{++}[e]	2.00	25.5°	—	ppt.	ppt.

(*Continued*)

Table I—(*Continued*)

Ligand[a]	Metal	$10^3[M^{++}]_0$	Temperature	Slope[b]	log K_1[c]	log K_2[c]
		0.800	25.5°	—	ppt.	ppt.
		2.00	35.0°	—	ppt.	ppt.
		0.800	35.0°	—	ppt.	ppt.
		2.00	45.0°	—	ppt.	ppt.
		0.800	45.0°	—	ppt.	ppt.
	Cd^{++}	2.00	24.8°	1.25	3.57	3.74
		0.800	25.0°	1.75	3.48	3.56
					3.52 ± 0.04	3.65 ± 0.09
		2.00	35.4°	1.54	3.50	3.72
		0.800	34.5°	2.28	—	—
		2.00	44.85°	1.73	3.79	3.98
		0.800	44.85°	2.03	3.55	3.94
					3.67 ± 0.12	3.96 ± 0.02

[a] The ligand concentration was 0.002 *M*, ionic strength was 0.006 *M*, and initial volume of the titrating solution was 25.00 ml. The ligand abbreviations represent the following compounds: (TU) 2-thiouracil; (PTU) 6-*n*-propyl-2-thiouracil; (6MTU) 6-methyl-2-thiouracil; (5MTU) 5-methyl-2-thiouracil; (5,6DMTU) 5,6-dimethyl-2-thiouracil; and (5CETU) 5-carboethoxy-2-thiouracil. [b] These are the slopes of plots of log $(1 - \bar{n})/\bar{n}$ *versus* $p[U^-]$, where $\bar{n}$ is the degree of formation of a postulated 1:1 complex (MU^+) in accordance with $\log (1 - \bar{n})/\bar{n} = pK_1 + p[U^-]$. For those cases where the slope was consistent with the theoretical expectation of unity, it can be postulated that the only complex present in significant concentration is the 1:1 complex, MU^+. The values of log K_1 estimated from the intercept of these plots for unit slopes are given in parentheses. The estimations of pK_1 and slope values were limited to those portions of the titrations where homogeneous solutions were maintained. [c] Log K_1 and log K_2 values were derived from the slope and intercept values of plots of $\bar{n}/(1 - \bar{n})[U^-]$ *versus* $[(\bar{n} - 2)/(\bar{n} - 1)][U^-]$ in accordance with $\bar{n}/(1 - \bar{n})[U^-] = K_1 + [(\bar{n} - 2)/(\bar{n} - 1)][U^-] K_1K_2$, where K_1 is the stability constant for the formation of the 1:1 complex, MU^+, and K_2 is the stability constant for the formation of MU_2 from MU^+. The mean values of the log K values are given for each temperature with the estimated standard deviations. [d] This value was considered anomalous and was not included in the calculation of the mean values. [e] There was immediate precipitation on addition of $Pb(NO_3)_2$ to the 5CETU solution.

The resulting suspension was warmed again, cooled to room temperature, and filtered through a medium fritted-glass funnel. The product was washed with cold water and acetone and dried in a vacuum oven at 60°. IR spectrum, $\bar{\nu}$ in cm.$^{-1}$ (Nujol mull): 1620, 1550, 1530, 1300, 1210, 1180, 827.

Anal.—Calcd. for $C_8H_6CdN_4O_2S_2$: Cd, 30.65. Found: Cd, 31.54, 30.96.

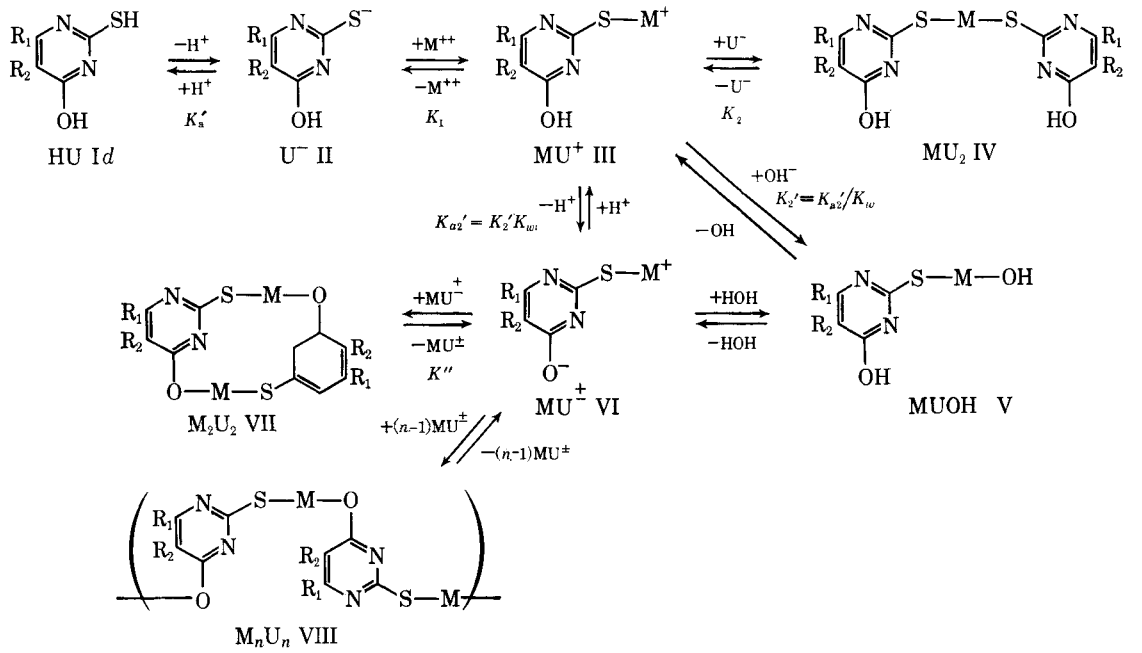
Synthesis of Bis(2-thiouracil)lead (II) or $Pb(TU)_2$ (IV)—The procedure for the synthesis of bis(2-thiouracil)lead (II) was exactly the same as in the case of bis(2-thiouracil)cadium (II) except that lead nitrate was used in place of cadmium nitrate. IR spectrum, $\bar{\nu}$ in cm.$^{-1}$ (Nujol mull): 1660, 1630, 1560, 1500, 1280, 1000, 815.

Anal.—Calcd. for $C_8H_6N_4O_2PbS_2$: Pb, 44.90. Found: Pb, 44.51.

Synthesis of Bis(2-thiouracil-cadmium) (II) or $Cd_2(TU)_2$ (VII)—A solution containing 0.06 mole of 2-thiouracil in a minimum of hot water was added slowly, with stirring, to a 1-l. solution containing 0.06 mole of cadmium nitrate heated to the same temperature (about 80°) as the hot thiouracil solution. The resulting mixture was maintained at the initial temperature for 0.5 hr. and then allowed to cool to room temperature. Concentrated sodium hydroxide was added to pH 6.8, and the resulting suspension was reheated. After 30 min. the suspension was cooled to room temperature and the product filtered through a medium fritted-glass funnel. The resulting product was washed with water and then acetone and dried in the vacuum oven at 60°. IR spectrum, $\bar{\nu}$ in cm.$^{-1}$ (Nujol mull): 3400, 1570, 1510, 1335, 1020.

Anal.—Calcd. for $C_8H_4Cd_2N_4O_2S_2$: Cd, 47.2. Found: Cd, 45.8.

Synthesis of Bis(2-thiouracil-lead) (II) or $Pb_2(TU)_2$ (VII)—The procedure for bis(2-thiouracil-lead) (II) was exactly the same as in the case of bis(2-thiouracil-cadmium) (II) with lead nitrate substituted for cadmium nitrate. IR spectrum, $\bar{\nu}$ in cm.$^{-1}$ (Nujol mull): 1560, 1520, 1430, 1330, 1000, 820.



Scheme I—Relations among the divalent metal-ion complexes of thiouracils except that no experimental evidence exists in support of MUOH (V). MU^+ (III) and MU_2 (IV) exist in significant concentrations in solution, and characterized MU_2 (IV), M_2U_2 (VII), and/or M_nU_n (VIII) are precipitated from solutions of metal-ion and thiouracil mixtures.

Table II—Intrinsic Solubilities[a] at 25.0° and pKa′ Values of Various Thiouracils

Ligand	Solubility, moles/l.	pKa′[b] 25.0°	35.0°	45.0°
2-Thiouracil	5.53×10^{-3}	7.46(7.52)	7.22	7.09
6-*n*-Propyl-2-thiouracil	7.07×10^{-3}	7.76(7.80)	7.48	7.17
6-Methyl-2-thiouracil	3.75×10^{-3}	7.73(7.94)	7.65	7.41
5-Methyl-2-thiouracil	3.58×10^{-3}	7.71(7.80)	7.57	7.35
5,6-Dimethyl-2-thiouracil	8.79×10^{-3}	8.08	8.06	7.76
5-Carboethoxy-2-thiouracil	7.97×10^{-3}	6.43	6.40	6.27
2-Ethylmercapto-4-hydroxypyrimidine	—	7.01	—	—
6-Amino-2-thiouracil	1.79×10^{-3}	—	—	—

[a] Determined from the absorbances of saturated solutions in 0.1 *M* $HClO_4$ where the absorptivity values for wavelengths of maximum absorbance have been given in the *Experimental* section. [b] Determined by potentiometric titration with standard alkali with an initial ionic strength of 0.006 *M*, where the pKa′ was estimated from the pH of half-neutralization. The pKa′ values at 25.0° were the averages of at least three separate determinations and had standard deviations less than 0.05. The parenthetical pKa′ values at 25.0° were determined by spectrophotometric titration of 10^{-4} *M* thiouracil from the intercept values of plots of log $[(A - A_{H+})/(A_{OH-} - A)]$ *versus* pH, where A is the absorbance at a given wavelength at a given pH value, A_{H+} is the absorbance in 0.10 *M* $HClO_4$, and A_{OH-} is the absorbance at pH 9 in accordance with the expression log $[(A - A_{H+})/(A_{OH-} - A)]$ = pKa′ − pH.

Anal.—Calcd. for $C_8H_4N_4O_2PbS_2$: Pb, 62.15. Found: Pb, 62.54.

Synthesis of Bis(6-*n*-propyl-2-thiouracil)cadmium (II) or Cd(PTU)$_2$ (IV)—The preparation of this complex was performed in the same manner as for bis(2-thiouracil)cadmium (II). The molar amounts of 6-*n*-propyl-2-thiouracil and cadmium nitrate were 0.06 and 0.03, respectively. IR spectrum, $\bar{\nu}$ in cm.$^{-1}$ (Nujol mull): 3100, 1630, 1500, 1270, 1220, 1175, 1015, 970, 830.

Anal.—Calcd. for $C_{14}H_{18}CdN_4O_2S_2$: C, 37.29; H, 4.02; Cd, 24.9; N, 12.43; S, 14.22.[12] Found: C, 37.94; H, 4.15; Cd, 24.7; N, 11.95; S, 13.77.

Synthesis of Bis(6-*n*-propyl-2-thiouracil-lead) (II) or Pb$_2$(PTU)$_2$ (VII)—This complex was prepared by the same procedure as for bis(2-thiouracil-cadmium) (*II*). The molar amounts of 6-*n*-propyl-2-thiouracil and lead nitrate used were 0.06. IR spectrum, $\bar{\nu}$ in cm.$^{-1}$ (Nujol mull): 1550, 1420, 1280, 1165, 1020, 825.

Anal.—Calcd. for $C_{14}H_{18}N_4O_2PbS_2$: Pb, 55.2. Found: Pb, 55.4.

Analysis of Cadmium Content of Complexes—Accurately weighed (200-mg.) samples of the dried cadmium complex were dissolved in 150 ml. of 0.01 *M* H_2SO_4 and heated (70°) until all of the sample had dissolved. Approximately 150 mg. of sodium hydrogen sulfide in 15 ml. of water was added, and the resulting cadmium sulfide precipitate was digested for about 2 hr. until the crystals were large. The precipitate was filtered onto a tared, fritted-glass funnel, washed with warm water, and dried in a vacuum oven at 50° overnight. The dried precipitate was weighed in the funnel, and the cadmium was calculated by multiplying the weight of cadmium sulfide by the gravimetric factor 0.7780 (*25a*).

Analysis of Lead Content of Complexes—Accurately weighed samples (300 mg.) of the lead complex were digested in 100 ml. of 1.0 *M* nitric acid until everything had dissolved. The volume was reduced to 25 ml. by evaporation; 100 ml. of a solution 2.0 *M* in sulfuric acid and 1.0 *M* in sodium sulfate was added. The precipitate was digested to give large crystals, and the volume was reduced by evaporation to about 50 ml. The precipitate was collected on a tared, fritted-glass funnel, washed with water, dried at 120° overnight, and weighed. The gravimetric factor is 0.6832 (*25b*).

THEORY AND METHODS OF CALCULATION

The derivation of the general equation for the calculation of stability constants from potentiometric titration data was first given by Bjerrum (26). An excellent summary of computational techniques is also available (27). The following derivations are made for the specific circumstances in this study. They do not assume the formation or precipitation of significant amounts of the hydroxides of the free metal ion, *i.e.*, MOH^+ or $M(OH)_2$, and require all species (ligands, metal ions, and complexes) to be in solution and in instantaneous equilibrium. They can be and were applied only under such valid circumstances. All possible species and complexes and the rational equilibria among them are shown in Scheme I. The discussion of the following section is in respect to these relationships.

[12] Elemental analysis by Huffman Laboratories Inc., Wheatridge, Colo.

Equations for Stability Constants of Complexes of Thiouracil (HU) and Doubly Charged Metal Cations (M^{++}) where the Significant Complexes in Solution Have Only the Forms MU^+ and MU_2—The formation of 1:1 (MU^+) and 2:1 (MU_2) complexes of thiouracil anion (U^-) and metal ion (M^{++}) in homogeneous solution can be formulated as:

$$\underset{\text{I}}{HU} \underset{+H^+}{\overset{-H^+}{\rightleftarrows}} \underset{K_a'}{U^-} \underset{-M^{++}}{\overset{+M^{++}}{\rightleftarrows}} \underset{\text{III}}{MU^+} \underset{-U^-}{\overset{+U^-}{\rightleftarrows}} \underset{K_2\ \text{IV}}{MU_2} \qquad \text{(Eq. 2)}$$

The apparent acid-dissociation constant of the thiouracils is:

$$K_a' = \frac{[U^-][H^+]\gamma_\pm}{[HU]} \qquad \text{(Eq. 3)}$$

where $[U^-]$ and $[HU]$ are the molar concentrations of thiouracil anion, II, and undissociated thiouracil acid, I, respectively; and $[H^+]\gamma_\pm = a_{H^+} = 10^{-pH}$ is the hydrogen-ion activity, where $\gamma_\pm$ is the mean activity coefficient of the hydrogen-ion concentration, $[H^+]$. The stability constant for the first complex of metal ion with thiouracil is:

$$K_1 = \frac{[MU^+]}{[M^{++}][U^-]} \qquad \text{(Eq. 4)}$$

where $[MU^+]$ is the concentration of the first complex, III; and $[M^{++}]$ is the concentration of free metal ion. The step stability constant for the formation of the 1:2 complex is:

$$K_2 = \frac{[MU_2]}{[MU^+][U^-]} \qquad \text{(Eq. 5)}$$

where $[MU_2]$ is the concentration of the second complex, IV. The overall stability constant, the product of K_1 and K_2, is:

$$\beta_2 = K_1K_2 = \frac{[MU_2]}{[M^{++}][U^-]^2} \qquad \text{(Eq. 6)}$$

The mass balance equations for thiouracil, metal-ion, and sodium hydroxide titrant are:

$$[HU]_0 = [U^-] + [HU] + [MU^+] + 2[MU_2] \qquad \text{(Eq. 7)}$$

$$[M^{++}]_0 = [M^{++}] + [MU^+ + [MU_2] \qquad \text{(Eq. 8)}$$

$$[NaOH] = [U^-] + [MU^+ + 2[MU + [OH^-] - [H^+] \qquad \text{(Eq. 9)}$$

The initial stoichiometric concentrations of thiouracil and metal ion in the solution to be titrated are given by $[HU]_0$ and $[M^{++}]_0$. The stoichiometric concentration of alkali, calculated on the basis that of the amount added at any point in the titration none had yet been consumed, is given by [NaOH]. The concentration of hydroxyl ion in Eq. 9 is the sum of the hydroxyl ion from the titrant and from the dissociation of water. Since a hydrogen ion is produced when a water molecule dissociates, the hydrogen-ion concentration corrects the hydroxyl-ion concentration for this phenomenon, so the resultant equation only accounts for the hydroxyl ion due to the titrant.

The degree of formation, $\bar{n}$, is defined as the average number of ligands bound to a metal ion:

$$\bar{n} = \frac{[MU^+] + 2[MU_2]}{[M^{++}]_0} \qquad \text{(Eq. 10)}$$

When the appropriately rearranged Eqs. 3 and 7 are substituted into Eq. 10,

$$\bar{n} = \frac{[HU]_0 - [U^-]\left(1 + \frac{[H^+]\gamma_\pm}{K_a'}\right)}{[M^{++}]_0} \qquad \text{(Eq. 11)}$$

When Eq. 9 is subtracted from Eq. 7,

$$[HU_0] - [NaOH] = [HU] - [OH^-] + [H^+] \qquad \text{(Eq. 12}a\text{)}$$

If the potentiometric titrations are performed near neutrality and/or significant thiouracil is present during the titrations, the differences between the relatively small quantities of $[OH^-]$ and $[H^+]$ can be ignored and

$$[HU]_0 - [NaOH] = [HU] \qquad \text{(Eq. 12}b\text{)}$$

This was true for all cases. The value for [HU] in Eq. 12*b* may be obtained from a rearrangement of Eq. 3. After substitution of this value for [HU] into Eq. 12*b*, the following equation is obtained on rearrangement:

$$[U^-] = \frac{[HU]_0 - [NaOH]}{[H^+]\gamma_\pm/K_a'} \qquad \text{(Eq. 13)}$$

The right-hand side of Eq. 13 contains only experimentally obtainable quantities; therefore, $[U^-]$ can be calculated. Substitution of $[U^-]$ into Eq. 11 allows the calculation of $\bar{n}$.

Substitution of the rearranged equilibrium expressions for $[MU^+]$, $[MU_2]$, (Eqs. 4 and 6) and the mass balance (Eq. 8) for $[M^{++}]_0$ into Eq. 10 gives, on simplification and rearrangement, a relation between $\bar{n}$, K_1, and β_2:

$$\frac{\bar{n}}{(1 - \bar{n})[U^-]} = \left(\frac{\bar{n} - 2}{\bar{n} - 1}\right)\beta_2[U^-] + K_1 \qquad \text{(Eq. 14)}$$

Equation 14 is linear when $\bar{n}/(1 - \bar{n})\,[U^-]$ is plotted against $[(\bar{n} - 2)/(\bar{n} - 1)]\,[U^-]$. The slope is β_2 and the intercept is K_1. If β_2 is assumed to be zero, Eq. 14 reduces to an equation whose logarithmic transformation is:

$$\log \frac{1 - \bar{n}}{\bar{n}} = pK_1 + p[U^-] \qquad \text{(Eq. 15)}$$

where pK_1 and $p[U^-]$ represent the negative logarithm of K_1 and $[U^-]$, respectively. Equation 15 is linear when $\log (1 - \bar{n})/\bar{n}$ is plotted against $p\,[U^-]$ and has a slope of 1 and an intercept of pK_1.

Equations for Stability Constants of Complexes of Thiouracil (HU) and Doubly Charged Metal Cations (M^{++}) where Significant Complexes in Solution Have Only the Forms MU^+, MU_2, and MUOH (or $MU^\pm$)—The formation of MUOH (V), the mixed ligand complex (or its reaction equivalent zwitterion $MU^\pm$, VI) can conceivably occur by reaction of III, Scheme I, or Eq. 2, with OH^- (or by its equivalent, the removal of a H^+):

$$\begin{array}{ccccc} MU^\pm & \underset{+H^+}{\overset{-H^+}{\rightleftarrows}} & MU^+ & \underset{-OH^-}{\overset{+OH^-}{\rightleftarrows}} & MUOH \\ \text{VI}\ K_{a_2}'/K_2'K_w & & \text{III}\ K_2' = K_{a_2}'/K_w & & \text{V} \end{array} \qquad \text{(Eq. 16)}$$

This derivation of the equations for the calculation of the stability constants of MU^+ (III) and MUOH (V) assumes that no significant amounts of MOH^+ and/or $M(OH)_2$ are formed and all species are in solution and at equilibrium. The use of the symbol MUOH in the following equations may stand for either MUOH (V) or $MU^\pm$ (VI) or the sum of both. The fact that both are products of hydroxyl-ion reaction with MU^+ (III) makes them mathematically equivalent in all calculations.

The expressions for the apparent acid-dissociation constants, K_a', and the equilibrium constant, K_1, for the first complex, MU^+ (III), have already been given (Eqs. 3 and 4). The step stability constants, K_2', of the mixed ligand complex is:

$$K_2' = \frac{[MUOH]}{[MU^+][OH^-]\gamma_\pm'} \qquad \text{(Eq. 17)}$$

where [MUOH] is the molar concentration of the mixed ligand complex (V), and $[OH^-]\gamma_\pm' = a_{OH^-} = 10^{-pOH} = 10^{-(pK_w - pH)}$ is the activity of hydroxyl ions. The mean activity coefficient is given by $\gamma_\pm'$. The expression for the autoprotolytic constant of water is:

$$K_w = [H^+]\,\gamma_\pm\,[OH^-]\,\gamma_\pm' \qquad \text{(Eq. 18)}$$

The overall stability constant, the product of K_w, K_1, and K_2', for the mixed ligand complex is:

$$\beta_{11} = K_1K_2'K_w = \frac{[MUOH][H^+]\gamma_\pm}{[M^{++}][U^-]} \qquad \text{(Eq. 19)}$$

The value of $[OH^-]\,\gamma_\pm'$ has been substituted by $K_w/[H^+]\,\gamma_\pm$ from Eq. 18. The mass balance equations for thiouracil, metal-ion, and sodium hydroxide titrant are:

$$[HU]_0 = [U^-] + [HU] + [MU^+] + [MUOH] + 2[MU_2] \qquad \text{(Eq. 20)}$$

$$[M^{++}]_0 = [M^{++}] + [MU^+] + [MUOH] + [MU_2] \qquad \text{(Eq. 21)}$$

$$[NaOH] = [U^-] + [MU^+] + 2[MUOH] + 2[MU_2] + [OH^-] - [H^+] \qquad \text{(Eq. 22)}$$

When the degree of formation for the complexes MU^+, MUOH, and MU_2 is considered

$$\bar{n} = \frac{[MU^+] + [MUOH] + 2[MU_2]}{[M^{++}]_0} \qquad \text{(Eq. 23)}$$

Substitution of rearranged Eqs. 3 and 20 into Eq. 23 results in:

$$\bar{n} = \frac{[HU]_0 - [U^-]\left(1 + \frac{[H^+]\gamma_\pm}{K_a'}\right)}{[M^{++}]_0} \qquad \text{(Eq. 11)}$$

Subtracting Eq. 22 from Eq. 20, substituting [HU] from Eq. 3 and [MUOH] from Eq. 19, and dropping the relatively small quantities $[OH^-]$ and $[H^+]$ give:

$$\frac{[HU]_0 - [NaOH]}{[H^+]\gamma_\pm/K_a' - \beta_{11}[M^{++}]/[H^+]\gamma_\pm} = [U^-] \qquad \text{(Eq. 24)}$$

The left-hand side of Eq. 24 contains the free metal-ion concentration; therefore, the value of $[U^-]$ cannot be accurately calculated unless the free or uncomplexed metal-ion concentration is determinable. If the assumption is made that MUOH is not present in any significant amount during some interval in the titration, then Eq. 24 reduces to Eq. 13. This assumption would permit the observed data to conform to Eq. 14. Equation 24 is valid when MUOH is present, whether or not significant amounts of MU_2 are formed.

The relation of $\bar{n}$ to K_1, β_2, and β_{11} for mixed ligand complexes is derived by substitution of the equilibrium expressions for $[MU^+]$ (Eq. 4), [MUOH] (Eq. 19), $[MU_2]$ (Eq. 6), and $[M^{++}]$ (Eq. 21) into Eq. 23 to give:

$$\bar{n} = \frac{K_1[U^-] + \beta_{11}\frac{[U^-]}{[H^+]\gamma_\pm} + 2\beta_2[U^-]^2}{1 + K_1[U^-] + \beta_{11}[U^-]/[H^+]\gamma_\pm + \beta_2[U^-]^2} \qquad \text{(Eq. 25)}$$

Rearrangement of Eq. 25 by multiplication of both sides by the denominator of the right-hand expression and collection of similar terms gives:

$$\frac{\bar{n}}{(1 - \bar{n})[U^-]} = K_1 + \frac{\beta_{11}}{[H^+]\gamma_\pm} + \frac{\bar{n} - 2}{\bar{n} - 1}\beta_2[U^-] \qquad \text{(Eq. 26)}$$

which is not linear when $\bar{n}/(1 - \bar{n})\,[U^-]$ is plotted against $1/[H^+]\gamma_\pm$ or $[(\bar{n} - 2)/(\bar{n} - 1)]\,[U^-]$ when $\bar{n}$ is calculated from Eq. 11 for $[U^-]$ calculated from Eq. 24. When it is assumed that the concentration of MUOH is not significant, β_{11} approaches zero, Eq. 26 reduces to Eq. 14, $[U^-]$ may be calculated from Eq. 13, and only potentiometric titration data are needed. When it is assumed that the concentration

of MU_2 is not significant and that only MU^+ and MUOH complexes may exist, β_2 approaches zero and Eq. 26 becomes

$$\frac{\bar{n}}{1 - \bar{n}\,[U^-]} = K + \frac{\beta_{11}}{[H^+]\gamma_\pm} \qquad \text{(Eq. 27)}$$

which is linear when $\bar{n}/(1 - \bar{n})\,[U^-]$ is plotted against $1/[H^+]\gamma_\pm$ with a slope of β_{11} and an intercept of K_1 when $\bar{n}$ is calculated from Eq. 11 for $[U^-]$ calculated from Eq. 24, which demands an independent estimate of metal-ion concentration in addition to the potentiometric titration data.

Equations for Stability Constants of Thiouracil (HU) and Doubly Charged Metal Cations (M^{++}) in the General Case where Complexes Have Only the Possible Forms MU^+, MU_2, $MU^\pm$ (or MUOH), and M_2U_2 or n Complexes as M_nU_n—The formation of positively charged MU^+ (III) and neutral $MU^\pm$ (VI) [or its equivalent MUOH (V)] 1:1 complexes, as well as the polynuclear complexes, M_2U_2 (VII), can be formulated as an extension of Eq. 16:

$$\underset{\text{VII}}{M_2U_2} \underset{-MU^\pm}{\overset{+MU^\pm}{\rightleftharpoons}} \underset{K_2''}{\underset{\text{VI}}{MU^\pm}} \underset{-(n-1)MU^\pm}{\overset{+(n-1)MU^\pm}{\rightleftharpoons}} \underset{\text{VIII}}{M_nU_n} \qquad \text{(Eq. 16}a\text{)}$$

Molecular models of M_2U_2 (VII) in Scheme I are easily formed and exhibit no strain. It is also possible to write polynuclear complexes, M_nU_n, of variable n in the linear form of VIII in Scheme I. This derivation of the equations to relate stability constants of MU^+, $MU^\pm$, M_2U_2, and polynuclear complexes, M_nU_n, assumes that no significant amounts of MOH^+ are formed and all species are in solution and in equilibrium.

The expressions for the apparent acid-dissociation constant of the ligand and the stability constant of the first complex (MU^+, III) have been given (Eqs. 3 and 4). The expression for the acid-dissociation constant of MU^+ (III) to $MU^\pm$ (VI) is:

$$K_{a_2}' = \frac{[MU^\pm][H^+]\gamma_\pm}{[MU^+]} \qquad \text{(Eq. 28)}$$

The equation for the step stability constant of M_2U_2 (VII) is:

$$K_2'' = \frac{[M_2U_2]}{[MU^\pm]^2} \qquad \text{(Eq. 29)}$$

Substitution of the equilibrium expression for $[MU^+]$ (Eq. 4) into Eq. 17 and collection of constants give:

$$\beta_{a2} = K_{a_2}'K_1 = \frac{[MU^\pm][H^+]\gamma_\pm}{[M^{++}]\,[U^-]} \qquad \text{(Eq. 30)}$$

where β_{a2} has the same value as β_{11} in Eq. 19. Substitution of the expression for $[MU^\pm]$ from Eq. 30 into Eq. 29 and collection of constants give:

$$\beta_{22} = K_2''\beta_{a2} = \frac{[M_2U_2][H^+]^2\,\gamma_\pm{}^2}{[M^{++}]\,[U^-]^2} \qquad \text{(Eq. 31)}$$

The mass balance equations for thiouracil, metal-ion, and sodium hydroxide titrant are:

$$[HU]_0 = [U^-] + [HU] + [MU^+] + [MU^\pm] + 2[M_2U_2] + 2[MU_2] \qquad \text{(Eq. 32)}$$

$$[M^{++}]_0 = [M^{++}] + [MU^+] + [MU^\pm] + 2[M_2U_2] + [MU_2] \qquad \text{(Eq. 33)}$$

$$[NaOH] = [U^-] + [MU^+] + 2[MU^\pm] + 4[M_2U_2] + 2[MU_2] + [OH^-] - [H^+] \qquad \text{(Eq. 34)}$$

The degree of formation when the complexes MU^+, MU_2, $MU^\pm$, and M_2U_2 are considered is:

$$\bar{n} = \frac{[MU^+] + [MU^\pm] + 2[M_2U_2] + 2[MU_2]}{[M^{++}]_0} \qquad \text{(Eq. 35)}$$

Equation 35, when substituted by rearranged Eqs. 3 and 32, is

$$\bar{n} = \frac{[HU]_0 - [U^-]\left(1 + \dfrac{[H^+]\gamma_\pm}{K_a'}\right)}{[M^{++}]_0} \qquad \text{(Eq. 11)}$$

Subtracting Eq. 34 from Eq. 32; substituting Eqs. 3, 30, and 31 for [HU], $[MU^\pm]$, and $[M_2U_2]$, respectively; and dropping the relatively small quantities $[OH^-]$ and $[H^+]$ give:

$$[U^-] = \frac{[HU]_0 - [NaOH]}{[H^+]\gamma_\pm/K_a' - \beta_{a2}[M^{++}]/[H^+]\gamma_\pm - 2\beta_{22}[M^{++}]^2[U]/[H^+]^2\gamma_\pm{}^2} \qquad \text{(Eq. 36)}$$

where β_{a2} (Eq. 30) has the same value as β_{11} (Eq. 19).

The general equation for the ligand-anion concentration, where n polynuclear complexes M_nU_n (VIII) exist for all n values in addition to the complex MU^+ (III) and independent of whether an MU_2 (IV) complex is present or not, is:

$$[U^-] = \frac{[HU]_0 - [NaOH]}{[H^+]\gamma_\pm/K_a' - \sum_0^n \left(\dfrac{n\beta_{nn}[M^{++}]^n[U^-]^{n-1}}{[H^+]\,\gamma_\pm{}^n}\right)} \qquad \text{(Eq. 37)}$$

where $MU^\pm$ (or its equivalent, MUOH) is considered to be a polynuclear complex of the form M_1U_1. When $n = 1$, the only complexes in solution can be MU^+, $MU^\pm$, and possibly MU_2, and Eq. 37 reduces to Eq. 24. When $n = 0$ or if it is assured that M_nU_n complexes including $MU^\pm$ (or MUOH) are not significant during the titration, the only complexes in solution are MU^+ and possibly MU_2, and Eq. 37 reduces to Eq. 13 which can be calculated from the homogeneous potentiometric titrations. The values of $[U^-]$ in Eqs. 25 and 37 are functions of the free or uncomplexed metal-ion concentration and cannot be calculated accurately unless this concentration is obtained in addition to the potentiometric titration data.

The relation of $\bar{n}$ to K_1, β_2, β_{a2}, and β_{22} is derived by substitution of the equilibrium expressions for $[MU^+]$ (Eq. 4), $[MU_2]$ (Eq. 6), $[MU^\pm]$ (Eq. 30), $[M_2U_2]$ (Eq. 31), and $[M^{++}]_0$ (Eq. 33) into Eq. 35 to give:

$$\bar{n} = \frac{K_1[U^-] + 2\beta_2[U^-]^2 + \beta_{a2}[U^-][H^+]^{-1}\gamma_\pm{}^{-1} + 2\beta_{22}[M^{++}][U^-]^2[H^+]^{-2}\gamma_\pm{}^{-2}}{1 + K_1[U^-] + \beta_2[U^-]^2 + \beta_{a2}[U^-][H^+]^{-1}\gamma_\pm{}^{-1} + 2\beta_{22}[M^{++}][U^-]^2[H^+]^{-2}\gamma_\pm{}^{-2}} \qquad \text{(Eq. 38)}$$

which can be rearranged to:

$$\frac{\bar{n}}{(1 - \bar{n})[U^-]} = K_1 + \frac{\beta_{a2}}{[H^+]\gamma_\pm} + \left(\frac{\bar{n} - 2}{\bar{n} - 1}\right)\beta_2[U^-] + \frac{2\beta_{22}[M^{++}][U^-]}{[H^+]^2\gamma_\pm{}^2} \qquad \text{(Eq. 39)}$$

The general equation to relate $\bar{n}$ and the stability constants for all possible complexes in solution, MU^+, MU_2, and n complexes of the form M_nU_n (which includes $MU^\pm$ or MUOH as M_1U_1) is:

$$\bar{n} = \frac{K_1[U^-] + 2\beta_2[U^-]^2 + \sum_0^n n\beta_{nn}[M^{++}]^{n-1}[U^-]^n[H^+]^{-n}\gamma_\pm{}^{-n}}{1 + K_1[U^-] + \beta_2[U^-]^2 + \sum_0^n n\beta_{nn}[M^{++}]^{n-1}[U^-]^n[H^+]^{-n}\gamma_\pm{}^{-n}} \qquad \text{(Eq. 40)}$$

which, when $n = 0$, 1, and 2, reduces to Eqs. 14, 25 or 26, and 38 or 39, respectively. Only in the case where $n = 0$ and the significant complexes in solution can be only MU^+ and MU_2 will $\bar{n}$ be independent of the free metal-ion concentration and can it be calculated from potentiometric titration data alone.

RESULTS

Potentiometric Titrations of Various Thiouracil–Metal-Ion Mixtures—The addition of an amount of cupric nitrate as low as 2×10^{-4} M to a 2×10^{-3} M aqueous solution of a 2-thiouracil (2-thiouracil, 6-*n*-propyl-2-thiouracil, 6-methyl-2-thiouracil, 5-methyl-2-thiouracil, and 5,6-dimethyl-2-thiouracil) caused an immediate drop in pH from about 5.5 to about 3.0 and the immediate formation of a precipitate, the amount of which increased with time. Attempts at potentiometric titration of such mixtures with smaller concentrations of thiouracils in the presence of minimal amounts of cupric nitrate were unsuccessful in maintaining a homogeneous solution. Since the complexes of cupric ion and the thiouracils had such low

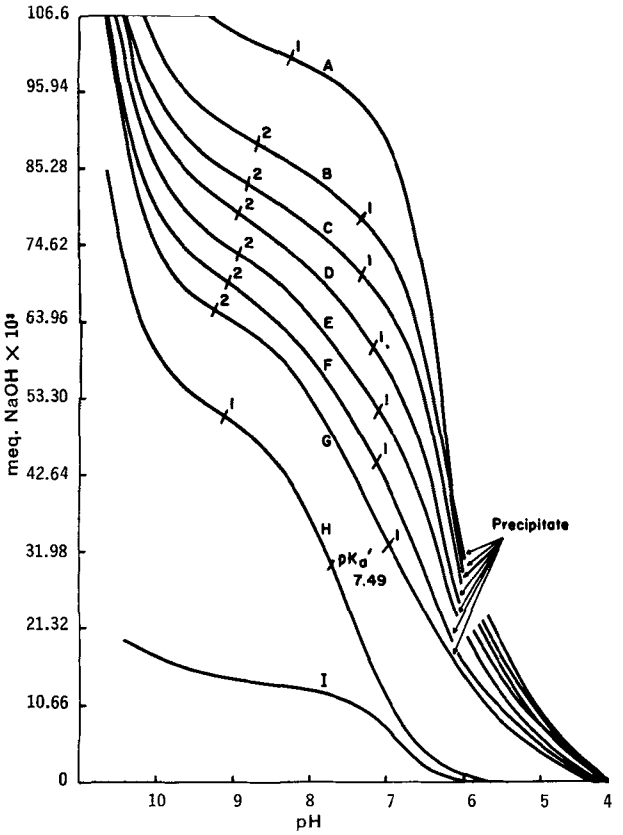


Figure 1—*Potentiometric titration curves of aqueous solutions of lead nitrate and 2-thiouracil with μ = 0.006 at 25.0°. Twenty-five-milliliter solutions were 2.00 × 10^{-3} M in 2-thiouracil and: (A), 2.00 × 10^{-3} M; (B), 1.60 × 10^{-3} M; (C), 1.40 × 10^{-3} M; (D), 1.20 × 10^{-3} M; (E), 1.00 × 10^{-3} M; (F), 8.00 × 10^{-4} M; (G), 6.00 × 10^{-4} M; and (H), 0 M in lead nitrate. Curve I is the titration of 25.0 ml. of 4.00 × 10^{-4} M lead nitrate. The titer of alkali between inflections 1 and 2 are: (B), 6.50 × 10^{-3}; (C), 1.14 × 10^{-2}; (D), 1.76 × 10^{-2}; (E), 2.10 × 10^{-2}; (F), 2.30 × 10^{-2}; and (G), 3.03 × 10^{-2} meq.*

solubilities, it was technologically infeasible to use the potentiometric titration method which demands instantaneous equilibration in homogeneous solution for the estimation of complexation constants of copper-ion–thiouracil complexes.

Fortunately this was not the general case. Homogeneous solutions were maintained for significant titer additions to mixtures of other metal-ion solutions and various 2-thiouracils.

Typical Potentiometric Titration Curves of Metal-Ion–Thiouracil Mixtures which Initially Form Homogeneous Solutions; Thiouracil–Lead-Ion Mixtures—A typical set of potentiometric titration curves is given in Fig. 1 for solutions of 25.00 ml. of 2.00 × 10^{-3} *M* 2-thiouracil (25.0°, μ = 0.006). Various amounts of lead nitrate have been added to each of these solutions so that the original concentration ranged from 2.00 × 10^{-3} *M* to 0.00 *M* $Pb(NO_3)_2$ for Curves A to H, Fig. 1. The plots are given in terms of the milliequivalent of NaOH necessary to achieve an observed pH value for each of these solutions. Homogeneous solutions were maintained for a portion of the titrations, and the points of precipitation are clearly indicated in Fig. 1. They occurred in excess of pH 6, except for the particular case (Curve H) of the thiouracil in the absence of lead ion where no precipitation was observed throughout the titration. The titration curve for 25.00 ml. of 4.00 × 10^{-4} lead nitrate is given in Curve I.

When the titrations of the precipitating solutions were continued past the points of precipitation, two apparent inflections, labeled as 1 and 2 in Fig. 1, were observed in all cases, except for the equimolar solution (Curve A) of Pb^{++} and 2-thiouracil when only one inflection was observed. The total milliequivalents of NaOH consumed by the equimolar solution (Curve A, Fig. 1) to the first observed inflection at pH 8.3 closely corresponded to twice the milliequivalents of NaOH necessary to neutralize the same concentration of 2-thiouracil alone (Curve H, Fig. 1). This strongly indicates that the *precipitated* lead–thiouracil complex is of 1:1 stoichiometry and that the precipitate is the net result of equal numbers of lead ions displacing two protons per molecule from equal numbers of thiouracil molecules. If the added milliequivalents of NaOH necessary to reach the pH of this inflection 1 (Curve A, Fig. 1) had been greatly in excess of twice the milliequivalents necessary to neutralize the ligand, it could be proposed that additional NaOH reacted with the precipitated complex and destroyed it or that the metal hydroxide $Pb(OH)_2$ was precipitated simultaneously. If all the metal had been reacted to form hydroxide, the milliequivalents of NaOH to this inflection 1 would have been three times the milliequivalents of NaOH necessary to neutralize the ligand alone. IR analysis of the precipitate, isolated at pH 7.5, gave a curve identical to the IR curve of bis(2-thiouracil-cadmium) (II), M_2U_2 (VII).

Further confirmation is obtained from the titrations (Curves B–G, Fig. 1) of solutions where the 2-thiouracil concentrations are in molar excess of $Pb(NO_3)_2$ concentrations. The titrations of the excess 2-thiouracil in these curves appear to occur after the completion of the precipitation of the Pb^{++}–thiouracil complex of apparent 1:1 stoichiometry at inflection 1. The milliequivalents of titer between this inflection 1 and inflection 2 may represent the neutralization of the excess 2-thiouracil. It is apparent that this titer between the inflections (Curves B–G, Fig. 1) is for a compound of pKa 7.5, a fact consistent with the pKa of 2-thiouracil (Curve H, Fig. 1).

The 10^2 meq. of NaOH consumed between inflections 1 and 2 for the various titrations of Fig. 1 were: B, 0.7 (1.0); C, 1.2 (1.5); D, 1.8 (2.0); E, 2.1 (2.5); F, 2.3 (3.0); and G, 3.0 (3.5). The parenthetical values are the molar excess of 10^2 meq. of 2-thiouracil over Pb^{++} ion; the close correspondence with the titration values is apparent. Exact

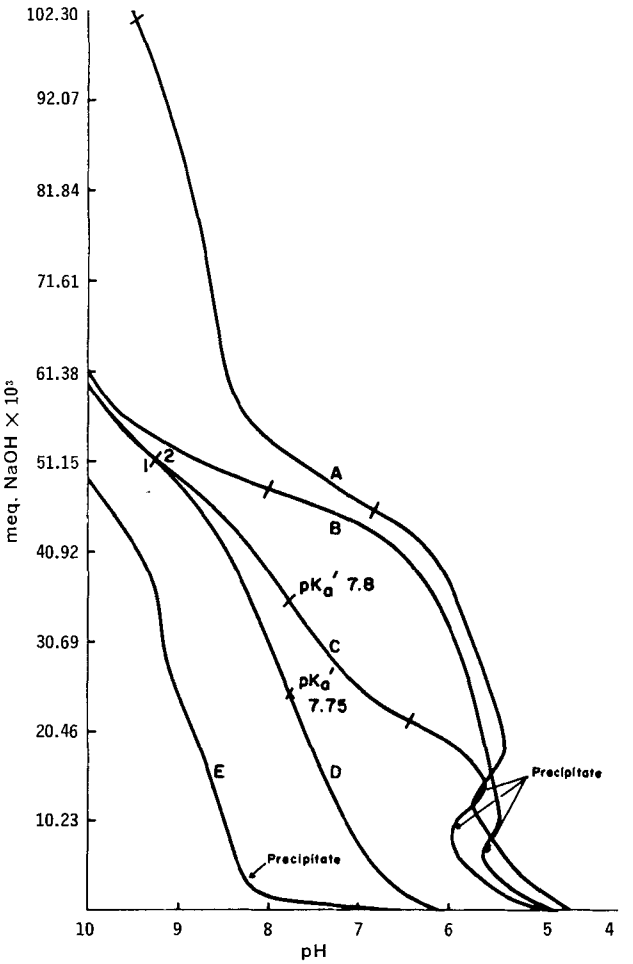


Figure 2—*Potentiometric titration curves of aqueous mixtures of cadmium nitrate and 6-n-propyl-2-thiouracil (PTU) with μ = 0.006 at 25.0°. Twenty-five-milliliter solutions were 2.00 × 10^{-3} M in PTU and: (A), 2.00 × 10^{-3} M; (B), 1.00 × 10^{-3} M; (C), 4.00 × 10^{-4} M; and (D), 0 M in Cd^{++}. Curve E is the titration of 25 ml. of 8.00 × 10^{-4} M cadmium nitrate.*

coincidence of these values is not to be expected since it is based on the titration of a heterogeneous and precipitating system which is not in instantaneous equilibria. If the values are taken as absolute, the precipitates may be a mixture of 1:1 stoichiometry and a compound of higher ratio of thiouracil to metal with the former predominating.

Similar titration curves with Pb^{++} ion were observed for the variously 5- and 6-alkyl-substituted 2-thiouracils listed in Table I. Only in the case of the ligand 5-carboethoxy-2-thiouracil was there immediate precipitation on the addition of lead ion.

Titration of Thiouracil–Cadmium-Ion Mixtures—Potentiometric titrations of mixtures of cadmium ion and the variously 5- and 6-alkyl-substituted 2-thiouracils listed in Table I, except 6-*n*-propyl-2-thiouracil, gave sets of curves very similar to those obtained on titration of thiouracil mixtures with lead ion (Fig. 1). Precipitation occurred during the titration at about pH 6.5, so the calculation of stability constants could be based on a region of homogeneous solution. The milliequivalents of NaOH consumed to inflection 1 for the equimolar mixtures of Cd^{++} and substituted 2-thiouracils (Curve A, Fig. 1) corresponded to twice the milliequivalents of NaOH consumed by the same concentration of ligand alone (Curve H, Fig. 1) to indicate strongly the precipitation of a complex of metal ion–thiouracil of 1:1 stoichiometry, which was not destroyed by the addition of further alkali to result in $Cd(OH)_2$. As stated previously, the formation or precipitation of $Cd(OH)_2$ would have consumed milliequivalents NaOH greatly in excess of twice the available milliequivalents of ligand. If the cadmium–thiouracil complex had been completely hydrolyzed, or if the cadmium had been completely precipitated as the hydroxide, three times the milliequivalents of ligand would have been consumed as NaOH.

The IR curve of the precipitate from such titrations was isolated at pH 10.5 and was identical to the IR curve of synthesized bis(2-thiouracil-cadmium) (II), M_2U_2 (VII).

Further confirmation was obtained from the titrations of solutions where the thiouracil concentrations were in molar excess of the $Cd(NO_3)_2$ concentrations. These titrations were similar to Curves B–G of Fig. 1 for the lead-ion studies in that the titration of excess thiouracil assigned to the milliequivalents NaOH between inflections 1 and 2 (about pH 7 and 9) were consistent with the thiouracil added to the original solutions in excess of 1:1 molar stoichiometry with the cadmium ion.

Anomalous Titration Curves of 6-*n*-Propyl-2-thiouracil–Cadmium-Ion Mixtures—The titration curves of cadmium-6-*n*-propyl-2-thiouracil solutions at 25 and 35° (Fig. 2) differed from the curves obtained from mixtures of cadmium ion and the other studied 5- and/or 6-substituted 2-thiouracils or obtained from thiouracil–lead-ion mixtures (Fig. 1). The titration curves for mixtures of cadmium ion and 0.002 *M* 6-*n*-propyl-2-thiouracil (Fig. 2) showed precipitation near pH 6 as before. However, the first inflection, near pH 8.0, for all concentrations of cadmium ion equal or greater than 0.001 *M* (Curves A and B, Fig. 2) occurred when milliequivalents of NaOH were consumed that were equal to the milliequivalents of NaOH consumed by the ligand alone. Only when the total cadmium concentration was less than 0.001 *M* (Curve C, Fig. 2), *i.e.*, when it was less than half of the ligand concentration, did the titration curve give any indication of any excess or uncomplexed ligand. Such excess 6-*n*-propyl-2-thiouracil is postulated to be titrated between the designated inflections of Curve C, Fig. 2, and characterized by the 7.8 pKa′ which is essentially the titration curve of 6-*n*-propyl-2-thiouracil alone (Curve D, Fig. 2) in the absence of cadmium ion. Such a behavior on titration, where the synonymous inflections of Curves A and B (Fig. 2) at the same milliequivalents of NaOH are considered to represent the complete precipitation of all available complex, must demand that the metal to thiouracil precipitate have a 1:2 stoichiometry. The fact that when the added Cd^{++} was in excess of this 1:2 stoichiometry (Curve A, Fig. 2) indicated hydroxide-ion consumption by the excess cadmium ion is confirmatory. This is readily seen from the similarities of the titration curves above pH values of 8 for Curve A and Curve E, where Curve E is for the alkaline potentiometric titration of cadmium ion alone.

The above analysis was performed on titration curves obtained at 25 and 35°. However, at 45° the potentiometric titrations of cadmium–6-*n*-propyl-2-thiouracil solutions gave curves which were similar to Fig. 1. This indicates that at elevated temperatures the precipitation of cadmium complexes of 6-*n*-propyl-2-thiouracil of 1:1 stoichiometry is preferred over the precipitation of cadmium–6-*n*-propyl-2-thiouracil complexes of 1:2 stoichiometry that occurs at lower temperatures.

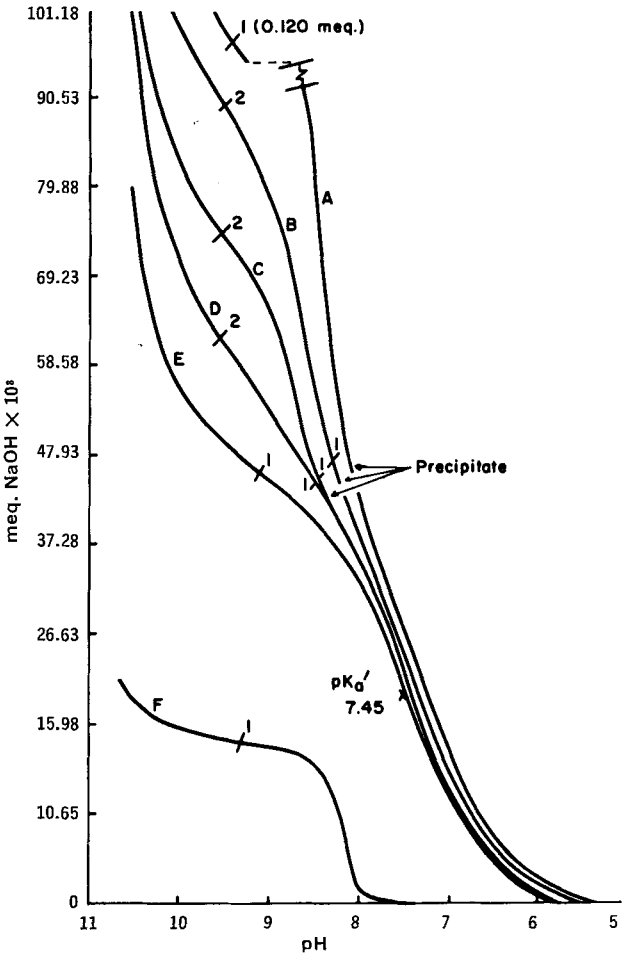


Figure 3—*Potentiometric titration curves of aqueous mixtures of nickel nitrate and 2-thiouracil (2TU) with μ = 0.006 at 25.0°. Twenty-five-milliliter solutions were 2.00 × 10⁻³ M in 2TU and: (A), 2.00 × 10⁻³ M; (B), 1.20 × 10⁻³ M; (C), 8.00 × 10⁻⁴ M; (D), 4.00 × 10⁻⁴ M; and (E), 0 M in nickel nitrate. Curve F is the titration of 25 ml. of 4.00 × 10⁻⁴ M nickel nitrate.*

Titration of Nickel–Thiouracil and Zinc–Thiouracil Mixtures—Titrations of 2-thiouracil, 6-*n*-propyl-2-thiouracil, 6-methyl-2-thiouracil, 5-methyl-2-thiouracil, and 5,6-dimethyl-2-thiouracil in the presence of nickel gave curves that showed an initial pH drop from 6.0 to 5.5 and precipitation during the titration near pH 8 (Fig. 3 Curves A–D).

Titration of 6-*n*-propyl-2-thiouracil in the presence of zinc gave an initial pH drop from 6.5 to 6.0 and precipitation occurred near pH 7.3. The titration curves for the zinc complexes were very similar to those found for nickel (Fig. 3).

The potentiometric titrations of equimolar solutions of Zn^{++} or Ni^{++} and thiouracil (Curve A, Fig. 3) when continued past the points of precipitation did not give evidence of clear-cut stoichiometry of the precipitating complexes as had been so evident in the lead and cadmium cases. The total milliequivalents of NaOH consumed to the observed inflection in such a titration was greatly in excess of twice the milliequivalents of NaOH which would have been necessary to neutralize the thiouracil ligand alone (Curve E, Fig. 3). This is definite indication that metal hydroxide precipitation, $M(OH)_2$, must also occur concomitant with the possible precipitation of a metal–thiouracil complex. The fact that the milliequivalents of NaOH consumed between inflections 1 and 2, in Curves B–D, Fig. 3, presumably assignable to the excess thiouracil if the metal–thiouracil complex was at least 1:1, had no relation to milliequivalents of such excess thiouracil, was further evidence that the added hydroxide ion was consumed by the metal and that any metal–thiouracil complexes were probably disrupted by the addition of this excess hydroxide ion.

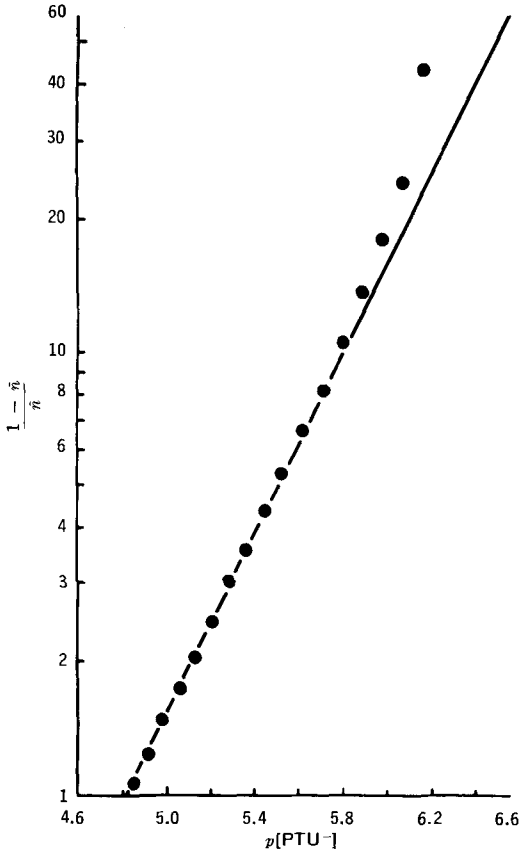


Figure 4—*Plot of log* $(1-\bar{n})/\bar{n}$ *against the negative logarithm of 6-n-propyl-2-thiouracil-anion concentration* (p[*PTU*$^-$]) *obtained from a lead nitrate* (*2.00* $\times$ 10^{-3} M)–*PTU* (*2.00* $\times$ 10^{-3} M) *mixture in water with* μ = *0.006 at 25.8°. Slope of plot is 1.00 and log* K_1 *is 4.82 from the* pK_1 *intercept.*

Titration of 2-Thiouracil and 6-*n*-Propyl-2-thiouracil in the Presence of Other Metal Ions—Potentiometric titrations of 2-thiouracil and 6-*n*-propyl-2-thiouracil in the presence of ferric, ferrous, manganese, calcium, and cobaltous ions gave no indication of any complex formation. The titration curves of the mixtures could be assigned to uncomplexed ligand in the case of calcium and manganese and to hydrolysis of the metal ion in the case of ferric, ferrous, and cobaltous ions.

Titrations of Sterically Blocked Thiouracil in the Presence of Cu (II), Cd (II), and Pb (II)—Solutions of 2-ethylmercapto-4-hydroxypyrimidine (2EM4HP) and *N,N'*-diethyl-6-methyl-2-thiouracil in the presence of cadmium, lead, and cupric ions were titrated with standard alkali. The titration curve of 2EM4HP in the presence of cadmium ion was the same as the titration of the ligand alone. The titration curves of 2EM4HP in the presence of cupric and lead ion could be assigned to a simple summation of the metal hydrolysis and ligand titration curves and indicated no apparent complexation. The titration of solutions of *N,N'*-diethyl-6-methyl-2-thiouracil alone showed no titratable group, and the titrations of metal ion mixtures gave curves showing only metal hydrolysis. In the case of 2EM4HP, the pKa′ of the 4-hydroxy group was 7.01 at 25°. The fact that no complexation occurred at the 4-hydroxy position, even when it could form an anion more easily than 2-thiouracil itself (pKa′ 7.49), argues for complexation at the sulfur position in the sterically unblocked compounds.

Calculation of Complexation Constants from Potentiometric Titrations—Those portions of the potentiometric titration curves where homogeneous solutions are maintained prior to the points of precipitation (Figs. 1–3) permit the estimation of complexation constants. The highest pH values at which usable data could be obtained in these studies were about 6.5 since the precipitation which occurred destroyed the equilibrium conditions.

Such feasible titration data were analyzed on the basis of the derived equations. First, the assumption was made that the only significant concentration of complex in solution derived from the doubly charged metal cation M^{++}, and the thiouracil was the 1:1 complex, MU^+, with the anion of the latter. If this were true, derived Eq. 15:

$$\log \frac{1-\bar{n}}{\bar{n}} = pK_1 + p\,[U^-] \qquad \text{(Eq. 15)}$$

would be applicable and the plot of log $(1-n)/n$ against $p\,[U^-] = -\log[U^-]$ should have a slope of one and an intercept of pK_1, a measure of the complexation constant of MU^+. The values of $\bar{n}$ were calculated from:

$$\bar{n} = \frac{[HU]_0 - [U^-]\left(1 + \frac{[H^+]\,\gamma_\pm}{K_a'}\right)}{[M^{++}]_0} \qquad \text{(Eq. 11)}$$

where $[HU]_0$ and $[M^{+2}]_0$ are the molar concentrations of the added thiouracil and metal ion, respectively, where K_a' is the dissociation constant of the thiouracil acid, where $[H^+]\,\gamma_\pm$ is the activity of the hydrogen ion, a_{H^+}, and is calculated from $a_{H^+} = 10^{-pH}$ where the pH is experimentally observed, and where the concentration of thiouracil anion $[U^-]$ is calculated at the same pH value from:

$$[U^-] = \frac{[HU]_0 - [NaOH]}{[H^+]\gamma_\pm/K_a'} \qquad \text{(Eq. 13)}$$

where [NaOH] is calculated on the premise that it would have been the concentration of the added milliequivalent of NaOH at the point in the titration if no NaOH had been reacted or consumed. Typical plots in accordance with Eq. 15 are given in Figs. 4 and 5 and the tabulated slopes of such plots are listed for all available titration studies in Table I. In those cases where the solutions were prepared so that the metal-ion and the thiouracil concentration were equimolar, the slopes of such plots were unity and it was reasonable that the intercept represented the pK_1 of the MU^+ complex (Table I). However, when the total metal-ion concentration $[M^{++}]_0$ was made up to be less than the total thiouracil concentration $[HU]_0$, the estimated slopes of such plots were in excess of unity (Table I). At very high ligand–metal ratios, these slopes approached two in some cases. This would be expected if appreciable amounts of MU_2 were formed which would be favored under conditions of high lig-

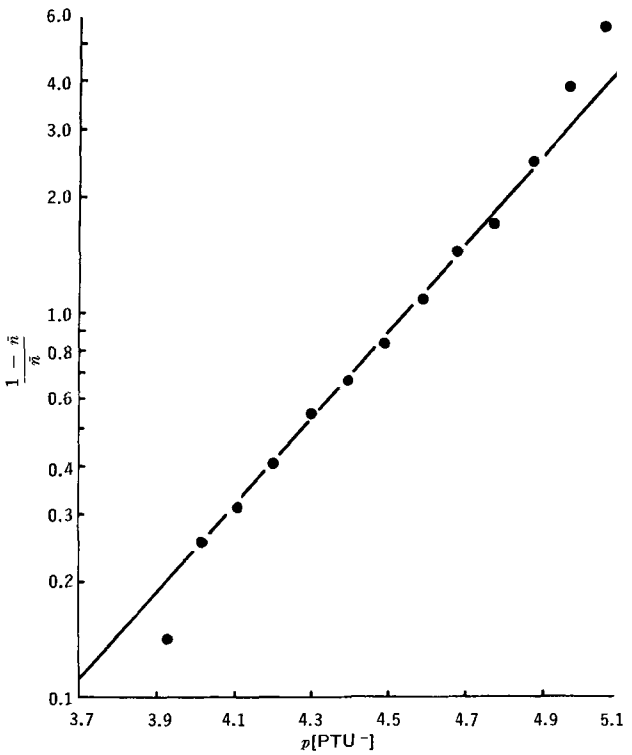


Figure 5—*Plot of log* $(1-\bar{n})/\bar{n}$ *against the negative logarithm of 6-n-propyl-2-thiouracil anion concentration* (p[*PTU*$^-$]) *obtained from a lead nitrate* (*2.00* $\times$ 10^{-4} M)–*PTU* (*2.00* $\times$ 10^{-3} M) *mixture in water with* μ = *0.006 at 25.8°. Slope of plot is 1.13.*

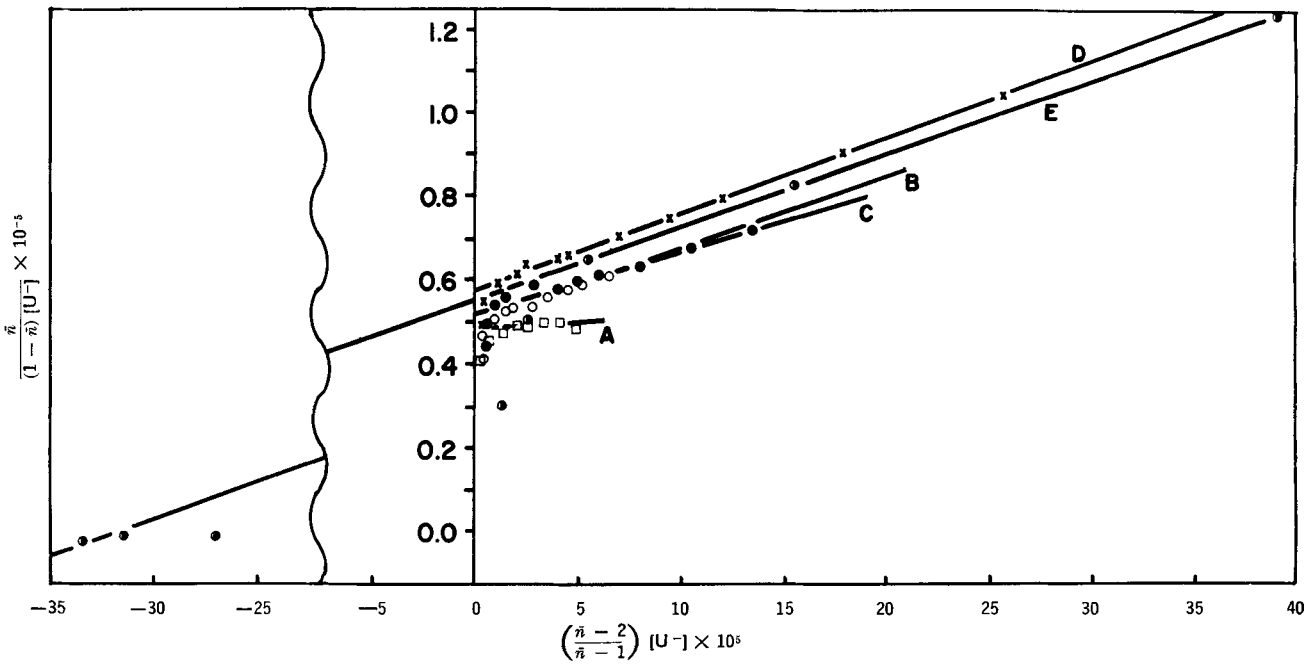


Figure 6—*Plots of* $\bar{n}/(1-\bar{n})[2TU^-]$ *against* $[(\bar{n}-2)/(\bar{n}-1)]$ $[2TU^-]$ *from aqueous mixtures of 2-thiouracil* ($[2TU] = 2.00 \times 10^{-3}$ M) *and lead nitrate with* $\mu = 0.006$ *at 25.0°. Key: (A), 2.00* $\times 10^{-3}$ M Pb^{++}; *(B), 1.80* $\times 10^{-3}$ M Pb^{++}; *(C), 1.40* $\times 10^{-3}$ M Pb^{++}; *(D), 8.00* $\times 10^{-4}$ M Pb^{++}; *and (E), 2.00* $\times 10^{-4}$ M Pb^{++}. *Intercept on ordinate is* K_1 *and slope is* K_1K_2.

and concentrations and as the titrations proceeded. At these higher slopes the premises for the use of such plots derived from Eq. 15 become invalid, and equations based on the postulates of additional complexes in solution must be used.

Thus, the assumption was made that there were two significant complexes in solution, the 1:1 complex MU^+ and the 1:2 complex MU_2. If this were true, the derived:

$$\frac{\bar{n}}{(1-\bar{n})[U^-]} = \left(\frac{\bar{n}-2}{\bar{n}-1}\right)\beta_2[U] + K_1 \qquad \text{(Eq. 14)}$$

would be applicable and the plot of $\bar{n}/\{(1-\bar{n})[U^-]\}$ against $(\bar{n}-2/\bar{n}-1)[U^-]$ would be linear for all thiouracil–metal-ion mixtures and the statistically significant estimated slopes β_2 and intercepts K_1 would be the same for all such mixtures. The $\bar{n}$ and $[U^-]$ data are calculated from the experimental values and Eqs. 11 and 13, as has been explained previously, and typical plots are given in Fig. 6.

The derived values of log K_1 and log K_2 (where $K_2 = \beta_2/K_1$) are related to the complexation constants of MU^+ and MU_2 (from MU^+), respectively, and are listed in Table I. The facts that the calculated values of log K_1 and log K_2 did not vary with the total metal-ion concentration (Table I) were consistent with the premise that only MU^+ and MU_2 complexes are in significant concentrations in the homogeneous solutions of mixtures of metal ions and thiouracils maintained prior to the observance of precipitation on the further addition of alkali. It has been shown in the *Theory and Methods of Calculation* section that the presence of significant amounts of other complexes in solution, such as $MU^{\pm}$ (VI) or its equivalent MUOH (V), M_2U_2 (VII) or M_nU_n (VIII) would make $[U^-]$ a function of the metal-ion concentration as denoted in Eqs. 24, 36, or 37. If this were true, plots (Fig. 5) made on the assumption of only significant concentrations of MU^+ (III) and MU_2 (IV) in the homogeneous solutions in accordance with Eq. 14 and on the premise of $[U^-]$ being independent of M^{++} concentration (Eq. 13) would not be expected to be linear. This can be readily seen from the forms of Eqs. 26 and 39 where it is apparent that log K_1 and log K_2 values estimated from plots in accordance with Eq. 14 would vary widely as a function of the metal-ion concentration, $[M^{++}]_0$. Since such plots were linear (Fig. 6) and there was no significant variation of the derived log K_1 and log K_2 values with M^{++} concentration (Table I), it is reasonable to accept the premise that only the MU^+ (III) and MU_2 (IV) complexes are in significant concentrations in the titrated homogeneous solutions prior to the observed precipitation on further addition of alkali.

DISCUSSION

Stability Constants of the Significantly Soluble MU^+ and MU_2 Complexes—Analyses of the homogeneous portions of the alkaline titration curves of solutions of mixtures of lead, cadmium, nickel, or zinc nitrate and various thiouracils [2-thiouracil (TU), 6-*n*-propyl-2-thiouracil (PTU), 6-methyl-2-thiouracil (6MTU), 5-methyl-2-thiouracil (5MTU), 5,6-dimethyl-2-thiouracil (5,6DMTU), and 5-carboethoxy-2-thiouracil (5CETU)] to the pH values of precipitation were consistent with the facts that the species present in significant concentrations in the homogeneous solutions of the titration must be the MU^+ (III) and MU_2 (IV) complexes of Scheme I. Plots (Fig. 5) in accordance with Eq. 14 where $[U^-]$ was calculated from Eq. 13 demonstrated linearity for all the metal ions and thiouracils studied that showed significant complexation. The values of log K_1 and log K_2 that were calculated from such plots (Eq. 14 and Fig. 5) did not show significant variation with various metal-ion concentrations $[M^{++}]_0$ (Table I). These facts are indicative that complexes such as MUOH (V), $MU^{\pm}$ (VI), M_2U_2 (VII), or M_nU_n (VIII) of Scheme I were not of significant concentrations in the alkaline titrated homogeneous solutions prior to precipitation.

The stability constant K_1 (Table I) is the largest for the formation of the MU^+ complex from Pb^{++} and Cd^{++} with 5,6DMTU and smallest from Cd^{++} with 5CETU. The log K_1 values were available for CdU^+ complexes with the substituted thiouracils that had the highest range in pKa′ values (Table II). A plot of such log K_1 values against these pKa′ values at 25.0° showed definite linearity and conformed to the expression:

$$\log K_1 = 0.50\,\text{pKa}' + 0.32 \qquad \text{(Eq. 41)}$$

Single alkyl substitution at the 5 or 6 position of 2-thiouracil slightly increased the pKa′ values to about 7.7 from 7.5 and similarly increased the log K_1 value of the CdU^+ complex. Simultaneous alkyl substitution at the 5 or 6 position significantly elevated the pKa′ to 8.1 and the log K_1.

Substitution of the electronegative carboethoxy group at the 5 position significantly reduced both the pKa′ to 6.43 and log K_1 value. This is readily understandable in that the electronegative 5-carboethoxy group (R_2 in Id, Scheme I) would be expected to reduce the electron availability of the *para* sulfur atom. Thus the sulfur's electronic charge would be reduced to result in lessened ability to bind both hydrogen ions and metal cations with the concomitant

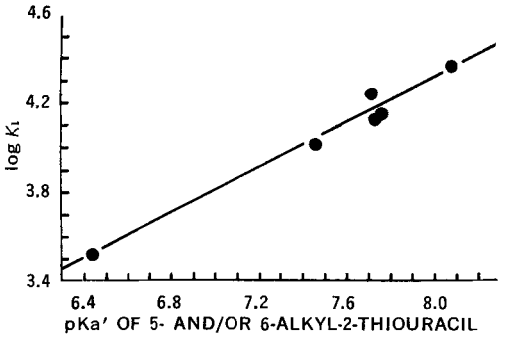


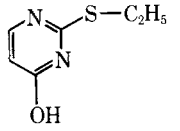
Figure 7—*Apparent linear relation between the logarithm of the stability constant* K_1 *for the formation of the* CdU^+ *complex in solution,* $Cd^{++} + U^- \overset{K_1}{\rightleftarrows} CdU^+$ *(where* U^- *is the 5- and/or 6-alkyl 2-thiouracil anion) and the pKa′ for the dissociation of the respective thiouracil acid,* $HU \overset{Ka'}{\rightleftarrows} H^+ + U^-$.

results of lowered pKa′ (or higher acidity) and diminished affinity, K_1, of thiouracils for metal ions.

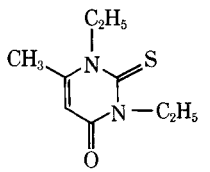
No obvious relations were observed as to the significant effects of 5 and/or 6 substituents of 2-thiouracil and their related pKa′ values on the formation constants, K_2, of the MU_2 complexes (Table I). No significant temperature effects could be concluded within the narrow temperature range studied.

The potentiometric titration studies demonstrated that the order of decreasing stability of complexes of divalent metal cations with thiouracils (Table I) to form MU^+ is $Pb^{++} > Cd^{++} \gg Ni^{++} \sim Zn^{++}$. Metal ions which do not complex thiouracils are Fe^{+++}, Fe^{++}, Co^{++}, Ca^{++}, and Mn^{++}.

Evidence for the Necessity of a Potential Anionic Sulfur in Thiouracils for Divalent Metal-Ion Complexation—The increase in pKa′ of the ionizable sulfhydryl group of the thiouracil is related to the stability of the metal complex (Fig. 7 and Table I) and implicates the need for an anionic sulfur in thiouracil for metal complex formation. In addition, when the dissociable proton is removed by alkylation as in 2-ethylmercapto-4-hydroxypyrimidine (IX), no complexation with metal ions was observed. Since the acidic hydroxyl group, pKa′ 7.01, still exists at the 4 position in IX, it can be stated that metal ions do not readily bind to the oxygen at the 4 position in the *parent* thiouracils. Alkylation of the N-1 and N-3 nitrogens of thiouracil, as in *N,N′*-diethyl-6-methyl-2-thiouracil (X) also destroyed the ability to complex metal ions. These substitutions on both the ring nitrogens prohibit the tautomeric formation of the dissociable sulfhydryl group of the complexing thiouracils, HU (I) in Scheme I. This is further evidence that metal-ion complexation occurs at the sulfur atom and is dependent on the formation of the sulfur anion.



IX



X

Possible Structures of Precipitates from Alkaline Titrated Solutions of Metal–Thiouracil Complexes—Although only concentrations of MU^+ and MU_2 complexes appear to be significantly present in the homogeneous solutions of mixtures of metal ions and thiouracils on alkaline potentiometric titration, this does not exclude the probability that the MUOH (V), $MU^{\pm}$ (VI), M_2U_2 (VII), and M_nU_n (VIII) complexes given in Scheme I may also be present.

It is apparent that if the concentration of any one of these complexes is limited by its solubility, precipitation will occur as the titrations proceed. It is also apparent from Scheme I that concentrations of all complexes must increase with the addition of hydroxyl ions. It may be presumed *a priori* that the charged complexes MU^+ and $MU^{\pm}$ would not readily or preferentially precipitate as such, or as salts with appropriate counterions.

Alkaline titrations of precipitating equimolar thiouracil–metal-ion solutions of Pb^{++} and Cd^{++} with all thiouracils (Fig. 1, Curve A), except for the Cd^{++}–PTU mixture (Fig. 2, Curve A), consumed titer up to the inflection pH of complete precipitation that was twice the alkaline titer expected for the titration of the thiouracil alone. Solutions (except for Cd^{++} and PTU mixtures) that contained less than equimolar amounts of metal to ligand showed that uncomplexed free ligand consumed equivalent moles of alkali but that the formed precipitate consumed twice the milliequivalents of alkali expected for the titration of that amount of thiouracil that was equimolar with the added Pb^{++} or Cd^{++} ions (Fig. 1, Curves B–G). These facts indicated that the complex precipitated must have a stoichiometry of 1:1, metal to ligand, or some multiple of 1:1. This behavior required that the species MU_2 present in homogeneous solutions for all Pb^{++} or Cd^{++} with all thiouracils (Table I), except for Cd^{++} and PTU mixtures, was not the precipitating species.

These phenomena may be summarized in the following expressions given in reference to Scheme I. The expected stoichiometry for neutralization of thiouracil is:

$$\underset{\text{I}}{HU} + OH^- \rightarrow \underset{\text{II}}{U^-} + HOH \qquad \text{(Eq. 42)}$$

If no more than the milliequivalent of NaOH necessary to neutralize the total amount of available thiouracil is necessary to complete the precipitation of adducts of divalent metal ion and thiouracil (Fig. 2), then:

$$M^{++} + \underset{\text{I}}{HU} + OH^- \rightleftarrows M^{++} + \underset{\text{II}}{U^-} + HOH \rightleftarrows \underset{\text{III}}{MU^+} + HOH \qquad \text{(Eq. 43)}$$

and

$$\underset{\text{III}}{MU^+} + \underset{\text{I}}{HU} + OH^- \rightleftarrows \underset{\text{III}}{MU^+} + \underset{\text{II}}{U^-} + HOH \rightarrow \underset{\text{IV}}{MU_2}\downarrow + HOH \qquad \text{(Eq. 44)}$$

and, as in the special case of 6-*n*-propyl-2-thiouracil and cadmium ion, the precipitated complex may have the stoichiometry, metal to ligand, of 1:2. Further confirmation was obtainable from the facts that when cadmium ion was equal to, or in excess of, one-half the available moles of PTU (Fig. 2, Curves A and B), the precipitation of complex (as monitored by the alkaline titration to the appropriate pH inflection where the precipitation of $Cd(OH)_2$ could not possibly interfere) was completed when the milliequivalents of added NaOH were just equivalent to the available PTU in accordance with Eqs. 43 and 44. Furthermore, $Cd(OH)_2$ precipitation, indicative of uncomplexed cadmium ion, was observed only when the cadmium-ion concentration was in excess of half the molar concentration of PTU (Fig. 2, Curve A). Free uncomplexed PTU was only observed (Fig. 2, Curve C) when the cadmium-ion concentration was less than half the molar concentration of PTU.

If twice the milliequivalents of NaOH necessary to neutralize the thiouracil completes the precipitation of equimolar amounts of divalent metal ion and thiouracil (Fig. 1), then in reference to Scheme I,

$$\underset{\text{I}}{HU} + M^{++} + 2OH^- \rightleftarrows \underset{\text{II}}{MU^+} + OH^- + H_2O \rightarrow \underset{\text{V}}{MUOH}\downarrow + H_2O \qquad \text{(Eq. 45)}$$

or

$$\underset{\text{I}}{HU} + M^{++} + 2OH^- \rightleftarrows \underset{\text{VI}}{MU^{\pm}} + 2H_2O \qquad \text{(Eq. 46)}$$

where

$$\underset{\text{VI}}{2MU^{\pm}} \rightarrow \underset{\text{VII}}{M_2U_2}\downarrow \qquad \text{(Eq. 47)}$$

or

$$\underset{\text{VI}}{nMU^{\pm}} \rightarrow \underset{\text{VIII}}{M_nU_n}\downarrow \qquad \text{(Eq. 48)}$$

There was no tendency for such precipitated complexes of lead and cadmium ion with the various thiouracils to be disrupted at relatively high concentrations of hydroxyl ions, at least to a pH of 9.0. This is indicative of the fact that the complexes of lead and cadmium of Scheme I have relatively high stabilities.

Consumption of more than twice the milliequivalents of NaOH necessary to neutralize the available thiouracil to the inflection corresponding to complete precipitation (Fig. 3) would be indicative of ready disruption and lessened stability of complexes such as those of Scheme I. It would imply that the metal hydroxides would be more readily formed on the further addition of hydroxide ion.

Consider the example when 3 times the milliequivalents of NaOH necessary to neutralize the total amount of available thiouracil complete the precipitation of an equimolar solution of a divalent metal ion and a thiouracil (Fig. 3, Curve A). Then,

$$\underset{\text{I}}{HU} + M^{++} + 3OH^- \rightarrow M(OH)_2 \downarrow + \underset{\text{II}}{U^-} + H_2O \quad \text{(Eq. 49)}$$

Alternatively the possible precipitated complexes of MU_2, MUOH, M_2U_2, or M_nU_n in equilibrium with their relatively unstable counterparts in solution can be disrupted by additional alkali as

$$\underset{\text{IV}}{MU_2} + 2(OH^-) \rightleftarrows \underset{\text{III}}{MU^+} + \underset{\text{II}}{U^-} + 2(OH^-) \rightarrow M(OH)_2 \downarrow + \underset{\text{II}}{2U^-} \quad \text{(Eq. 50)}$$

and

$$\begin{array}{ccc} & \underset{\text{V}}{MUOH} + OH^- \rightarrow M(OH)_2 \downarrow + \underset{\text{II}}{U^-} \\ & \uparrow\downarrow & \\ \frac{1}{n}\underset{\text{VII or VIII}}{M_nU_n} + HOH + OH^- & \uparrow\downarrow & \uparrow \\ & \uparrow\downarrow & \\ & \underset{\text{VI}}{MU^{\pm}} + OH^- + HOH \rightarrow \underset{\text{III}}{MU^+} + 2OH^- & \end{array} \quad \text{(Eq. 51)}$$

In the cases of the complete titrations after precipitation of the equimolar mixtures of Ni^{++} or Zn^{++} with thiouracils the alkaline titers to the completion of precipitation were greatly in excess of twice the titer necessary to neutralize the available thiouracil, HU, alone (Fig. 3, Curve A). This definitely indicates that the potential complexes of Scheme I for Ni^{++} and Zn^{++} with thiouracils were readily disrupted in solution by hydroxide ion in accordance with Eqs. 49–51. This is not unexpected since the stability constant of the MU^+ complexes for nickel and zinc are about a hundred times smaller than those for lead and cadmium (Table I).

Confirmation of Structures of Precipitates and Complexes of Cadmium and Lead Complexes of Thiouracils—The equilibria of Scheme I are consistent with the potentiometric titration studies. The precipitation of a relatively stable MU_2 (IV) complex from Cd^{++} and 6-*n*-propyl-2-thiouracil and of relatively stable either MUOH, M_2U_2, or M_nU_n complexes from Cd^{++} and Pb^{++} with the other thiouracils (Table I) is highly probable and consistent with the data.

These high probabilities were put to the test by the deliberate synthesis, isolation, and characterization of MU_2 (IV) and M_2U_2 (VII) or M_nU_n (VIII) complexes. The MU_2 complexes were prepared by the use of forcing conditions where a solution of the metal ion was added to the thiouracil solution in molar excess. The complexes of 1:1 stoichiometry were prepared from equimolar concentrations of thiouracil and metal ion where the thiouracil solution was added to that of the metal ion. The precipitation was effected by adjustment of the pH of the solutions to 6.5 (see *Experimental*).

The synthesized MU_2 (IV) complexes of bis(2-thiouracil)-cadmium (II), $Cd(TU)_2$; bis(2-thiouracil)-lead (II), $Pb(TU)_2$; and bis-(6-*n*-propyl-2-thiouracil)-cadmium (II), $Cd(PTU)_2$, and the synthesized M_2U_2 (VII) (or M_nU_n, VIII) complexes of bis(2-thiouracil-cadmium) (II), $Cd_2(TU)_2$; bis(2-thiouracil-lead) (II), $Pb_2(TU)_2$; and bis(6-*n*-propyl-2-thiouracil-lead) (II), $Pb_2(PTU)_2$, had the proper metal analyses and the proper complete elemental analysis [as in the Cd $(PTU)_2$ case] to confirm fully these assigned structures.

Further confirmation of the validity of the assignment of the MU_2 structure, IV, of Scheme I was obtained from the IR spectra. The synthesized $Cd(TU)_2$, $Pb(TU)_2$, and $Cd(PTU)_2$ had a strong absorption band at 1630 $cm.^{-1}$ assignable to the absorption of the tautomerizable carbonyl group at the 4 position of thiouracils (28). Strong absorption bands between 1440 and 1660 $cm.^{-1}$ indicated the presence of C=N bonds (29) that were not bound to metal ion. In contrast, the IR spectrum of the synthesized 6-methyl-*N,N'*-diethyl-2-thiouracil (X), a compound incapable of tautomeric formation o C=N bonds, did not demonstrate such C=N absorption bands.

Further confirmation of the validity of the assignment of an M_2U_2 (or M_nU_n) structure, VII (or VIII) of Scheme I, was obtained also from the IR spectra. The synthesized $Cd_2(TU)_2$, $Pb_2(TU)_2$, and $Pb_2(PTU)_2$ (or their M_nU_n equivalents) showed no significant band above 1570 $cm.^{-1}$ that could be assigned to a potential carbonyl group at the 4 position of the thiouracil ring (28) but did show bands assignable to the C=N group (29). The validity of secondary metal binding to the 4-oxygen is well indicated.

Further evidence for such an assignment as in VII or VIII of Scheme I is that the pKa′ of 2-ethylmercapto-4-hydroxypyrimidine (IX) is 7.01 compared to 7.46 for 2-thiouracil. Since alkyl substitution at the sulfur atom increased the acidity of the potential hydroxyl group at the 4 position, it is expected that substitution by a cation on the sulfur with retention of positive charge, as with MU^+ (III), would further increase the acidity. This facilitated dissociation of the 4-hydroxy group of the MU^+ (III) complex to $MU^{\pm}$ (VI) should be highly favored at lowered pH values and promote ready reaction with other MU^+ or $MU^{\pm}$ molecules to form the M_2U_2 (VII) or M_nU_n (VIII) polynuclear complexes of Scheme I early in the alkaline potentiometric titrations. Such neutral cyclic or polynuclear complexes with lessened hydrophilic groups must, in general, have lower solubilities and precipitate more readily than the MU_2 (IV) complexes which have been shown to exist readily at lower pH values (Fig. 5 and Table I).

The one observed exception was the cadmium and 6-*n*-propyl-2-thiouracil mixture where the neutral 1:2 complex $Cd(PTU)_2$ preferentially precipitated at the lower temperatures of 25 and 35°. Equations 43, 44, and 46–48 are valid explanations of the multiple equilibria and precipitation that may occur with some mixtures of metal ion and a thiouracil. It can be argued that the larger alkyl group significantly decreased the solubility of the MU_2 complex, significantly increased the pKa_2' of the 4-OH group of the $MU^{\pm}$ complex, or significantly increased the stability constant, K_2, of the MU_2 complex for PTU. Of these, the first and third arguments are most probable. The latter is confirmed by the data of Fig. 1, where K_2 for MU_2 formation exceeded K_1 for MU^+ formation by more than two-fold for the cadmium complex of PTU; whereas for the cadmium complexes of CETU and 5,6MTU, they were approximately equal and for lead and cadmium complexes of the other thiouracils studied, K_1 was 5–20-fold greater than K_2.

The precipitates produced by the potentiometric titrations of solutions containing 2-thiouracil in the presence of lead and cadmium ions were isolated, at pH 7.5 and 10.5, respectively, washed, and the IR spectra recorded. The IR spectra of these precipitates were identical with the spectra of the synthesized M_2U_2 complexes $Pb_2(TU)_2$ and $Cd_2(TU)_2$, respectively. Thus, it can be concluded that complexes of the form MUOH (V) are neither of significant concentration in homogeneous solutions of Cd^{++} or Pb^{++} ions with thiouracil, nor are they readily precipitated from such solutions on the addition of alkali. Equations 44, 47, and 48 from Scheme I are valid explanations of the multiple equilibria and precipitation that occur with most mixtures of Pb^{++} or Cd^{++} and thiouracils.

The elemental and IR analyses of the synthesized $Pb_2(TU)_2$, $Cd_2(TU)_2$ and $Pb_2(PTU)_2$ complexes do not permit rigorous discrimination between the preferred assignments as the cyclic dimers M_2U_2 (VII) or as the polynuclear polymers M_nU_n (VIII). When the synthesized $Cd_2(TU)_2$ was recrystallized from an ammoniacal solution and dried, its IR spectrum was almost exactly the same as the original $Cd_2(TU)_2$. However the physical form was noncrystalline in nature and appeared as "paper pulp." It is possible that the ammonia complexed with the cadmium and opened the ring of $Cd_2(TU)_2$, VII, and, on removal of the ammonia, the polymeric structure $Cd_n(TU)_n$ (VIII) was formed.

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In Vitro Release of Chloramphenicol from Polymer Beads of α-Methacrylic Acid and Methylmethacrylate

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Abstract □ The *in vitro* release behavior of chloramphenicol from four different bead polymers containing methylmethacrylate and α-methacrylic acid in various buffer solutions has been studied. The concentration of α-methacrylic acid in the copolymer beads and the pH and ionic strength of the buffer solutions were observed to influence the release rate of the chloramphenicol from these beads. The beads containing no α-methacrylic acid did not release the drug in any buffer solution, and the beads containing only α-methacrylic acid released the drug at almost the same rate in all buffer solutions. The smaller beads released the drug more quickly than the larger ones.

Keyphrases □ Polymer beads—chloramphenicol release □ Chloramphenicol release—α-methacrylic acid, methylmethacrylate beads □ α-Methacrylic acid, concentration effect—release rates, polymer beads □ pH, ionic strength effects—chloramphenicol release, polymer beads

In an earlier publication (1), the possibility of utilizing the bead polymerization method for the preparation of a sustained-release dosage form was discussed. Physical barriers are used in the majority of the prolonged-release dosage forms to decrease the rate of drug release to the absorption site. The swelling or dissolution property of the polymer materials in which the drug is embedded is the major contributing factor in the release of drug from such dosage forms. Nelson (2) reported that the dissolution or release rate of a drug from a dosage form is the rate-determining factor in the absorption and physiological availability of the drug. Hence, an *in vitro* release procedure may be used to screen the materials worthy of inclusion as a potential physical barrier for sustained-release products. Furthermore, it may show the direction in which the right copolymers or polymers for the purpose may be found. The final required sustained-release dosage form containing these beads may consist of a single specimen of the polymer beads or a mixture of many different polymer and copolymer beads.

As the drug is incorporated in a large number of small individual beads, the chances of consistent availability of the drug at the intended site of the gastrointestinal tract increase considerably. In the present work, the