Degradation of Chlorthalidone in Methanol: Kinetics and Stabilization

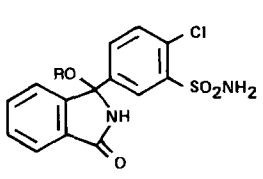
NIVEDITA K. PANDIT[x] AND JANET S. HINDERLITER

Received December 10, 1984, from the *Pharmaceutics Department, Research and Development, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT 06877.* Accepted for publication April 19, 1985.

Abstract □ The reaction of chlorthalidone with methanol to give the corresponding methyl ether was investigated. The kinetics are pseudo-first-order in chlorthalidone, but the observed pseudo-first-order rate constants show an unexpected dependence on the initial chlorthalidone concentration, attributable to the presence of trace catalytic impurities in commercial chlorthalidone. Evidence is presented to show that trace heavy metals are probably responsible for the primary catalytic effect. Trace quantities of acetic acid are also present and show a smaller secondary catalytic effect. Kinetics in the presence of added heavy metals and acetic acid were examined. EDTA and povidone reduce the degradation rate. Stabilization by EDTA is due to its ability to chelate heavy metals. Stabilization by povidone is also primarily due to its ability to complex heavy metals; complexation data of ferric and nickel ions with povidone and with 1-methyl-2-pyrrolidinone as a monomer model are presented. In addition, complexation constants were calculated for the interaction of povidone with chlorthalidone, which may also play a role in stabilization.

Chlorthalidone (1), 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl)benzenesulfonamide, is an oral diuretic administered alone and in combination with antihypertensive agents. It has been reported[1] that the absorption after oral administration in humans is incomplete. The aqueous solubility at 37°C is reported[2] to be 0.27 mg/mL. The drug is a weak acid with a pK_a of 9.35 at 25°C;[3] the molecule, therefore, exists in its unionized form at pH values normally encountered in the GI tract. The rather high melting point (224–226°C) is indicative of a large crystal lattice energy which limits the solubility and, therefore, the dissolution rate. Dissolution could be the rate-limiting step that results in incomplete absorption.

Several literature reports have indicated that dissolution rates of drugs can be significantly increased by using coprecipitates of the drug with povidone.[4-6] This laboratory investigated the possibility of enhancing dissolution rates of chlorthalidone by this technique. This report deals with a reaction between chlorthalidone and methanol that occurs during coprecipitation with povidone using methanol as the solvent. This reaction results in the formation of the methyl ether of chlorthalidone, 2. The conversion of 1 to its ethers by alcohols in the presence of strong acids was reported previously.[7,8] The coprecipitation system did not utilize acids, and ether formation was not expected to occur. Nevertheless, the methyl ether was formed in solutions of 1 in methanol. This paper discusses the nature and kinetics of the reaction, and possible ways to minimize formation of 2. Since the UV spectrum of 2 is identical to that of 1, an HPLC assay was required to quantitate both compounds.



1, R = H

2 R = CH_3

Experimental Section

Materials—Chlorthalidone (1) (Armour Medicamente); methanol (spectral grade), ferric chloride (purified grade), glacial acetic acid (reagent grade), and EDTA (Fisher Scientific Co.); methanol (HPLC grade) (MCB Reagents); povidone (Plasdone 26/28, GAF) were used as received. Chlorthalidone from Armour Medicamente was used for all studies unless otherwise noted.

Purification of Chlorthalidone—Commercial chlorthalidone (150 g) was dissolved in 5 L of boiling ethanol. The mixture was filtered hot to remove insoluble impurities. After cooling to room temperature, 4 L of petroleum ether (b.p. range 40–60°C) was added with stirring. The crystals were filtered, washed with ether, and dried at 90°C under reduced pressure at 2 mm Hg. The product which contained ethanol of crystallization, was suspended in 10 L of distilled water and refluxed for 6 h. After cooling overnight, the crystalline material was removed by filtration and dried at 80°C to yield 111 g [m.p. 231–233°C (lit.[7] 218°C)].

Preparation of Chlorthalidone Methyl Ether—Anhydrous HCl was added with stirring into an ice-cold suspension of 10 g of chlorthalidone in 150 mL of methanol until a clear solution was obtained. The mixture was stirred at room temperature overnight, then the solvent was removed under reduced pressure. Addition of methanol and cooling to 5°C gave 4.9 g of white crystals [m.p. 112–114°C (lit.[7] 112–114°C)].

Analytical Procedure—A high-performance liquid chromatograph (HPLC) with a variable-wavelength detector was used. The mobile phase consisted of 65% pH 6.5 phosphate buffer at 0.05 M:35% acetonitrile, 2.0 mL/min through a C_{18} column (Waters Associates, 10 μm, 25 cm). Retention times were 2.73 min for 1 and 4.67 min for 2. The hydrolysis product of 1, which is not formed in the reaction with methanol, was nevertheless separated from 1 and 2 and gave a retention time of 1.71 min. The peak areas were computed using an integrator, and external standards were used for quantitation. The responses of all three compounds versus amount injected were linear in the concentration ranges investigated.

Reaction of Chlorthalidone in Methanol—Solutions of chlorthalidone (commercial or purified) in methanol were prepared in the range from 1 to 60 mg/mL. In all cases, ultrasonification was necessary to hasten dissolution. An initial analytical sample was withdrawn before filling the solution into glass vials. The vials were sealed and placed in a 41°C constant-temperature room. Samples were withdrawn periodically, rapidly cooled to room temperature, diluted appropriately with the HPLC mobile phase, and assayed by HPLC. Dilution was shown to arrest any reaction, and the diluted solution was stable for at least 24 h. Diluted solutions were refrigerated if storage for longer than 24 h was required. Under these conditions, the solution was stable for at least 1 week.

Reaction of Chlorthalidone in Methanol Containing Heavy Metals and Acetic Acid—A solution of chlorthalidone (purified) in methanol was prepared as described above except that methanol solutions of ferric chloride, nickel(II) chloride, or acetic acid were added after ultrasonification and cooling. The final diluted concentration of 1 in these samples was 40 mg/mL. Storage and sampling were identical to the previous study.

Reaction of Chlorthalidone in Methanol Containing Povidone—Solutions of various concentrations of povidone in methanol were prepared, and chlorthalidone (commercial) was added to each solution. Upon final dilution, the concentration of 1 was 40 mg/mL, while those for povidone were 0, 4, 5, 10, 13.3, and 20 mg/mL. Storage and sampling were identical to previous studies.

Reaction of Chlorthalidone in Methanol in Contact with Stainless Steel—The procedure of previous studies was repeated in certain instances with the exception that the solutions were stored in

0022-3549/85/0800-0857$01.00/0

type 316 stainless steel beakers rather than glass vials. Storage and sampling were identical in all respects.

Reaction of Chlorthalidone in Methanol Containing Ferric Chloride and EDTA—A solution of chlorthalidone (purified) in methanol was prepared and added to an aliquot of an aqueous solution of EDTA of known concentration. A volume of methanolic ferric chloride was added prior to final dilution to the combined solutions. On dilution, the concentration of 1 was 40 mg/mL, ferric chloride was 1.0 mg/mL, and EDTA ranged from 0 to 0.4 mg/mL. The final solvent composition was 90:10, methanol:water.

For all studies, storage and sampling were identical to that described previously. All reactions were carried out in glass vials except where specifically mentioned.

Solubility of Chlorthalidone in Povidone–Methanol Solutions—The solubility of 1 (purified) in methanol was measured as a function of povidone concentration. Excess solid 1 was added to povidone solutions varying between 0–25% w/v in concentration. The solutions were rotated at 26°C until equilibrium was reached. The solutions with the higher providone concentrations required 2 weeks for equilibration because the viscosity of these solutions depressed the dissolution rate of 1. The solutions were then filtered, appropriately diluted, and analyzed by HPLC.

Results and Discussion

Reaction Kinetics—Chlorthalidone, **1**, is susceptible to degradation in the presence of methanol and forms the methyl ether, **2**. The reaction could be followed when **1** and **2** were separated and quantitated by HPLC with UV detection at 254 nm. The reaction is truly in equilibrium[7] but, in the presence of excess methanol (as is the case when methanol is the solvent), the forward reaction goes to completion. Similar behavior is observed with other alkanols. Pseudo-first-order kinetics were observed over four half-lives at 41°C and a given initial concentration of **1**, and reproducibility was good.

Effect of Initial Concentration of Chlorthalidone—The pseudo-first-order rate constants, k_{obs}, were measured as a function of initial **1** concentration ranging from 1 to 60 mg/mL. It was observed that k_{obs} depends on the initial concentration of **1**; the data are shown in Fig. 1. However, at any given concentration, well-behaved pseudo-first-order kinetics were obtained. The concentration dependence of k_{obs} could not be rationalized in terms of higher order reactions. The rate of the reaction is large enough at high **1** concentrations such that substantial degradation occurs while **1** is dissolving in methanol during preparation of the solution samples. Consequently, these samples at $t = 0$ (defined as the first sample taken after dissolution is complete) showed some degradation. Since the reactions are pseudo-first-order, this does not affect the kinetic interpretation.

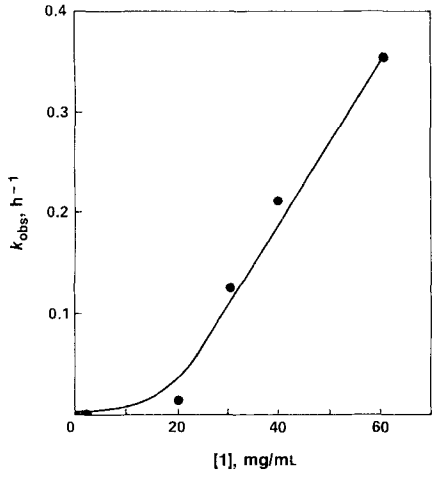


Figure 1—*Effect of total initial chlorthalidone concentration on the pseudo-first-order rate constant.*

The increase of k_{obs} with the concentration of **1** can be explained in terms of a possible impurity present in **1** that catalyzes the reaction with methanol. Since the samples of **1** used met USP specifications, this impurity would have to be ≤2% by weight of **1**. If the molar concentration of this impurity is designated as [A], it can be related to the total **1** concentration $[1]_t$ by:

$$[A] = x[1]_t \quad (1)$$

where x is a fraction representing the moles of the impurity per mole of **1**. Since methanol is present in excess, the rate expression for the reaction can be written as:

$$\frac{-d[1]}{dt} = k_0[1] + k_A[A][1] \quad (2)$$

where k_0 is the pseudo-first-order rate constant for the uncatalyzed reaction and k_A is the pseudo-second-order rate constant for the catalyzed reaction. Since methanol is present in excess, the methanol term has been included in the rate constants. Methanol is both a reactant and a solvent, and these two effects were not separated. The experimental rate expression is:

$$\frac{-d[1]}{dt} = k_{obs}[1] \quad (3)$$

therefore:

$$k_{obs} = k_0 + k_A[A] \quad (4)$$

Substituting eq. 1 into eq. 4 gives:

$$k_{obs} = k_0 + xk_A[1]_t \quad (5)$$

Thus, the presence of one or more impurities in **1** that catalyze the reaction would result in a dependence of k_{obs} on $[1]_t$. To confirm this, similar reactions were carried out with purified **1**; no degradation was observed in these reaction mixtures after 4 d. This strengthens the argument that an impurity, or several impurities, are present in commercially available **1**, and that these impurities catalyze the reaction of **1** with methanol.

Identification of Catalytic Impurities—A sample of commercial **1** used for these studies was examined by NMR and GC; both tests revealed that commercial **1** contained 1.0 mol % (or 0.2%, w/w) acetic acid. Literature reports have mentioned acid catalysis of the conversion of **1** to its ethers in the presence of alcohols.[7,8] However, when acetic acid (corresponding to 0.2% w/w of **1**) was added to a solution of purified **1** (which contained no detectable acetic acid), no increase in the degradation rate constant was observed.

Trace quantities of heavy metals could also be present since the synthesis of **1** involves the use of a cupric chloride catalyst for the Meerwein diazotization.[9] Also, the manufacture of **1** may be carried out in stainless steel reactor vessels which could yield heavy metal contamination, e.g., iron, nickel, and chromium from type 316 stainless steel. Metal oxides and salts can catalyze the conversion of alcohols to ethers, and are in fact used during the synthesis of ethers from alcohols.[10] Samples of commercial **1** were tested for the presence of copper, iron, nickel, and chromium by atomic absorption spectroscopy (courtesy of Perkin-Elmer, Norwalk, CT). These metals, if present, were at <1 ppm concentration. Methanol used as a solvent for the reactions was also tested for heavy metal contamination with similar results.

Effect of Metals—Since concentrations of metals <1 ppm could still catalyze the reaction, a study was performed to determine the effect of metal ions. Purified **1** was used for

these studies, and the effect of ferric chloride and nickel chloride as representative metal ion contaminants was examined at varying concentrations. Both metal ions were found to catalyze the reaction, with the ferric ion being a much stronger catalyst. All kinetics were pseudo-first-order. The effect of ferric chloride concentration on k_{obs} is shown in Fig. 2.

Since acetic acid impurity had been found in commercial **1**, the effect of acetic acid on catalysis by ferric chloride and nickel chloride was investigated. Pseudo-first-order kinetics were obeyed; the effect of acetic acid concentration on catalysis by ferric chloride and nickel chloride is shown in Fig. 3. The catalytic effect of acetic acid in the presence of these metal ions levels off at higher concentrations of acetic acid in both cases. This catalytic activity is probably due to specific acid and/or a general acid–general base catalysis. The pK_a of acetic acid in methanol is reported to be 9.52.[11] Using this, the concentration of solvated hydrogen ions, acetate ions, and undissociated acetic acid can be calculated. Less than 1% of the acid is dissociated in methanol, and therefore the concentration of undissociated acid can be approximated by the total acetic acid concentration $[HAc]_t$. Since the plot of k_{obs} versus $[HAc]_t$ is not linear, general acid catalysis can be ruled out. Specific acid and general base catalyses are kinetically indistinguishable, and thus the observed pseudo-first-order rate constant can be written as:

$$k_{obs} = k_0 + k_M[M] + k'_M[M][H^+] \quad (6)$$

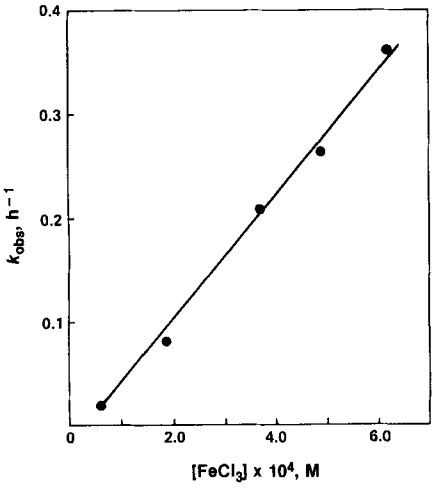


Figure 2—*Effect of added ferric chloride on the degradation of purified chlorthalidone (1). Total purified 1 concentration = 40 mg/mL.*

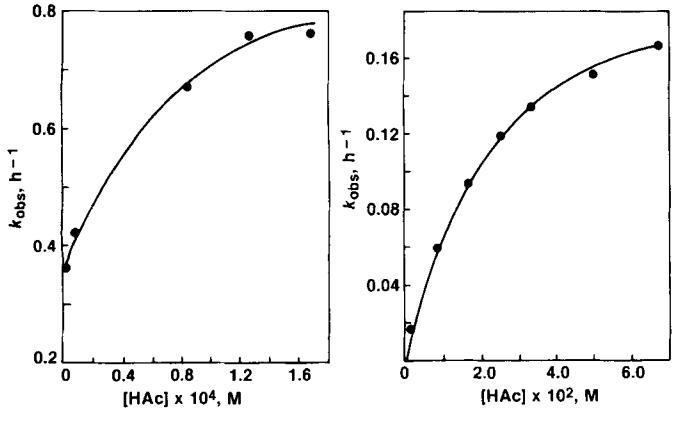


Figure 3—*Effect of acetic acid concentration on the degradation of purified chlorthalidone (1) in the presence of 6.15 × 10^{-4} M (0.1 mg/mL) $FeCl_3$ (left figure) and 0.193 M (25 mg/mL) $NiCl_2$ (right figure). The concentration of 1 was 40 mg/mL in both cases.*

where k_M is the pseudo-second-order rate constant for the metal ion catalyzed reaction, [M] is the concentration of the metal ion, k'_M is the pseudo-third-order rate constant for the metal ion and acid-catalyzed reaction, and $[H^+]$ is the concentration of solvated hydrogen ions present.

Plots of k_{obs} versus $[H^+]$ are shown in Fig. 4 for ferric chloride and nickel chloride catalyses, respectively. Figure 4 shows curvature at higher acetic acid concentrations. This may be due to activity coefficient effects since activity coefficients are much smaller in methanol than in water at the same ionic strength.[12] This has not been investigated further because the quantities of acetic acid found in commercial **1** were low. The values of k_M and k'_M calculated from Figs. 2 and 4 for ferric chloride and nickel chloride are shown in Table I.

If both metal and acetic acid impurities are present in **1**, we can write:

$$k_{obs} = k_0 + xk_M[1]_t + xk'_M[H^+][1]_t \quad (7)$$

and $[H^+]$ can be related to $[1]_t$ by:

$$[H^+] = (K_a[HAc]_t)^{1/2} = (K_a y[1]_t)^{1/2} \quad (8)$$

where K_a is the acid dissociation constant for acetic acid in methanol, and y is a fraction given by:

$$[HAc]_t = y[1]_t \quad (9)$$

therefore, we can write:

$$k_{obs} = k_0 + xk_M[1]_t + xzk'_M[1]_t^{3/2} \quad (10)$$

where:

$$z = (yK_a)^{1/2} \quad (11)$$

If more than one metal impurity that catalyzes the reaction is present, as is probably the case for commercial **1**, then the general equation becomes:

$$k_{obs} = k_0 + (x_1k_{M_1} + x_2k_{M_2} + \ldots)[1]_t + (x_1k'_{M_1} + x_2k'_{M_2} + \ldots)z[1]_t^{3/2} \quad (12)$$

where the subscripts correspond to the different metal impurities. The equation shows a complex dependence of k_{obs} on $[1]_t$ as is suggested by the data shown in Fig. 1 for commercial **1**.

Contact with Stainless Steel—In view of the catalysis of the degradation of **1** by ferric and nickel ions, it was desirable to examine the **1**–methanol system in contact with stainless steel, since stainless steel is the predominant material of construction of pharmaceutical manufacturing equipment.

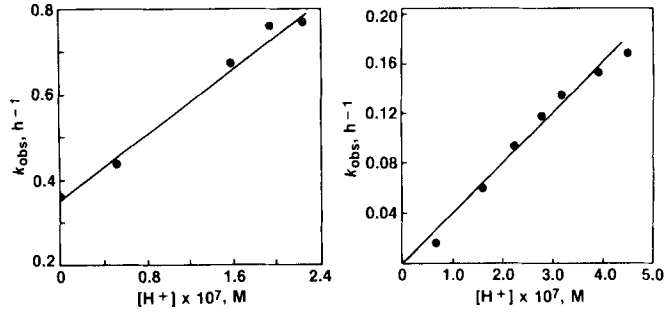


Figure 4—*Data in Fig. 3 plotted versus hydrogen ion concentration instead of total acetic acid concentration. Key: (left) $FeCl_3$ catalysis; (right) $NiCl_2$ catalysis.*

Table I—Second- and Third-Order Rate Constants for the Degradation of Purified Chlorthalidone in the Presence of Added Catalysts

Catalysts	k_M, $M^{-1} \cdot s^{-1}$ [a]	k'_M, $M^{-2} \cdot s^{-1}$
$FeCl_3/H^+$	0.169	8.66×10^5
$NiCl_2/H^+$	~0	5.80×10^2

[a] Rate constant independent of the concentration of acetic acid.

Pseudo-first-order kinetics were also observed for the reaction between 1 and methanol in stainless steel beakers. For a 40-mg/mL solution of commercial 1, the k_{obs} in stainless steel beakers was 0.185 h^{-1} as compared to 0.0785 h^{-1} in glass containers. The faster rate in stainless steel containers indicates that either (*a*) heterogenous catalysis by the steel surface occurs and/or (*b*) trace quantities of metal ions leached out from the container further catalyze the reaction.

Stabilization by EDTA—If the catalytic impurities are indeed heavy metal ions, then the inclusion of a chelating agent such as EDTA in the reaction mixture of commercial 1 should stabilize it. Since EDTA is poorly soluble in methanol, the reaction had to be carried out in a methanol:water (90:10, v/v) solvent. A control reaction was carried out in this solvent system without EDTA. Water at this concentration causes a decrease in k_{obs} from 0.0785 h^{-1} in pure methanol to 0.0110 h^{-1} in methanol–water. This is expected since water is a product of the equilibrium reaction; the presence of water will also have a medium effect on the reaction. When EDTA was present at 10 mg/mL or 1 mg/mL, no degradation was seen in 24 h; presumably, EDTA decreases the reaction rate by complexing with the heavy metal impurities. This is another indication that the trace catalytic impurities may be heavy metals.

To confirm that EDTA would complex with heavy metal ions in such a system, a similar reaction with purified 1 and 0.1-mg/mL ferric chloride was carried out in methanol:water (90:10), with and without the inclusion of EDTA. At 0.1 mg/mL, EDTA reduced k_{obs} from 0.0558 h^{-1} to 0.0351 h^{-1}. At 0.4-mg/mL EDTA, no degradation was observed in 24 h. This confirms that EDTA will complex with ferric ions to stabilize the system.

Stabilization by Povidone—The effect of povidone on the reaction of 1 with methanol was examined in glass as a function of povidone concentration; the data are shown in Table II. Povidone stabilizes 1 from degradation to the methyl ether, and the degree of stabilization depends on the povidone concentration. Similar stabilization is seen in stainless steel beakers, although slightly higher concentrations of povidone are required. The stabilization by povidone can be due to an interaction between povidone and 1 that exerts a protective effect on 1, an interaction between the catalytic impurities and povidone to make them unavailable for catalysis, and a medium effect on the reaction mixture. All three effects probably exist in the 1–povidone–methanol system.

Interaction Between Ferric Ions and Povidone in Methanol—The interaction between ferric ions (used as a model for heavy metal ions that may be present as impurities in 1) and povidone in methanol was examined by the spectral technique. The method of Kramer and Connors,[13] was used, and it was assumed that a 1:1 complex formed between the ferric ion and each monomer molecule of the povidone chain. It should be understood that the molar concentrations of the povidone or the monomer units cannot be expressed exactly since only an average molecular weight is available for povidone. The ferric chloride spectrum in methanol has a maximum at 366 nm. This maximum shifts to lower wavelengths as the concentration of ligand, povidone, is increased. An isosbestic point is seen at 346 and at 280 nm; these points

Table II—Effect of Povidone on the Degradation of Commercial Chlorthalidone[a]

Povidone, mg/mL	k_{obs}, h^{-1}
0	0.0782
4.0	0.0185
5.0	0.0119
10.0	—[b]

[a] Concentration of chlorthalidone = 40 mg/mL. [b] No degradation in 24 h.

disappear at high ligand concentrations, presumably indicating the formation of higher-order complexes. A similar study was carried out using 1-methyl-2-pyrrolidinone (1-MP) as a ligand to act as a monomer model for povidone. An isosbestic point is observed at 346 nm for this system also, but there is no similar point at 280 nm.

The equation used by Kramer and Connors[13] is used to analyze the data:

$$b/\Delta A = 1/K_{11}S_t\Delta\epsilon[L] + 1/S_t\Delta\epsilon \qquad (13)$$

where b is the cell path length in cm, ΔA is the difference in absorbance at the selected wavelength, K_{11} is the 1:1 complexation constant, S_t is the total substrate concentration, $\Delta\epsilon$ is the difference in the molar absorptivities between the complex and the substrate, and [L] is the concentration of the free ligand. If [L] can be approximated by L_t, the total ligand concentration, a plot of $b/\Delta A$ versus $1/L_t$ will be linear. Figure 5 shows this plot for povidone (expressed as moles of monomer) and 1-MP as ligands. The linearity of the plots shows that the 1:1 complexation model is adequate to interpret these data, although a strict 1:1 stoichiometry may not exist for the povidone–1 system. The complexation constant is taken as the ratio *y*-intercept/slope and is found to be 2.43 M^{-1} for the ferric chloride–povidone monomer interaction and 1.1 M^{-1} for the ferric chloride–1-MP interaction. This may indicate that the polymerization of the monomer molecules confers additional stability to the complex or that several types of complexes of varying stoichiometry are possible with the polymer.

Interaction Between Chlorthalidone and Povidone in Methanol—This interaction was examined by the solubility technique; the spectral method could not be used because the presence of povidone in solution did not substantially change the spectrum of chlorthalidone in methanol. The approach of Cohen and Connors for the formation of a soluble complex[14] was used and should be referred to for the derivation of the

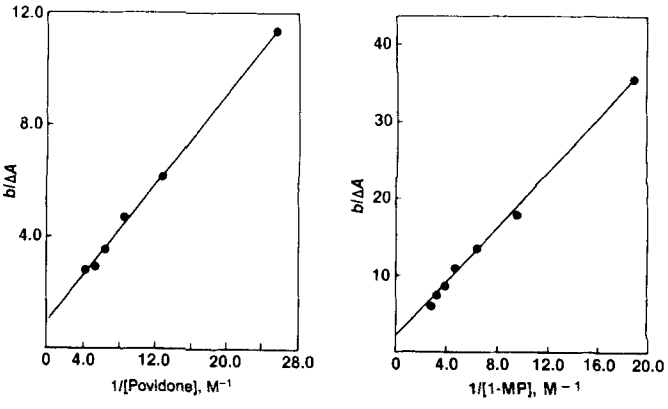


Figure 5—*Change in absorbance of chlorthalidone (1) in the presence of povidone and 1-methyl-2-pyrrolidinone (1-MP) plotted according to eq. 13. Povidone concentration is expressed in terms of monomer units.*

equations. The presence of the ligand, povidone, in methanol increases the solubility of chlorthalidone. If it is assumed that a 1:1 complex is formed between chlorthalidone and each monomer unit of the povidone molecule, the solubility of chlorthalidone can be expressed as:

$$S_t = [K_{11}S_0L_t/(1 + K_{11}S_0)] + S_0 \qquad (14)$$

where S_t is the total concentration of dissolved chlorthalidone, K_{11} is the 1:1 complexation constant, S_0 is the equilibrium solubility of the drug in the absence of L, and L_t is the total added concentration of the ligand expressed in monomer units. A plot of S_t versus L_t should, therefore, yield a straight line, from which K_{11} can be calculated. The phase solubility diagram for chlorthalidone and povidone is shown in Fig. 6. The plot is linear and gives $K_{11} = 0.69\ M^{-1}$ for the chlorthalidone–povidone monomer interaction.

Thus, the primary mechanism by which EDTA and povidone stabilize the solution is the chelation of heavy metal impurities present in chlorthalidone. In addition, povidone can complex with the drug in solution, although this complexation constant is much smaller than that between povidone and ferric ions. Complexes of povidone with certain organic compounds in aqueous solution are reported in the literature.[15–21] Povidone at high concentrations may also exert a medium effect on the reaction.

Variation of Reaction Rate with Source of Chlorthalidone—Since impurities in the raw material are implicated in the reaction, different kinetics can be observed when the source of the drug is varied. Significant variation is observed between two lots of chlorthalidone from the same source. Table III shows the observed rate constants for various samples. These rate constants could not be correlated with the levels of acetic acid impurity present in the samples, again confirming that the undetectable heavy metal impurities were primarily responsible for the catalysis.

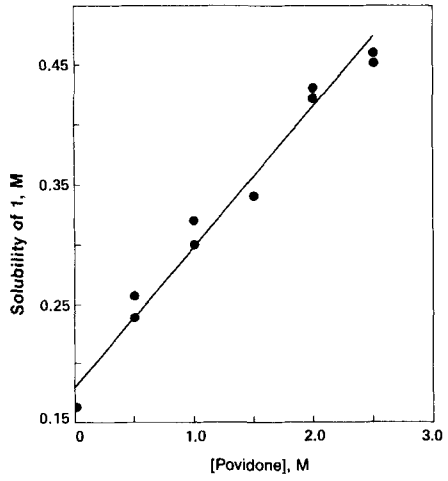


Figure 6—*Phase solubility diagram showing solubility of chlorthalidone in methanol as a function of povidone concentration. Povidone concentration is expressed in monomer units.*

Table III—Variation of Degradation Rate with Source of Commercial Chlorthalidone[a]

Source	k_{obs}, h^{-1}
Armour Medicamente	0.0785
Farchemia (lot L10)	0.00016
Farchemia (lot L12)	0.00015
Welding Pharma (lot 381)	0.0116
Welding Pharma (lot 181)	0.0268

[a] Concentration of chlorthalidone = 40 mg/mL.

References and Notes

1. Fleuren, H. L. J.; Thien, T. A.; Verwey-van Wissen, C. P. W.; van Rossum, J. M. *Eur. J. Clin. Pharmacol.* **1979**, *15*, 35.
2. Poirier, H.; Lewis, G. A.; Shott, M. J.; Stevens, H. N. E. *Drug Dev. Ind. Pharm.* **1983**, *9*, 443.
3. Fleuren, H. L. J.; van Ginneken, C. A. M.; van Rossum, J. M. *J. Pharm. Sci.* **1979**, *68*, 1056.
4. Chiou, W. L.; Riegelman, S. *J. Pharm. Sci.* **1971**, *60*, 1281.
5. Simonelli, A. P.; Mehta, S. C.; Higuchi, W. I. *J. Pharm. Sci.* **1976**, *65*, 355.
6. Sugimoto, I.; Kuchiki, A.; Nakagawa, H.; Tohgo, K.; Kono, S.; Iwane, I.; Takahashi, K. *Drug Dev. Ind. Pharm.* **1980**, *6*, 137.
7. Graf, W.; Girod, E.; Schmid, E.; Stoll, W. G. *Helv. Chim. Acta* **1959**, *42*, 1085.
8. Auterhoff, H.; Wessinger, W. *Arch. Pharm.* **1979**, *312*, 876.
9. "Pharmaceutical Manufacturing Encyclopedia," Chemical Technology Review No. 124; Settig, M., Ed.; Noyes Data Corp.: Park Ridge, NJ, 199; p 125.
10. Harrison, I.; Harrison, S. "Compendium of Organic Synthetic Methods"; Wiley Interscience: New York, 1979; p 370.
11. "Thermodynamic Behavior of Electrolytes in Mixed Solvents-II," Advances in Chemistry Series; Furter, W. F., Ed.; American Chemical Society: Washington, DC, 1979; p 215.
12. Kolthoff, I. M.; Bruckenstein, S.; Bates, R. G. "Acid–Bases in Analytical Chemistry"; Interscience: New York, 1966; p 518.
13. Kramer, P. A.; Connors, K. A. *Am. J. Pharm. Ed.* **1969**, *33*, 193.
14. Cohen, J. L.; Connors, K. A. *Am. J. Pharm. Ed.* **1967**, *31*, 476.
15. Higuchi, T.; Kuramoto, R. *J. Am. Pharm. Assoc., Sci. Ed.* **1954**, *43*, 393.
16. Jürgensen Eide, G.; Speiser, P. *Acta Pharm. Suec.* **1967**, *4*, 201.
17. Jürgensen Eide, G.; Speiser, P. *Acta Pharm. Suec.* **1967**, *4*, 185.
18. Anderson, J. C.; Boyce, G. M. *J. Pharm. Sci.* **1969**, *58*, 1425.
19. Plaizier-Vercammen, J. A.; De Neve, R. E. *J. Pharm. Sci.* **1980**, *69*, 1403.
20. Horn, D.; Ditter, W. *J. Pharm. Sci.* **1982**, *71*, 1021.
21. Plaizier-Vercammen, J. A. *J. Pharm. Sci.* **1983**, *72*, 1042.

Acknowledgments

The authors would like to thank Dr. Stephen Horhota and Dr. James Wright for helpful discussions, Ms. Maureen Wilson for helping with experiments, Dr. Karl Grozinger for purifying 1 and synthesizing 2, Mr. Ray Oksala, Dr. Phil Pitner, and Mr. Jerry Fogel for assistance in identifying and quantitating impurities in 1, and Ms. Susan Lawrence for typing the manuscript.