EFFECT OF COMPLEXING AGENTS ON THE DISSOLUTION KINETICS OF PREDNISOLONE

by

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TABLE OF CONTENTS

INTRODUCTION

Dissolution kinetics becomes important to pharmaceutics when the active drug is given orally in the solid state. In this instance, the drug cannot manifest activity until it first dissolves. It may then, through the process of absorption governed by diffusion, arrive at its site of action. The importance of the drug's dissolution rate in the above process is directly related to its solubility. A drug with good water solubility has a rapid dissolution rate, and, therefore, its effectiveness depends on it being absorbed, assuming the simple case above. If the drug exhibits poor water solubility and, therefore, a slow dissolution rate, the availability of this drug is then dependent on its dissolution rate. It is then important to design a drug system to provide maximum effect from a given amount of drug.

Solutions to this problem are many and varied. A common approach places the drug solids into the smallest particle state feasible, since the dissolution rate is proportional to the available surface area (1-3). Also important is the addition of some agent to prevent particle aggregation and the corresponding loss in available surface area (1,3,4). Thus, surfactants added to the dissolution medium

maintain a maximum dissolution rate due to maximization of surface and other effects. Since the dissolution rate is proportional to the solubility, as stated previously, it would appear then that an increase in the total solubility of a drug would result in an increase in its dissolution rate. Generally substances that cause an increase in total solubility are compounds that form micelles within which the drug is solubilized and those that form apparent interactions or complexes with the drug.

The complex formation can be represented by

$$nS + mL \rightleftharpoons S_n \cdots L_m$$

where S is the substrate, drug of low solubility, L is the ligand or complexing agent present in greater concentration than S, and $S_n \cdots L_m$ is the complex species. An apparent 1:1 complex is of interest since it involves one molecule of ligand interacting with one of substrate. In this case, it is possible to chemically change the ligand and substrate to gain knowledge as to what part of their molecular structure is important in forming a complex. Then, in the presence of a ligand capable of forming an apparent 1:1 complex with a drug increasing its total aqueous solubility, the effect on the dissolution rate of the drug could be studied.

It is the goal of this investigation to examine various chemicals that would act as ligands and complex with prednisolone, a steroid of low water solubility. The results here might lead to an indication of what part of the prednisolone molecule is important in interacting with certain ligands. Also, characteristics of the ligand important to complexing with prednisolone might be revealed.

Since previous work was done on the dissolution kinetics of certain crystalline forms of prednisolone by Wurster and Taylor (5), it was of interest to follow this by studying the effect of various ligands on the dissolution rate of prednisolone. The resulting data would be treated theoretically and compared to the previous study. Interest in this system can be seen from a biological viewpoint, whereby an increase in the dissolution rate of prednisolone would produce an increased availability and possible increased absorption. This would certainly be true if both complexed and free species are absorbed.

PAST WORK

It is not possible to derive an all inclusive equation for the dissolution process because of the variety of conditions under which dissolution may occur. This has resulted in considerable study into the parameters controlling dissolution. The results of these studies have thus yielded various theories on the dissolution process.

The earliest quantitative study of the dissolution of solids into aqueous media was published by Noyes and Whitney (6). Their experiment consisted of rotating cylinders of benzoic acid and lead chloride in water and analyzing the solution at various time intervals. From their results, they arrived at the equation

$$\frac{dc}{dt} = k(C_s - C) \qquad \text{(Eq. 1)}$$

where C is the concentration of solute at time t, and C_s is the equilibrium solubility of the compound at the experimental temperature. They theorized that a thin film of saturated solution surrounded the dissolving solid and consequently the dissolution rate was dependent on solute diffusion from this layer. In later experiments (7,8), the surface area was incorporated into the equation to give

$$\frac{dc}{dt} = k_1 S(C_s - C) \qquad \text{(Eq. 2)}$$

Nernst (9), in 1904, extended the concepts of Noyes and Whitney to include all heterogeneous reactions. This was, however, with certain assumptions and restrictions. These were: (i) a stationary liquid film is assumed to exist through which diffusion into the main body of the stirred liquid takes place; and (ii) the reaction at the solid liquid interface is required to be infinitely rapid, to provide a saturated film at this interface.

King and Braverman (10) stated that "Five observed facts have, in general, been accepted as criteria of the validity of the diffusion rate theory: (1) a number of different solids dissolve at nearly the same rate, while chemical reaction rates are seldom so nearly the same for such widely different substances; (2) the rates of stirring the solution or rotating the specimen has a very large influence on the observed rates, which is not typical of chemical processes; (3) the rate of solution is nearly inversely proportional to the viscosity of the solution; (4) the rates observed with different acids follow, in general, the diffusion coefficients of the acids rather than their acid strengths, although strict proportionality to diffusion coefficients obtained under entirely different experimental conditions

cannot be expected; (5) the temperature coefficient of these heterogeneous reactions is usually 1.1 to 1.5 per 10° rise, while chemical reaction rates seldom have temperature coefficients less than 2.0. Their experimental work substantiated facts 2, 3, and 5.

Brunner (11), working with Nernst, established, by using Fick's law of diffusion, a relationship between the constant from equation 2 and the diffusion coefficient, $k_1 = DA/Vh$, where D is the diffusion coefficient, A is the area of dissolving surface or area of the diffusion layer, V is the solution volume, and h is the diffusion layer thickness. He also calculated the thickness of the proposed diffusion layer and found this thickness to be in the order of magnitude of 30 microns. This large film thickness has been criticized as being physically unacceptable (12). Spangenberg (13) found by observation under the microscope that the slightest disturbance of a saturated solution in contact with a crystal of sodium chloride was transmitted to within about 0.4 microns of the crystal surface. Roller (14) calculated the diffusion layer thickness to be less than 0.2 microns.

Van Name and Hill (15) viewed the outer portions of the diffusion layer as having considerable motion relative to the solid, but only in a plane essentially parallel to the solid surface. Since this is normal to the direction of the concentration gradient, the rate of

transport of dissolved material across the diffusion layer is not affected by the motion of the liquid layer. The diffusion layer thickness then is not necessarily constant and should be considered as an average distance.

As originally postulated, the Nernst-Brunner theory was found to be nonapplicable to those reactions where secondary influences, such as the formation of a gas or insoluble coating at the interface, existed. Friend and Vallance (16) noticed the retardation in dissolution rates of certain crystals in the presence of different colloids which they attributed to adsorption on the dissolving surface. This phenomenon of surface adsorption was treated mathematically by Toubin (17) and has been the reported cause of deviation in several recent reports (18,19).

Instances have been observed, in the absence of any apparent secondary influences, that pure diffusion theory apparently does not hold in all cases of heterogeneous reactions (20,21). In order to explain those reactions where the theory did not hold, Brunner (21) introduced the idea that the reaction velocity at the interface was not necessarily infinite. Other cases were encountered where the surface reaction appeared to take part in the dissolution rate (5,17,20,22-31).

The true diffusional process is extremely slow, such that even a slight agitation will cause a much

greater distribution of the diffusing substance than that caused by the diffusion process alone. The effect of agitation rate on the velocity of heterogeneous reactions has been investigated. Most investigations with agitation have led to the following empirical relation

$$K = a(N)^b$$

where N is the agitation or stirring rate, K the reaction rate, and a and b are constants. When the reaction taking place was thought to be diffusion controlled, it was observed that the value of the exponent b was one or approximately one (10,15,32). This was in agreement with the Nernst-Brunner theory, since it was expected that the diffusion layer thickness was nearly inversely proportional to the stirrer speed, and hence the reaction rate constant was directly proportional to the speed. In the case of reactions in which the interfacial reaction was assumed to be rate controlling, values for b were found to approach zero (10). If both processes are influential in the control of the rate, b should vary between zero and one if a sufficiently wide range of agitation intensities could be employed.

Fage and Townsend (33), when studying water flow characteristics near a solid boundary, found that three-dimensional turbulence persisted up to the boundary itself, or at least to within 0.6 microns.

Most of the disturbance at this distance, however, is parallel to the boundary, approaching the appearance of laminar flow. Since the motion of the fluid changes from laminar to turbulent extending away from the interface, the value of the exponent b may also vary with the type of agitation used. Hixson and Baum (34) observed this in measuring the dissolution of benzoic acid pellets as a criterion for the efficiency of agitation. Using dimensional analysis they assigned a Reynold's number to the point where the relationship between the variables changed. They attributed this change to turbulence and obtained separate relationships for high and low Reynold's number values. In a subsequent study (35), they found that by changing only the type of stirring another empirical relation must be assigned. Agar (36) applied the method of dimensional analysis to the diffusion and convection processes which govern the transfer of a solute between an electrode and the bulk of the solution. Three other dimensionless quantities besides the Reynold's number were used in analyzing both forced and natural convection. Garner and Hoffman (37) found that even in cases of natural convection, turbulence existed in the boundary layer. Variance in the stirring rate-reaction rate relationships was contended by Levich (38) to be due to the variable degree of turbulence in the solvent near the interface.

In cases of forced convection, he felt this may be due, in part, to the different surface characteristics of the dissolving substance.

The above studies indicate that a number of inherent variables can conceivably influence the relationship between the dissolution rate and the intensity of agitation, restricting the applicability of a generalized relationship between them. Thus, the exponent, b, in the aforementioned equation will not only depend on the process controlling the dissolution rate but also on the characteristics of fluid motion in the boundary layer.

The influence of viscosity on heterogeneous reaction rate control has been investigated (12,23,39-43). The results, in general, appear to be complex. However, it has been shown that the dissolution rate is a function of viscosity raised to some power where the exponent varies from -0.25 to -0.8. Because of the complex nature viscosity plays in dissolution it would be difficult to use it in determining control of the reaction. However, diffusion controlled reactions should decrease in rate with an increase in viscosity, whereas viscosity should have no effect on interfacially controlled reactions. Therefore an increase in viscosity could cause a corresponding shift towards interfacial control of the reaction.

Dissolution characteristics of polymorphic and solvate forms of various drugs have recently been investigated. Hamlin, et al. (44) studied the rates of dissolution of two polymorphic forms of methyl prednisolone using different methods to determine the rates. They found that at higher agitation intensities there resulted a loss of sensitivity in distinguishing between the dissolution rates. This change was ascribed to relative changes in their calculated diffusion layer thickness, assuming complete diffusion control of dissolution. Other studies (45-48) compared dissolution rates of various polymorphs of different chemicals and calculated some of the thermodynamics involved (45,46). This was also carried out for some hydrated and nonhydrated pharmaceuticals (49,50). Higuchi, et al. (51) and Goyan (52) gave theoretical considerations to the dissolution process of a polymorph. Wurster and Taylor (5), in studying the dissolution rates of prednisolone polymorphs, found the process to be partially controlled by the interfacial reaction.

Although there has been extensive research done in the areas of complex formation and drug interaction, the effect of complex formation on dissolution rates has received light attention. Wurster and Kildsig (31) reported on the effect of complex formation on the dissolution kinetics of m-aminobenzoic acid. Complexing

agents used in this study were tartaric, d,l-malic and succinic acids and creatinine. In these systems the dissolution process was best described in two parts: 1) surface reaction, and 2) diffusion. The theoretical and mathematical treatment of dissolution rates with simultaneous solution interactions involving additives in the solvent was presented by Higuchi (53). In the field of inorganic chemistry the dissolution of silver chloride and bromide was carried out in the presence of sodium thiosulfate (54). The results here are difficult to correlate to organic systems due to the multiple complexes formed and the ionic nature of the material studied. There have been a number of dissolution studies (55-63) in the presence of micellular surfactants. All studies report an increase in dissolution rates with increasing surfactant concentration, with some reporting the theoretical implications involved.

Since the Noyes-Whitney (6) theory on diffusion controlled dissolution was developed, additional theories have been proposed to help clarify experimental results that failed to fit the former theory. As mentioned, there has been the introduction of the interfacial reaction in combination with diffusion as the controlling factor. Another theory presented was

that by Danckwerts (64) and later modified by Toor and Marchello (65). In this model, one imagines macroscopic packets of solvent reaching the solid-liquid interface by eddy diffusion in some random fashion. During its residence at the interface, the packet is able to absorb solute according to the usual laws of diffusion. They are then continuously replaced by new packets. This surface renewal process may then be related to the solute transport rate. The Danckwerts theory was found to hold only in non-stirred conditions (56), but, in another study (57), it failed to hold in either stirred or non-stirred conditions.

There are a number of methods available to quantitatively study dissolution kinetics. Some of the methods available are the beaker method (66), the hanging disk method (67), the static disk method (68), the fixed disk method (69), and the rotating disk method (70). The method used in the present study was similar to that published by Parrott, et al. (71), the free rotational pellet method. The mechanics of the method are described in the Experimental Section. The mathematical treatment of the data uses a derivation of the Noyes-Whitney equation altered to account for variable surface. Hixson and Crowell (72) derived a general expression for the reaction velocity taking into account the variable surface. This derivation, termed

the "cube root law", was based on the following assumptions: the process of dissolution takes place normal to the surface; the effect of the agitation of the liquid against all parts of the surface is essentially the same; the agitation in the system is of such a magnitude that no stagnation of the liquid occurs resulting in a changing diffusion rate; and the particle remains intact throughout dissolution.

The Noyes-Whitney (7) equation can be written as

$$\frac{dW}{dt} = K_2 S(C_s - C) \qquad \text{(Eq. 3)}$$

where dW/dt is the change in weight of the particle with time, K_2 is a positive constant, and the surface area, S, no longer a constant. Letting W_o represent the initial weight of the particle, W, the weight at time t, W_s, the weight of the solid needed to saturate the liquid, S the effective surface area, V the solution volume, and d the crystal density, the following relationship can be set up:

$$\frac{(W_o - W)}{V} = C \quad \text{and} \quad \frac{W_s}{V} = C_s.$$

Substitution into equation 3 yields

$$V\left(\frac{dW}{dt}\right) = -K_2 S(W_s - W_o + W) \qquad \text{(Eq. 4)}$$

Provided that there is no change in the shape of the particle during dissolution, the surface may be related to the weight by means of shape-volume factors, S being proportional to $V^{2/3}$. With the consideration of density, $S = aW^{2/3}$, where a includes the density and a shape-volume constant.

By substituting for S in equation 4 and setting $W_s - W_o = g$, the following equation is obtained

$$V\left(\frac{dW}{dt}\right) = -K_1 W^{2/3}(g + W) \qquad \text{(Eq. 5)}$$

Rearrangement and integration gives

$$V\int \frac{dW}{gW^{2/3} + W^{5/3}} = -K_1 \int dt + C \qquad \text{(Eq. 6)}$$

where C is the constant of integration.

By imposing $t = 0$, $W = W_o$, and $C = 0$ as a limit of integration and letting $g^{1/3} = b$, $W_o^{1/3} = c$, and $W^{1/3} = x$, the integrated equation for the general case is obtained.

$$K_1 t = \frac{V}{b^2}\left(\sqrt{3}\tan^{-1}\frac{2\sqrt{3}\,b(c-x)}{3b^2 + (2c-b)(2x-b)} + 1.1513\log\frac{(b+c)^2(b^2-bx+x^2)}{(b+x)^2(b^2-bc+c^2)}\right) \qquad \text{(Eq. 7)}$$

If certain conditions are invoked, by imposing certain experimental restrictions, this equation can be greatly simplified. Any one of the following could be used: 1) $W_o = W_s$; 2) $C_s - C$ is constant; or 3) the surface area remains constant.

A complex has been defined by Kennon and Chen (73) in the following manner: "A and B are complexed when there are more A species around and/or closer to B species than a random distribution of A's and B's would bring about." For the case of an apparent 1:1 complex, this can be mathematically represented as

$$A + B \rightleftharpoons A\cdots B \qquad (a)$$

$$K_{App}^{1:1} = \frac{[A\cdot\cdot B]}{[A][B]} \qquad (b)$$

Other types of complexes, forces involved, mathematical treatment, and various examples have been presented (74,75).

In general the forces (74) responsible for complex interactions are: 1) electrostatic-operate between polar molecules; 2) induction-attraction between a polar and a nonpolar molecule; and 3) dispersion (London forces)-operate between two nonpolar molecules. In chemical terms these are: hydrogen bonds, charge-transfer forces, and other interactions which may be classed as electrostatic in nature; such as inductive forces between

an ion and an isolated double bond or hydrophobic bonding between hydrocarbons, arising partly from dispersion interactions and partly from disruption of solvent structure.

Complexes arising from the above interactions may be soluble or insoluble. In the case of the insoluble complex crystallographic studies may be carried out to determine the molecular arrangement of the complex (76). Where a soluble complex occurs, the exact molecular configuration and type of forces involved in the complex may only be postulated (77-79).

Past studies (78,79) have investigated the complexation of prednisolone with various hydroxy aromatic acids and their salts. In their results they have indicated the interaction between prednisolone and various compounds as being a non-specific interaction. The type of interaction in the complex was postulated to be either of the donor-acceptor theory, which states that the intermolecular interaction involves the π orbitals of the aromatic nucleus with the electrons of the donor, or on the basis of the hydrophobic bonding mechanism.

PLAN OF STUDY

Prednisolone Stability

It was of primary importance in this study to find conditions in an aqueous environment where prednisolone would be stable for the duration of the experiment. This is necessary, first, since only prednisolone is desired in the system, and, second, the degradation products of prednisolone absorb at the same wavelength as the parent compound. Thus a special colorimetric assay (80) specific for prednisolone would be necessary if both degraded and stable forms are present.

Complexation

To quantitatively study the effect of various complexing agents or ligands on prednisolone, the substrate, a solubility method was employed (74). In the present studies, the complex is treated as an apparent 1:1 association. The equilibrium equation may be written as

$$S + L \rightleftharpoons S\cdots L \qquad \text{(Eq. 1)}$$

where S is the substrate, L, the ligand and S···L, the complex. Then the apparent 1:1 stability constant for the complex, $K_{1:1}$, is given by

$$K_{1:1} = \frac{[S...L]}{[S][L]} \qquad \text{(Eq. 2)}$$

The concentration terms in equation 2 can be expressed in terms of known quantities:

$$[S] = S_o \qquad \text{(Eq. 3)}$$

$$[S...L] = S_t - S_o \qquad \text{(Eq. 4)}$$

$$[L] = L_t - [S...L] = L_t - S_t + S_o \qquad \text{(Eq. 5)}$$

where S_o is the equilibrium solubility of S in the absence of L, S_t is the total concentration of dissolved S, and L_t is the total concentration of L present. Substitution of equations 3-5 into equation 2 yields:

$$K_{1:1} = \frac{S_t - S_o}{S_o(L_t - S_t + S_o)} \qquad \text{(Eq. 6)}$$

and rearrangement gives:

$$S_t = \frac{K_{1:1} S_o L_t}{(1 + K_{1:1} S_o)} + S_o \qquad \text{(Eq. 7)}$$

Then a plot of S_t vs. L_t should give a straight line for a 1:1 complex with the slope given by

$$\text{Slope} = \frac{K_{1:1} S_o}{1 + K_{1:1} S_o} \qquad \text{(Eq. 8)}$$

and by rearrangement

$$K_{11} = \frac{\text{Slope}}{S_o(1 - \text{slope})} \qquad \text{(Eq. 9)}$$

Using this treatment, K_{11} can be calculated for various ligands.

By examining the resulting K_{11} of various compounds and comparing this with their structure, possible conclusions might be drawn as to what part of the prednisolone and/or ligand molecule is important in complexing.

Rate of Dissolution

In order to quantitatively study the dissolution process in a system in which the surface area is changing, special case two of the Hixson-Crowell general equation (72) was utilized. For this case the term $(C_s - C)$ must be constant. This is accomplished by keeping the concentration in the dissolution medium much less than C_s. Then, since $(C_s - C)$ is constant, the rate becomes proportional to the surface, and equation 3 from the Past Work Section,

$$\frac{dW}{dt} = -K_2 S(C_s - C) \qquad \text{(a)}$$

becomes

$$\frac{dW}{dt} = -K_3 S \qquad \text{(b)}$$

Now, in order to integrate this equation, S must be equated to W, the weight. Since $S \propto V^{2/3}$, where V is

the volume for a sphere since spherical pellets were used, $S = 4.85V^{2/3}$. Then, by introducing density, $d = W/V$, it is possible to derive a term a, such that $aW^{2/3} = 4.85V^{2/3} = S$, where $a = 4.85/d^{2/3}$. Letting $K_3 = 3K$ and substituting S for $aW^{2/3}$ results in

$$\frac{dW}{dt} = -3KaW^{2/3} \qquad (c)$$

Rearranging for integration gives:

$$\int_{W_o}^{W} \frac{dW}{W^{2/3}} = -3Ka \int_{t_o}^{t} dt \qquad (d)$$

and after integration

$$W_o^{1/3} - W^{1/3} = Kat \qquad (e)$$

Plotting $W_o^{1/3} - W^{1/3}$ ($grams^{1/3}$) vs. t (hours) gives a straight line with slope = $Ka(gm^{1/3}hr^{-1})$. Since a can be calculated from the density, K = slope/a. Then the dissolution rate $(\frac{-dW}{Sdt})$ in gm $cm^{-2}hr^{-1}$ is equal to 3K.

Effect of C_s on the Dissolution Rate

As predicted by Noyes-Whitney (6), the dissolution rate is proportional to C_s, the equilibrium solubility.

If C_s increases, as would be the case in the presence of a complexing agent or micellular solubilizer, the resulting equation would predict, plotting dissolution rate vs. C_s, a straight line with intercept zero. Looking at the basic assumptions of Noyes-Whitney, it would appear to be an over-simplification to apply this to the above situation, since none of the physical parameters of the additional species are considered. The theoretical consideration of this situation was presented previously (63); the equations derived predict that the effect on the dissolution rate as a function of colloidal solubilizer concentration will be less than that predicted by Noyes-Whitney (6). The general equation is given by:

$$G = \frac{1}{h}(D_o C_o + \sum_i D_i C_i)$$

where h is the diffusion layer thickness, G is the initial dissolution rate per cm^2, D_o is the diffusion coefficient of the free dissolving molecule, C_o is the solubility of the dissolving substrate in the pure solvent, D_i is the diffusion coefficient of solubilized species, i, and C_i is the contribution of species, i, to the total solubility. Experimental evidence confirming this theoretical prediction was given by Singh, et al. (56). Their experiments studied the effect of polysorbate 80 on the dissolution rate of benzocaine.

If a dissolution system contained a complexing agent that formed a 1:1 complex with the dissolving substance, there would be two species of the dissolving substance present, free and complexed. The above equation could then be simplified to:

$$G = \frac{1}{h}(D_o C_o + D_x C_x)$$

where D_x is the diffusion coefficient of the complexed species and C_x is the contribution of the complex, x, to the total solubility. In the present study it will be of interest to check the fit of the above equation and compare the results obtained with those of Wurster and Taylor (5,30) and others (6,64).

EXPERIMENTAL

Chemicals Used

2-Naphthalene sulfonic acid (Eastman Organic Chemicals).

1-Naphthol-2-sulfonic acid,potassium salt (Eastman Organic Chemicals). Recrystallized from methanol.

2,6-Naphthalene disulfonic acid, disodium salt (Aldrich Chemical Co.).

2-Naphthol-6,8-disulfonic acid, dipotassium salt, recrystallized (Eastman Organic Chemicals).

2,3-Dihydroxy naphthalene-6-sulfonic acid, sodium salt (Aldrich Chemical Co.).

2-Naphthol-3,6-disulfonic acid, disodium salt (Matheson, Coleman and Bell). Recrystallized from 66% methanol-water.

4,5-Dihydroxynaphthalene-2,7-disulfonic acid, disodium salt (Aldrich Chemical Co.).

2,7-Dihydroxynaphthalene-3,6-disulfonic acid, disodium salt (Aldrich Chemical Co.).

5,5'-Methylenedisalicyclic acid (Eastman Organic Chemicals). Disodium salt prepared with NaOH and pH adjusted with HCl.

2,4-Dinitrobenzene sulfonic acid (Eastman Organic Chemicals).

3,5-Dinitrobenzoic acid sodium salt (Aldrich Chemical Co.).

Tropaeolin O (Matheson, Coleman and Bell).

Nicotinic acid, U.S.P.

Disodium ethylenediamine tetraacetic acid.

Hydrocortisone, U.S.P. (Schering Co.).

Prednisolone (Upjohn Co.).

Prednisolone-T(G), specific activity 500 mc/mM (TRA215) (Amersham/Searle).

PPO (Amersham/Searle).

POPOP (Amersham/Searle).

1,4-Dioxane (Baker Analyzed Reagent).

Naphthalene (Purified) (Mallinckrodt).

All other chemicals used were reagent or U.S.P. grade.

Preparation of the Prednisolone Crystal Forms

The prednisolone crystal forms were prepared according to the method used by Wurster and Taylor (5).

Form I - Anhydrous. The prednisolone was recrystallized from 70% (v/v) methanol-water maintained at refrigeration temperatures. The crystals were then dried at a temperature slightly less than 100°C for not less than 18 hours.

Form III - Hydrous. An excess of Form I (2.5 mg per 1 ml water) was equilibrated in twice distilled water for 72 hours at 30±0.1°C. The resulting crystals were then collected on a Millipore Filter (Millipore Corp., Bedford, Mass.) (HAWP 02500 HA 0.45 μ).

The absorptivity determined in water at 242 mμ for Form III (a = 39 Lgm^{-1} cm^{-1}) and for Form I (a = 42 Lgm^{-1} cm^{-1}) along with the weight loss of Form III upon drying enabled the formula weight of Form III to be calculated. (Form I F. Wt. = 360.5; Form III F. Wt. = 387.6).

Dilution of Tritrated Prednisolone

The prednisolone-T was obtained in 5 ml ampoules containing one mc per ml in ethanol. The contents of the vial were added to 800 mg of anhydrous prednisolone and sufficient ethanol to insure solution. The solvent was then evaporated and the prednisolone carried through the procedures for Form I and then Form III, the desired form. The resulting hydrous prednisolone-T had a specific activity of about 6 μc/mg.

Prednisolone Stability

The oxidative cleavage of the dihydroxyacetone function of prednisolone has been investigated (80-83). It was found that no significant degradation occurred below pH 8 in a two week period (84). Due to this, all solutions of chemicals used as ligands in complexing

studies and dissolution experiments were at a pH less than 8. Taking this precaution allowed the analysis of prednisolone to be carried out using ultraviolet analysis without having to use a specific colorimetric assay (80). Also due to the photolytic degradation of ring A (85), care was taken in all studies to prevent excessive exposure of prednisolone to light.

General Apparatus

The pH measurements were made using a Beckman Model H2 pH meter (Beckman Instruments, Inc., Fullerton, Calif.) with a Beckman #39142 combination electrode (Beckman Instruments, Inc., Fullerton, Calif.).

Most absorbance measurements were made on a Cary 15 Recording Spectrophotometer (Applied Physics Corp., Monrovia, Calif.); the remainder of the readings were taken with a Beckman D.U. (Beckman Instruments, Inc., Fullerton, Calif.) equipped with a Gilford Digital Readout (Gilford Instrument Laboratories, Inc., Oberlin, Ohio).

Complexation and dissolution studies were carried out in a thermostated water bath controlled by a Precision Electronic Relay Control Box (#62690) (Precision Scientific Co., Chicago, Ill.) to $30 \pm 0.1°C$.

Complexation studies utilized a tumbling apparatus described by Mollica (86).

The dissolution apparatus used was similar to that described by Taylor (84). All studies were carried out in a two liter, three-necked round bottom flask secured in a constant temperature bath maintained at 30±0.1°C. Free rotational agitation of the pellet was achieved by a paddle stirrer mounted vertically through the center opening of the flask. The shaft was kept at minimum vibration by placing it through a number 3 cork borer which had been placed through a number 10 rubber stopper which fit securely in the center flask opening. The paddle stirrer consisted of a 0.25 inch steel shaft with two blades of dimensions 1.0 x 1.5 cm. The stirrer was immersed 5.3 cm below the surface of the quiescent liquid and coated with inert paraffin to prevent any reaction with the solutions. Care was taken to position the flasks and stirring rod in the same manner for each run.

The motors used were Heller Electronic Controller GT21 Laboratory Mixer Motors (Gerald K. Heller Comp., Las Vegas, Nevada). The motors had two shafts perpendicular to one another turning at a 18:1 ratio. The faster shaft was connected directly to the paddle shaft while the rpm of the slow shaft were determined periodically to maintain the paddle shaft turning at 835 rpm.

Liquid scintillation measurements were taken with the Packard Tri-Carb Liquid Scintillation Spectrometer model 2002 or 3002 (Packard Instrument Co., Downers Grove, Ill.).

Tablet production utilized a Carver Laboratory Press model B (Fred S. Carver, Inc., Summit, N.J.) equipped with a 0-1000 pound pressure gauge in 10 pound divisions. It is the pressure read off this gauge that is mentioned under Tablet Production and Characteristics.

Tablet measurements were obtained using a Gaertner Optical Slide Micrometer (Central Scientific Co.) that had an accuracy of 0.002 mm and a precision of 0.01 mm $\pm$0.001 mm.

Tablet weights were determined with a Mettler Single Pan Microbalance (Mettler, Hightstown, N.J.). Other weighings were done using a Right-a-Weight Single Pan Balance (Wm. Ainsworth and Sons, Inc., Denver, Colorado).

The suction device used to remove tablets from the dissolution flask consisted of a 10 ml pipette sectioned below the bulb and then joined together with a 1.5 inch piece of Tygon tubing. A one inch piece of Tycon tubing was placed on the tip so when suction was applied by a rubber bulb the tablet was pulled into the end piece of Tycon up to the pipette tip. The tablet could then be lifted from the dissolution vessel and

discharged from the suction device.

Complexation Studies* - Procedure

Approximately 20-25 mg of hydrous prednisolone was placed in a 15 ml screw cap vial. To this vial 10 ml of a specific concentration of a ligand was added and then sealed with Parafilm (American Can Company, Neenah, Wisconsin) and capped. The vials were placed on the tumbling apparatus and submerged in a constant temperature bath at 30±0.1°C for 48 hours.

The following procedure was similar to one used earlier (82). The vial contents were then filtered through a Millipore Filter (HAWP 02500 HA 0.45 μ) and the filtrate placed in a 60 ml separatory funnel containing 20 ml chloroform. The prednisolone in the aqueous layer was extracted with a total of four 20-ml portions of chloroform, leaving the ligand in the aqueous layer. The chloroform layers were combined and additional chloroform added to make 100 ml. An aliquot of the chloroform solution was placed in a 50 ml Erlenmeyer flask containing one glass bead and evaporated to dryness on a steam bath using a stream of air. Twenty ml of 95% ethanol were added and the flask stoppered. Absorbance was read at 242 mμ and

*For a review of the solubility method for studying complexation see Reference 74.

concentration calculated using a Beer's law plot.

The apparent 1:1 stability constant was determined by plotting total molar solubility of hydrous prednisolone versus increasing concentration of ligand (74).

$$S_t = \frac{K_{11} S_o L_t}{(1 + K_{11} S_o)} + S_o$$

Tablet Production and Characteristics

The hydrous prednisolone-T used in the dissolution experiments was first slugged to 900 pounds gauge using a 3/8 inch flat punch and die. The resulting discs were crushed to a coarse powder. This powder was compressed at 300 pounds gauge pressure with the Carver Press using a special steel cylinder assembly (87) that held a Colton 0.125 inch modified ball punch and die (Cherry-Burrell Corp., Elk Rapids, Mich.). The weight of material compressed was adjusted so the formed tablet was of spherical dimensions. In order to prevent the prednisolone from sticking to the punch surfaces, the punches were dipped in a slurry of magnesium stearate in ethanol and allowed to dry. The dried magnesium stearate was wiped off and one tablet of non-tritiated prednisolone was made and discarded, since the first tablet showed an apparent lag time upon dissolution. Then three tablets of prednisolone-T could be made before the

procedure needed to be repeated.

The tablets were brushed free from loose surface particles with a camel's hair brush. The appropriate dimensions of each tablet were measured to 1 x 10^{-4} cm with the Gaertner Optical Micrometer equipped with a rotating substage. The total volume of each tablet was determined by calculating the volume of the cylindrical part and spherical segments of the tablet. This method was more reproducible than taking an average diameter and calculating the volume assuming the tablet a perfect sphere.

The tablets were weighed on the Mettler Microbalance to 0.01 milligrams, with the average weight being 22 mg. The average tablet density, calculated from the tablet weight and volume, was about 1.19 gm/cc.

Dissolution Rate Studies - Procedure

The dissolution flask was filled with two liters of the specified concentration of a ligand previously thermostated at 30±0.1°C. The stirrer was allowed to run five to ten minutes while the paddle speed was adjusted and a two ml aliquot removed as a blank. The tablet was then dropped into the solution and time zero was noted.

The analytical method employing the tritium-labeled prednisolone was necessary since the volume of the dissolution medium needed to extract sufficient

prednisolone to be measured quantitatively was impractical. Also, ultraviolet analysis of dissolution samples was impossible due to the interfering absorbance of the ligand.

Two ml samples were taken at 0.33, 0.5 or 1 hour intervals and placed in 20 ml polyethylene scintillation vials (Packard Instrument Co., Downers Grove, Ill. 60515). To each of the vials, 13 ml of scintillation cocktail (88) was added and then counted for 2, 5 or 10

PPO	6.0	gm
POPOP	0.275	gm
Naphthalene	112.0	gm
1,4-Dioxane	to 1.0	liter

minutes depending on which ligand and concentration was used. This procedure was followed on samples of known concentrations of prednisolone-T in a specific concentration of ligand. This gave a standard curve for each concentration of each ligand used.

At the end of the dissolution run, the tablet was removed rapidly with the previously described suction device. After being rinsed with distilled water and dried, the tablet was weighed. From the tablet weight loss, the final concentration of the dissolution solution was calculated and used to check the result obtained using the standard curve.

Since a total of only 1% of the dissolution solution volume was removed as samples, no correction was necessary in calculating the solution concentration at each time interval.

RESULTS AND DISCUSSION

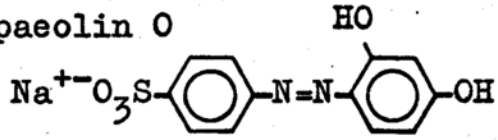
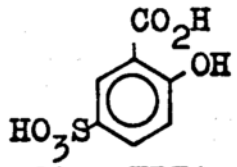
Complex Formation

In earlier work, Higuchi and Drubulis (78) investigated the complexation of prednisolone with various hydroxybenzoic acids and their salts. Because of the high pH needed and small apparent stability constants obtained ($K_{1:1}$ = 10-17), it was necessary in the current investigation to look at compounds similar in structure but that exhibited a lower pH. Using the solubility method, the compounds in Table 1 were thus checked for their ability to complex with prednisolone. As the table indicates, the results were generally negative.

In the abovementioned study (78) and also in a later one (79), hydroxy naphthoates and substituted salicylates were examined as ligands in an aqueous system with prednisolone as a substrate. The substituted naphthoates, especially, showed very good interactions with prednisolone. The only problem again with this system was that of a higher pH than was desired. Since the hydroxy naphthoates showed good interactions with prednisolone, it was desired to modify the ligand molecule to give a lower pH, yet retain its ability to interact with prednisolone. This was done successfully by changing the carboxylic acid group to a sulfonic acid

Table 1

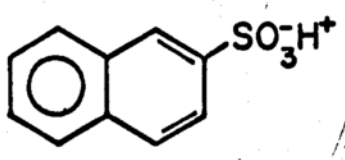
Compounds Checked for Ability to Complex with Prednisolone

Compound	Ligand effect
2,4-Dinitrobenzene sulfonic acid	$K_{11} \approx 10$
3,5-Dinitrobenzoic acid, sodium salt	$K_{11} \approx 10$
Tropaeolin O 	very slight
Sulfosalicylic acid 	very slight
Disodium EDTA	no effect
Nicotinic acid	no effect

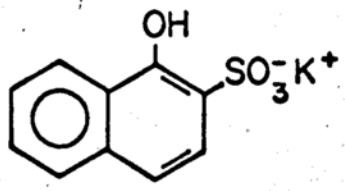
group. The compounds used as ligands are given in Figure 1. The numbers appearing in parentheses are the apparent 1:1 complex stability constants for that particular compound and prednisolone.

The graphs of total prednisolone solubility vs. ligand added are given in Figures 2-10. By examining Figures 2, 3 and 6, it is evident that there is positive curvature present. This is an indication that there are complexes present which are to some extent multiple in ligand (74). This was also found to be the case in some instances with similar compounds in previous work (78,79). The remainder of the graphs show a good linear relationship indicating that an apparent 1:1 complex exists.

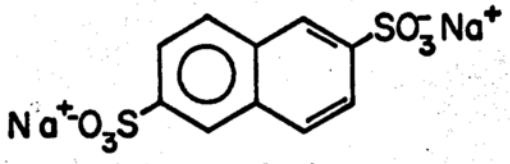
By comparing structures I-VIII and their corresponding $K_{1:1}$ values, it is evident that the maximum K values are obtained when two hydroxyl groups are present with the exception of compound II. In general, however, it is difficult to correlate an increase or decrease in ability to complex with an addition or subtraction of either a hydroxyl or sulfonic acid group. This fact, along with the following consideration, would tend to indicate that hydrogen bonding does not play a role in the complex interaction. Since the formation of prednisolone esters, such as the acetate with the 21 hydroxy group, results in a compound with a much lower



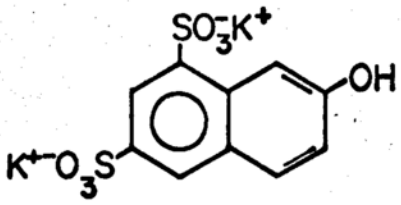
I (22)



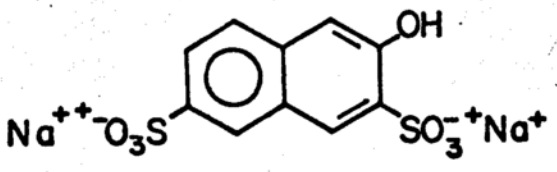
II (28)



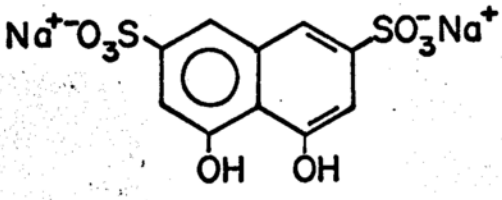
III (14)



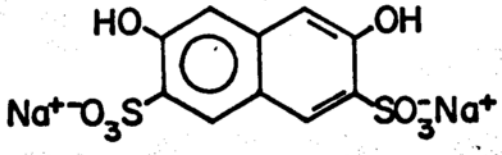
IV (13)



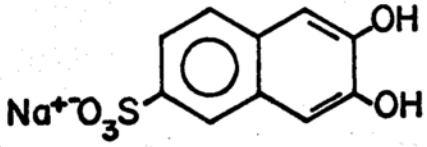
V (21)



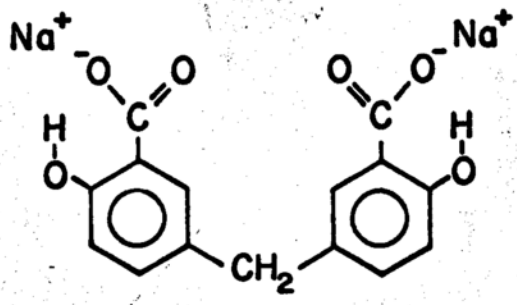
VI (29)



VII (26)



VIII (30)

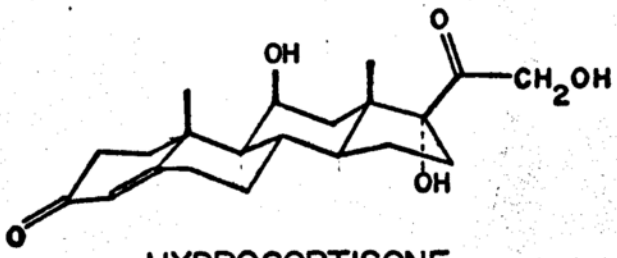


IX (63)

LIGANDS

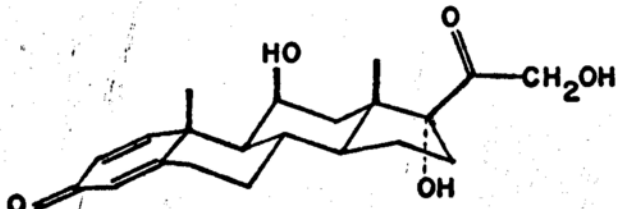
Fig. 1

SUBSTRATES



HYDROCORTISONE

X



PREDNISOLONE

XI

Figure 1, cont.

I	2-Naphthalene sulfonic acid
II	1-Naphthol-2-sulfonic acid, potassium salt
III	2,6-Naphthalene disulfonic acid, disodium salt
IV	2-Naphthol-6,8-disulfonic acid, dipotassium salt
V	2-Naphthol-3,6-disulfonic acid, disodium salt
VI	4,5-Dihydroxynaphthalene-2,7-disulfonic acid, disodium salt
VII	2,7-Dihydroxynaphthalene-3,6-disulfonic acid, disodium salt
VIII	2,3-Dihydroxynaphthalene-6-sulfonic acid, sodium salt
IX	5,5'-Methylenedisalicylic acid, disodium salt
X	Hydrocortisone
XI	Prednisolone

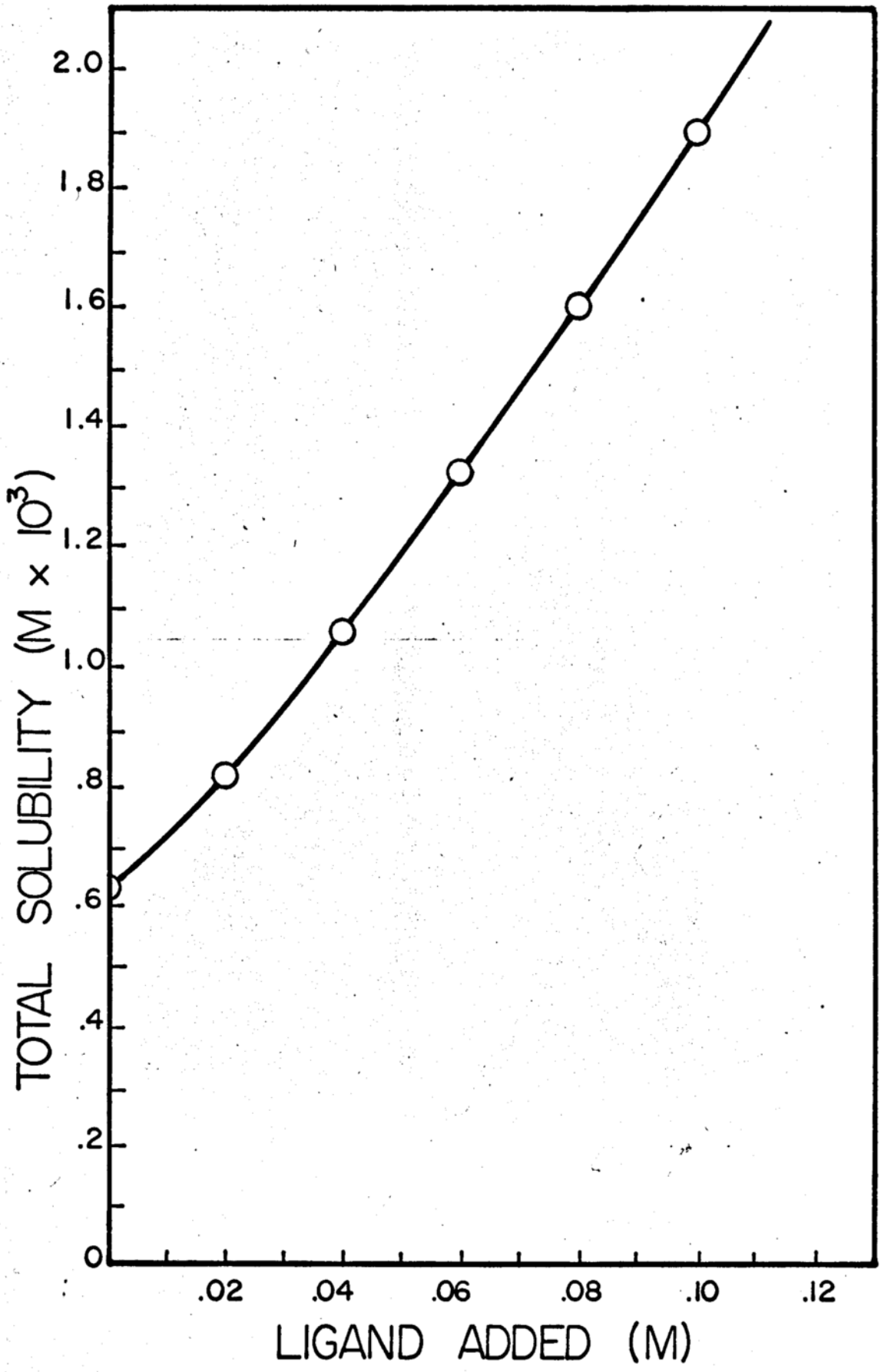


Fig. 2. Effect of the ligand, 2-naphthalene sulfonic acid, on the total solubility of hydrous prednisolone.

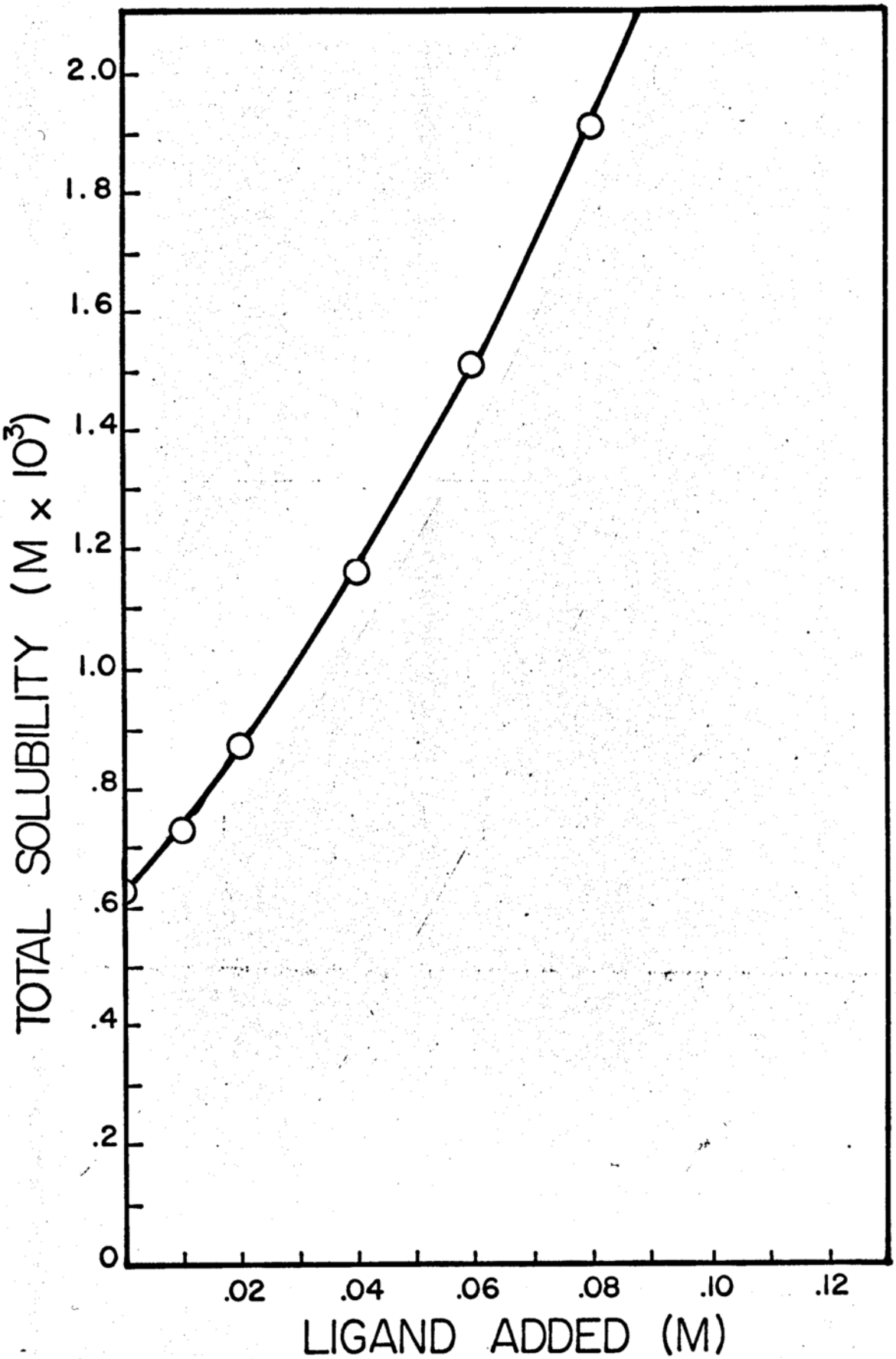


Fig. 3. Effect of the ligand, 1-naphthol-2-sulfonic acid, potassium salt, on the total solubility of hydrous prednisolone.

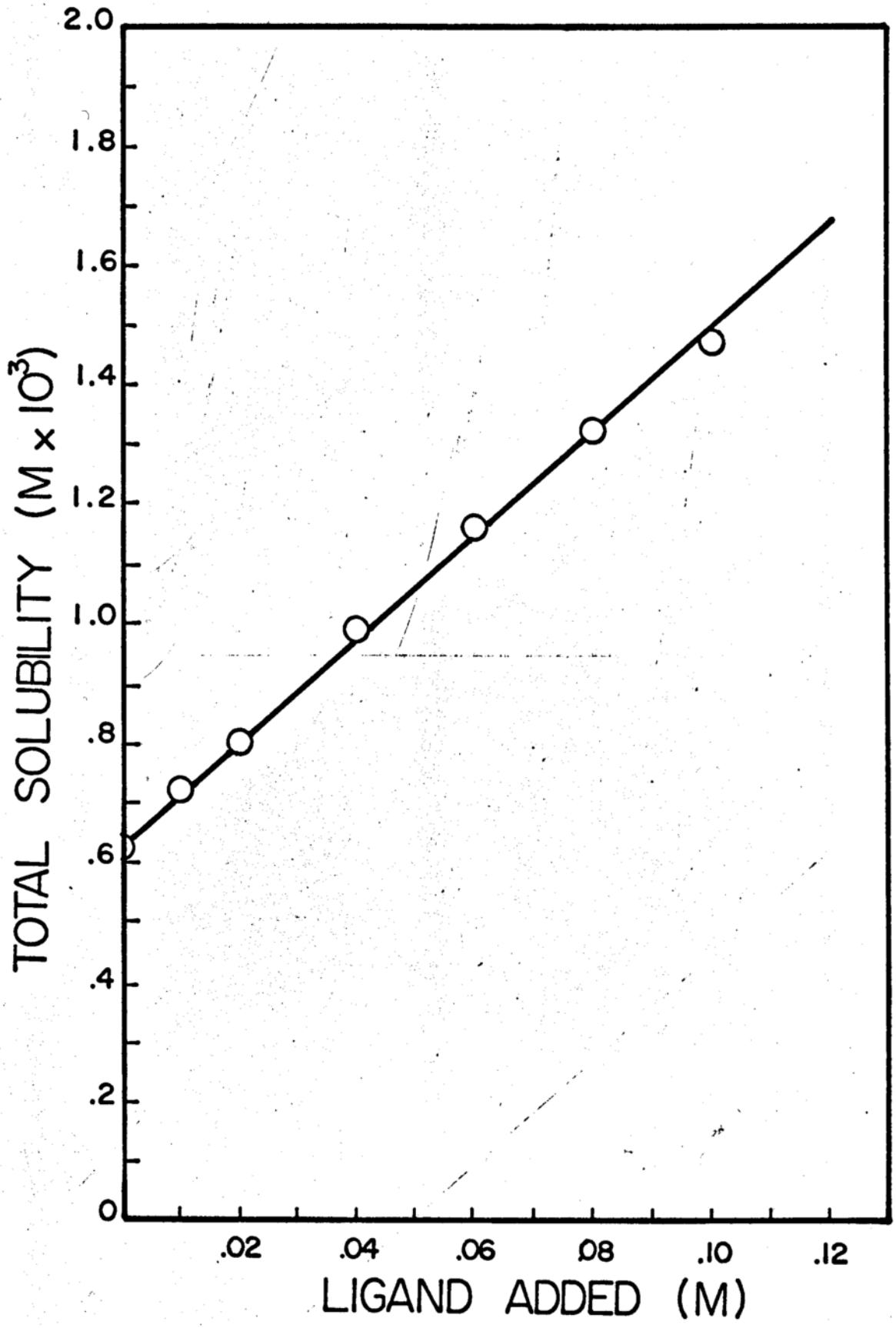


Fig. 4. Effect of the ligand, 2,6-naphthalene disulfonic acid, disodium salt, on the total solubility of hydrous prednisolone.

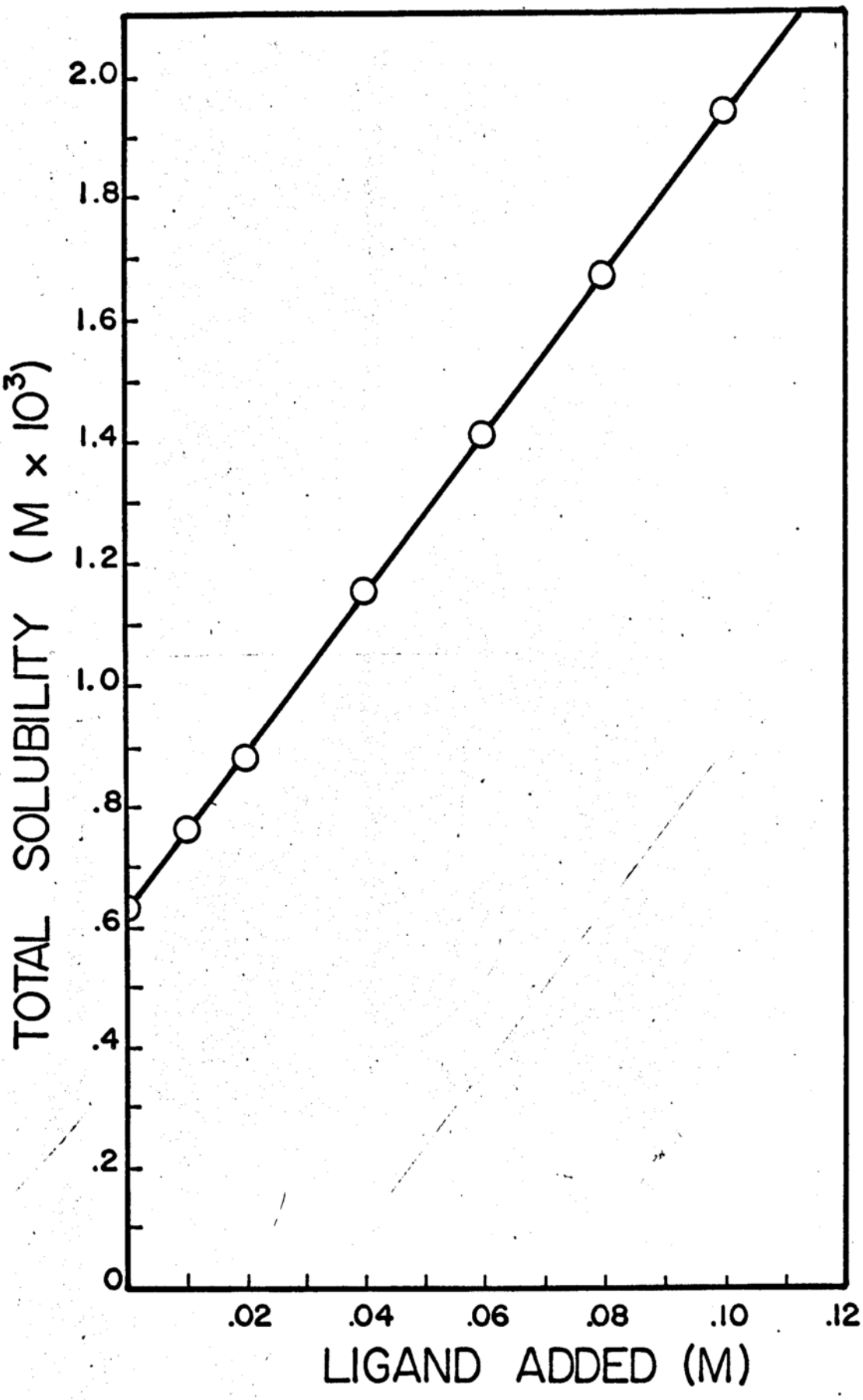


Fig. 5. Effect of the ligand, 2-naphthol 3,6-disulfonic acid, disodium salt, on the total solubility of hydrous prednisolone.

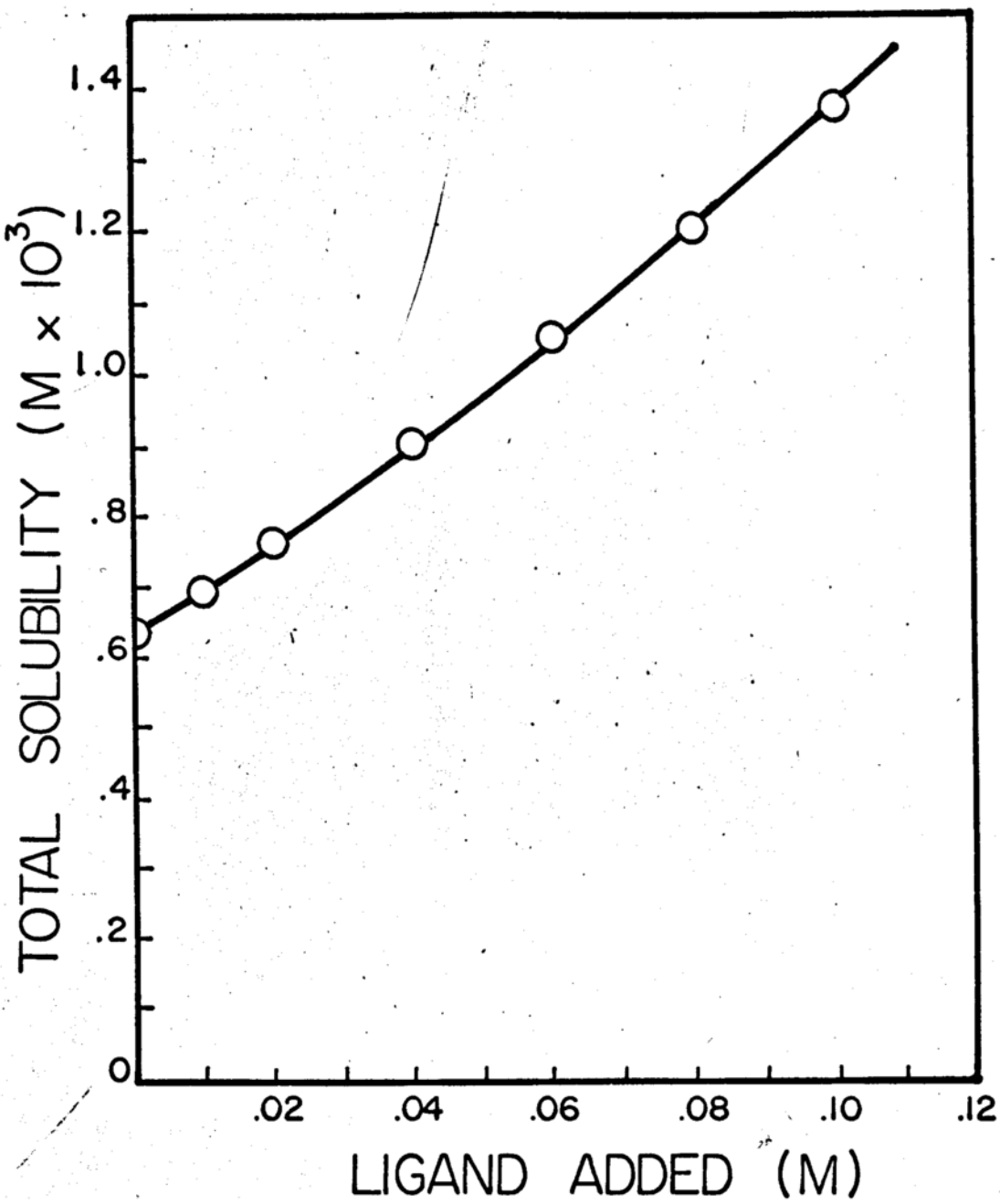


Fig. 6. Effect of the ligand, 2-naphthol 6,8-disulfonic acid, dipotassium salt, on the total solubility of hydrous prednisolone.

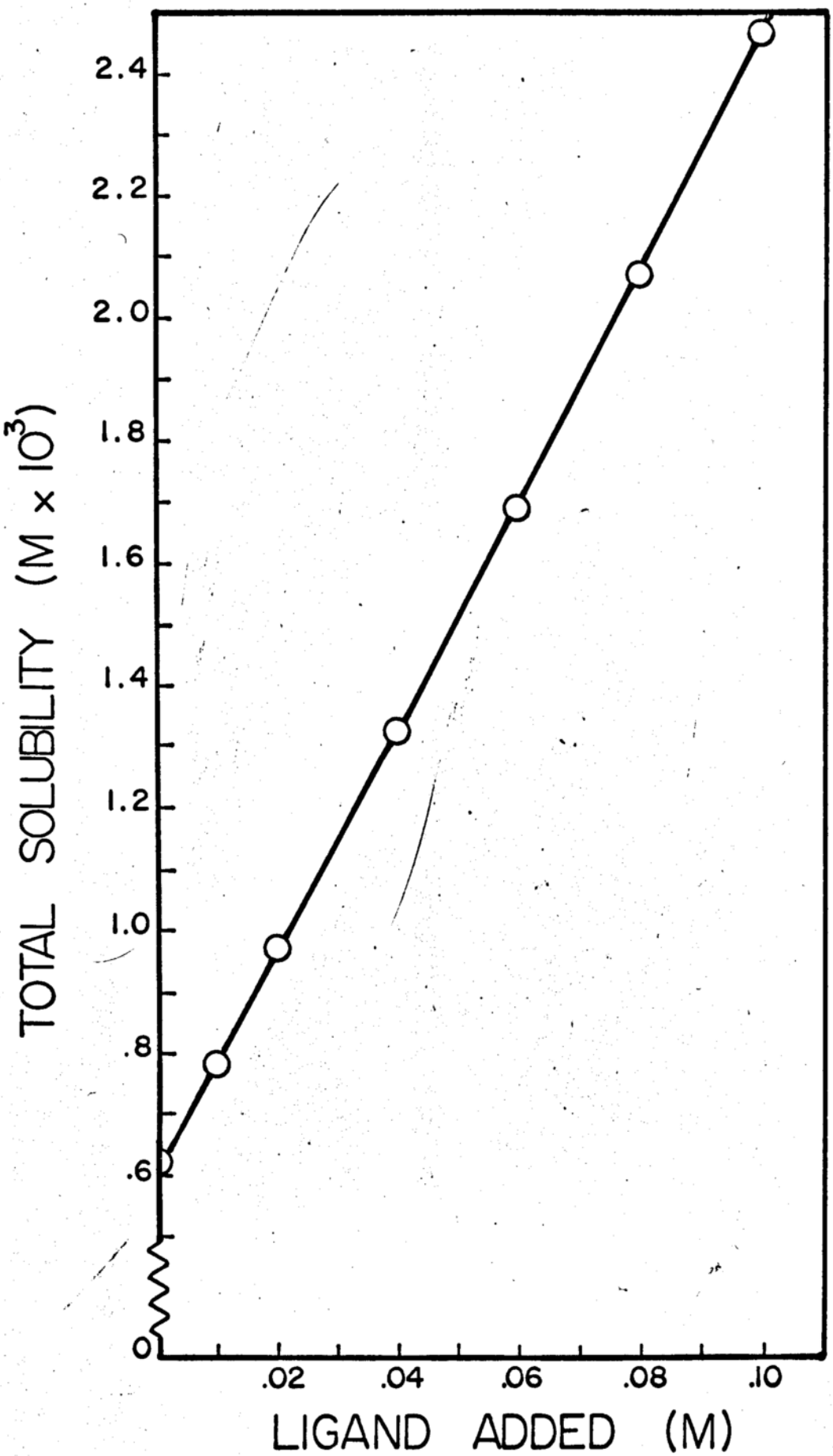


Fig. 7. The effect of the ligand, 4,5-dihydroxy naphthalene 2,7-disulfonic acid, disodium salt, on the total solubility of hydrous prednisolone.

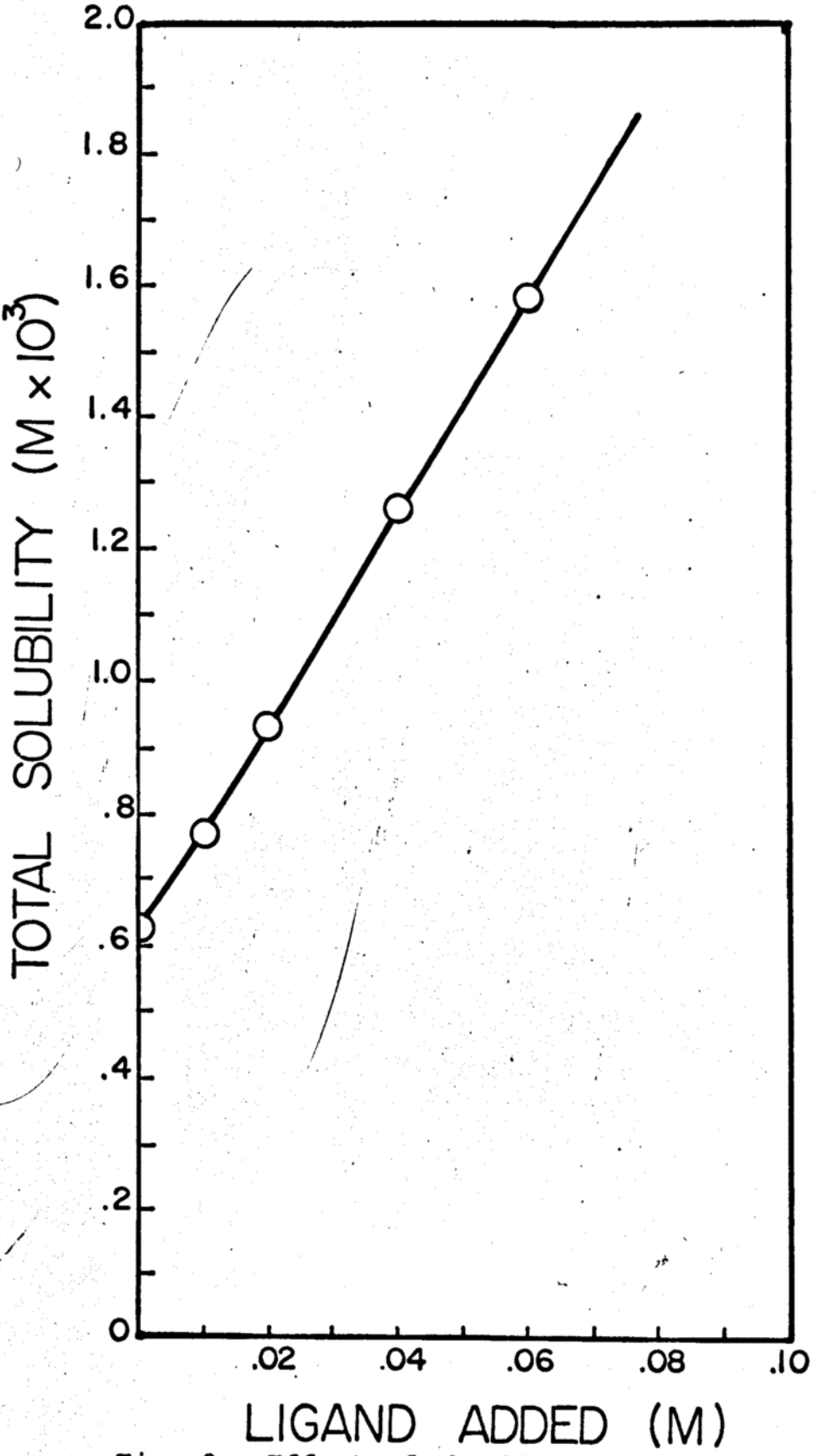


Fig. 8. Effect of the ligand, 2,7-dihydroxy-naphthalene 3,6-disulfonic acid, disodium salt, on the total solubility of hydrous prednisolone.

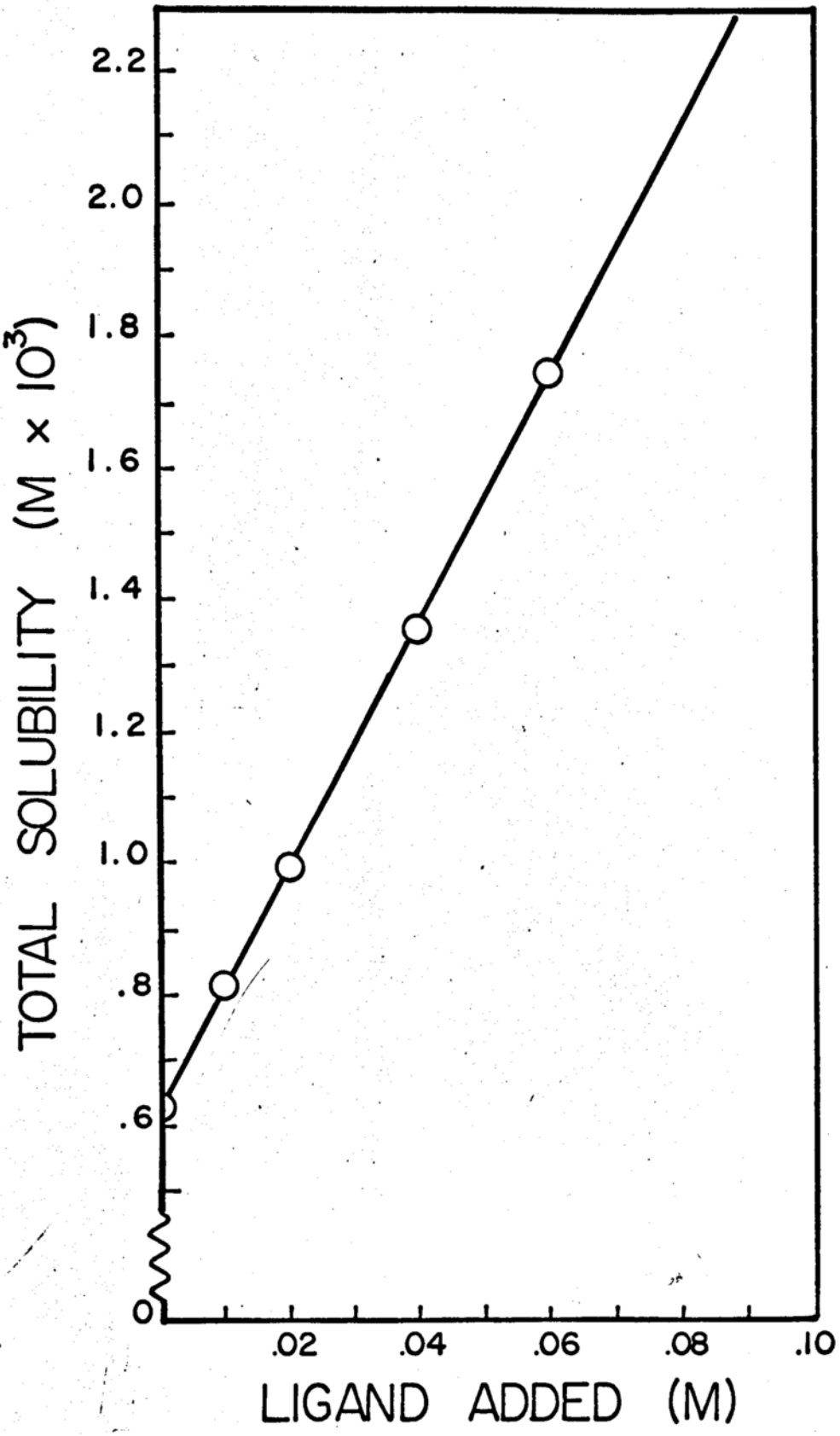


Fig. 9. Effect of the ligand, 2,3-dihydroxy-naphthalene 6-sulfonic acid, sodium salt, on the total solubility of hydrous prednisolone.

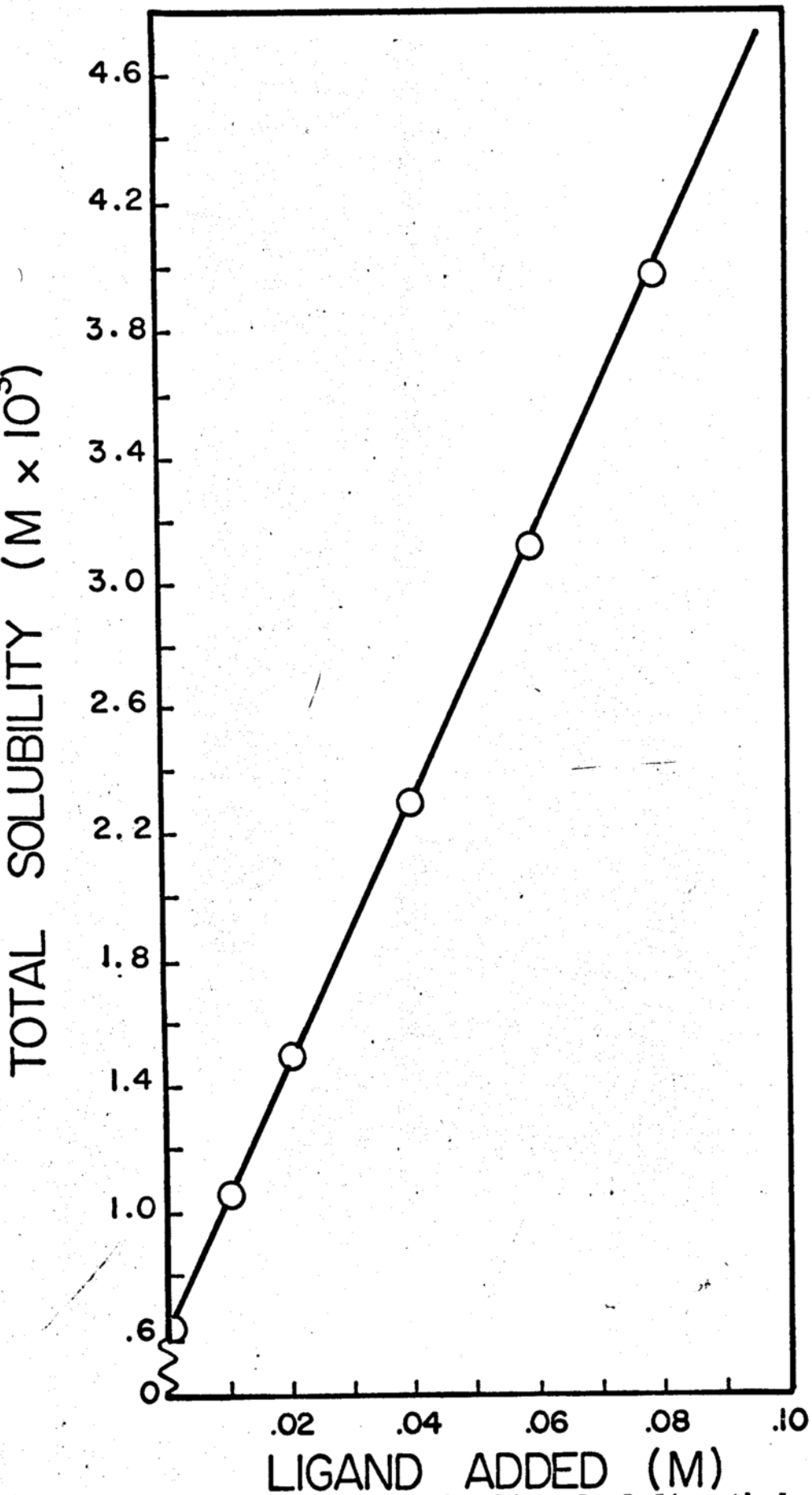


Fig. 10. Effect of the ligand, 5,5'-methylene-disalicylic acid, disodium salt, on the total solubility of hydrous prednisolone.

solubility, it would then appear that any hydrogen bonding occurring at this end of the prednisolone molecule with ligands used in the present study would result in a complex with lower rather than an increased solubility.

In examining the prednisolone molecule further for a possible site of the complex interaction, it is noted that the unsaturated A ring is flat. If the assumption is made that a strong complex interaction occurs between the Pi system of the A ring and the Pi system of the naphthalene molecule, then the saturation of one of the double bonds in the A ring should produce a marked drop in the complex formation which could be noted in the value of the resulting $K_{1:1}$ for such a system. This situation was carried out using hydrocortisone and ligand VIII with the resulting solubility plot given in Figure 11. The resulting $K_{1:1}$ of 35 indicates that the unsaturated system and flatness of the A ring is not essential for complexation to occur. At the same time, however, this does not mean that there is no interaction involving the A ring.

In examining the structures (XI and X) of prednisolone and hydrocortisone, one of the common features of both molecules is the relatively flat hydrophobic alpha surface. It can be postulated then that the interaction between the steroids and the

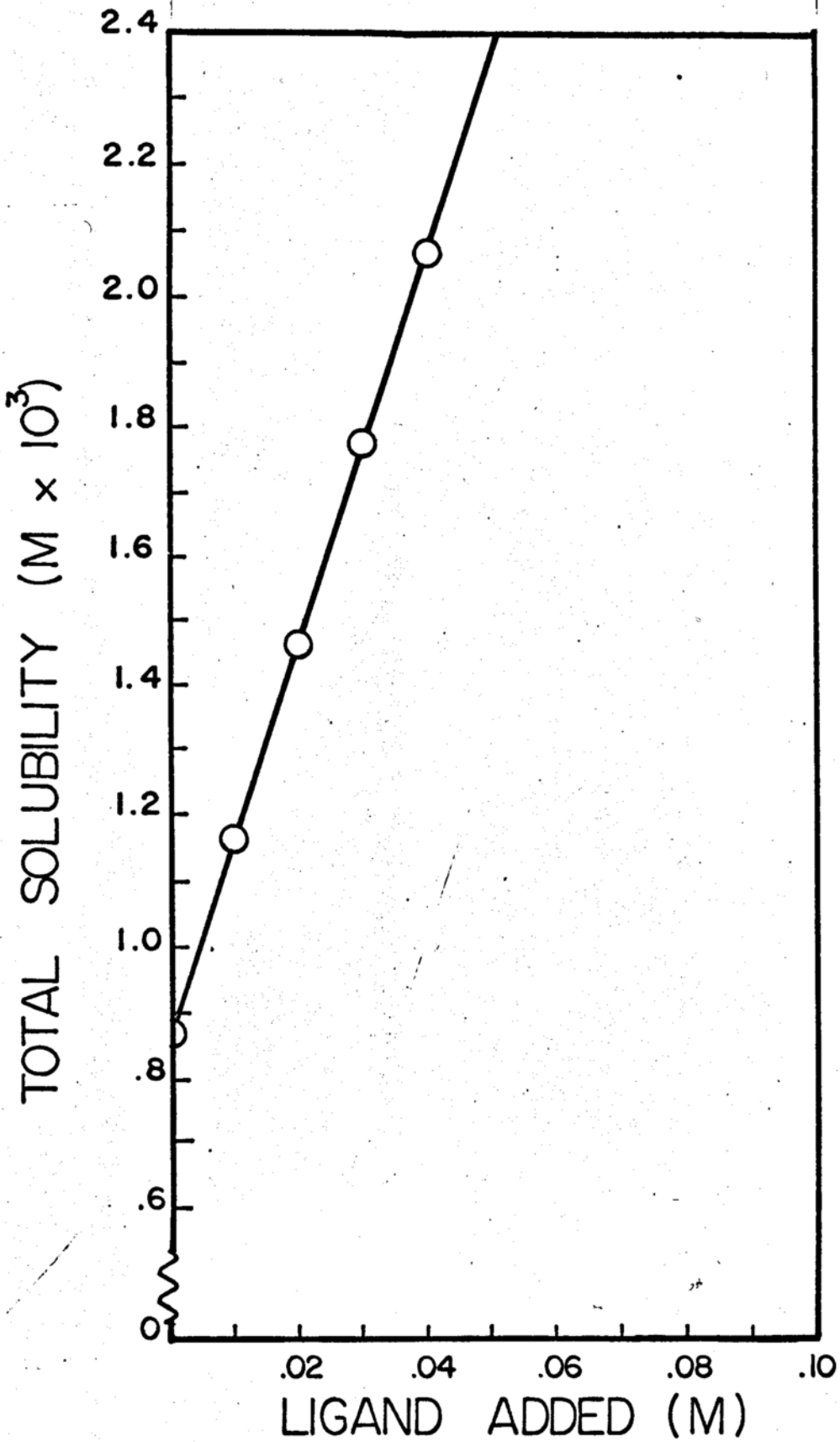


Fig. 11. Effect of the ligand, 2,3-dihydroxy-naphthalene 6-sulfonic acid, sodium salt, on the total solubility of hydrocortisone.

naphthalene ligands involves the hydrophobic surfaces of each molecule. A similar postulation was set forth previously (79) for the hydroxy naphthoate system.

The ligand IX was used previously (79) and gave a resulting $K_{1:1}$ of 62 with prednisolone as the substrate. A solubility study of ligand IX with prednisolone was carried out in conjunction with the present work and is given in Figure 10. The difference in experimental procedure was that the present experiment was carried out at a lower pH. This did not have any effect on the complex formation since the resulting $K_{1:1}$ was 63, approximately twice that obtained with the naphthalene-derivative ligands.

In order to correlate the $K_{1:1}$ value of ligand IX with those of the remaining ligands, the structures of all ligands must be examined. Ligand IX contains two salicylic acid molecules, each of which appears to act like one naphthalene-derivative ligand. It is possible then, that ligand IX forms a 1:2, ligand:substrate, complex. Alternatively, since it was postulated that the complex formation is a hydrophobic interaction, it may be that the probability of a complex interaction is dependent on the amount of hydrophobic surface available. In the case of ligand IX, since it has approximately twice the available hydrophobic surface of a naphthalene-derivative ligand, the probability for a

complex interaction to occur would be twice as great, which would account for $K_{1:1}$ being twice as large.

Dissolution Studies in the Presence of Complexing Agents

The dissolution rates of prednisolone in the presence of various ligands were determined as described under "Plan of Study" from the "Cube root" plots (72) given in Figures 12-16. The linearity of these plots indicates that the shape-volume factor is constant and does not affect the dissolution rate. The resulting rates, along with the data corresponding to these graphs, can be found in the Appendix, Tables 18-22.

In recent work (56,57) dealing with dissolution in the presence of micellular concentrations of surfactants, the experimental results best fit the diffusion layer theory. This model was originally discussed by Nernst (9) and recently modified (63) for the dissolution of a pure solid in a stirred medium containing a colloidal solubilizing agent. In this system the following assumptions are made: 1) equilibrium exists between the solid and the solution at the solid-solution interface; 2) the rate, therefore, is controlled by the diffusion of the free and solubilized solute across an effectively stagnant liquid diffusion layer of thickness, h; 3) equilibrium exists at every point in the diffusion

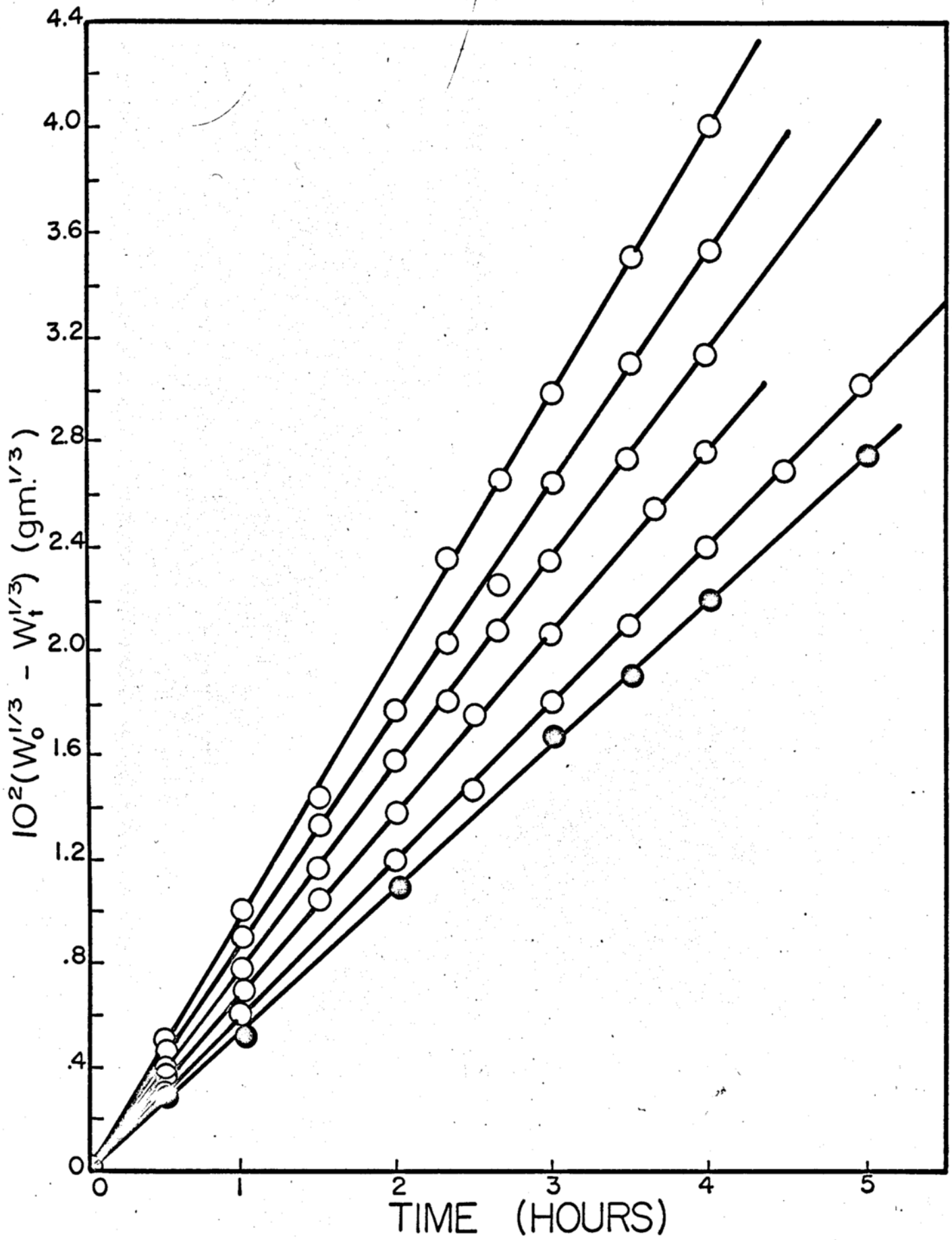


Fig. 12. Hixson-Crowell Plot. ◎ Dissolution in distilled water. ○ Dissolution in 2-naphthalene sulfonic acid solutions of increasing concentrations, .01, .02, .03, .04, and .05 molar.

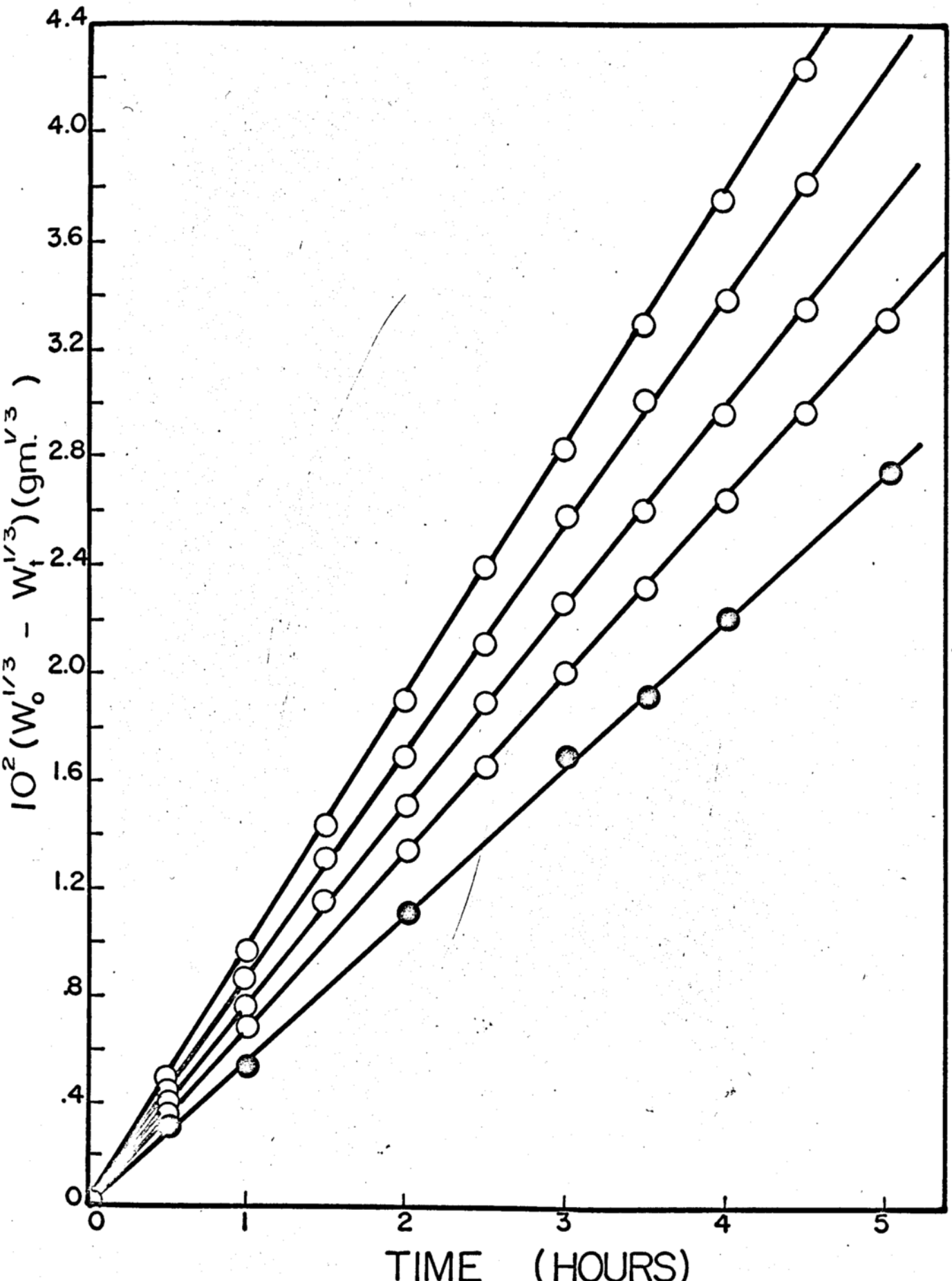


Fig. 13. Hixson-Crowell Plot. ○ Dissolution in distilled water. ○ Dissolution in 2-naphthol 3,6-disulfonic acid, disodium salt solutions of increasing concentrations, .01,.02,.03, and .04 molar.

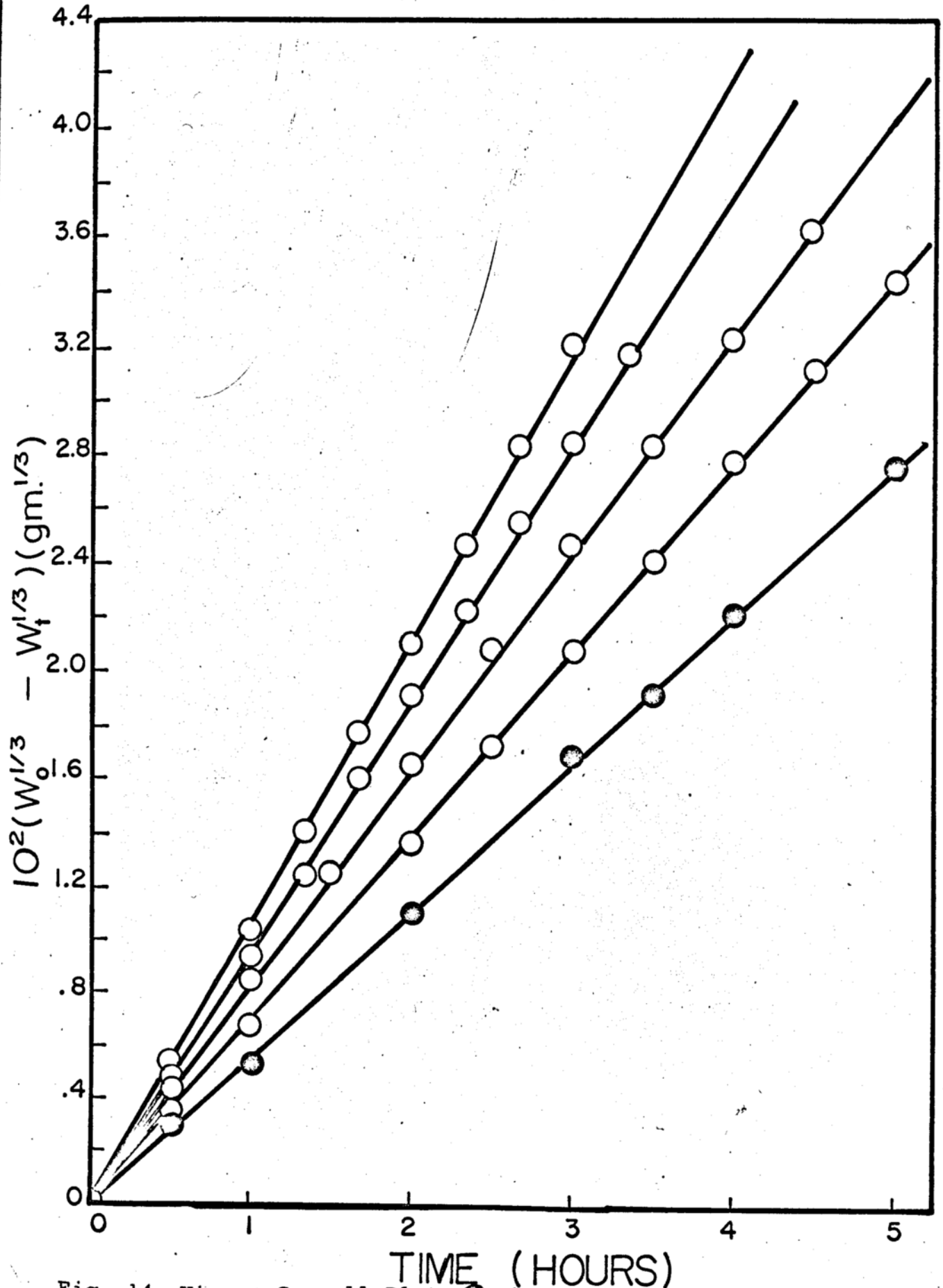


Fig. 14. Hixson-Crowell Plot. ○ Dissolution in distilled water. ○ Dissolution in 4,5-dihydroxynaphthalene 2,7-disulfonic acid, disodium salt solutions, of increasing concentrations, .01, .02, .03, and .04 molar.

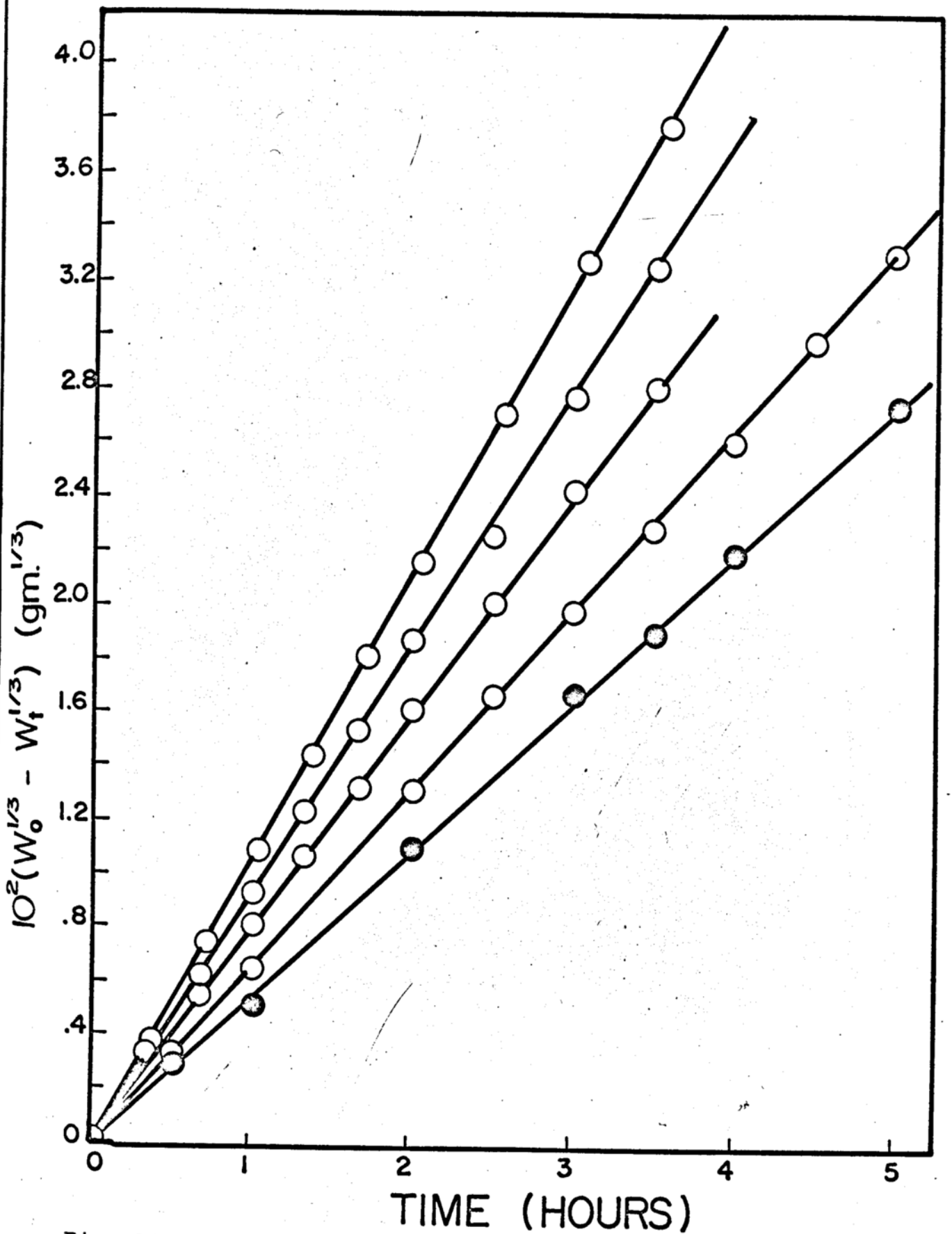
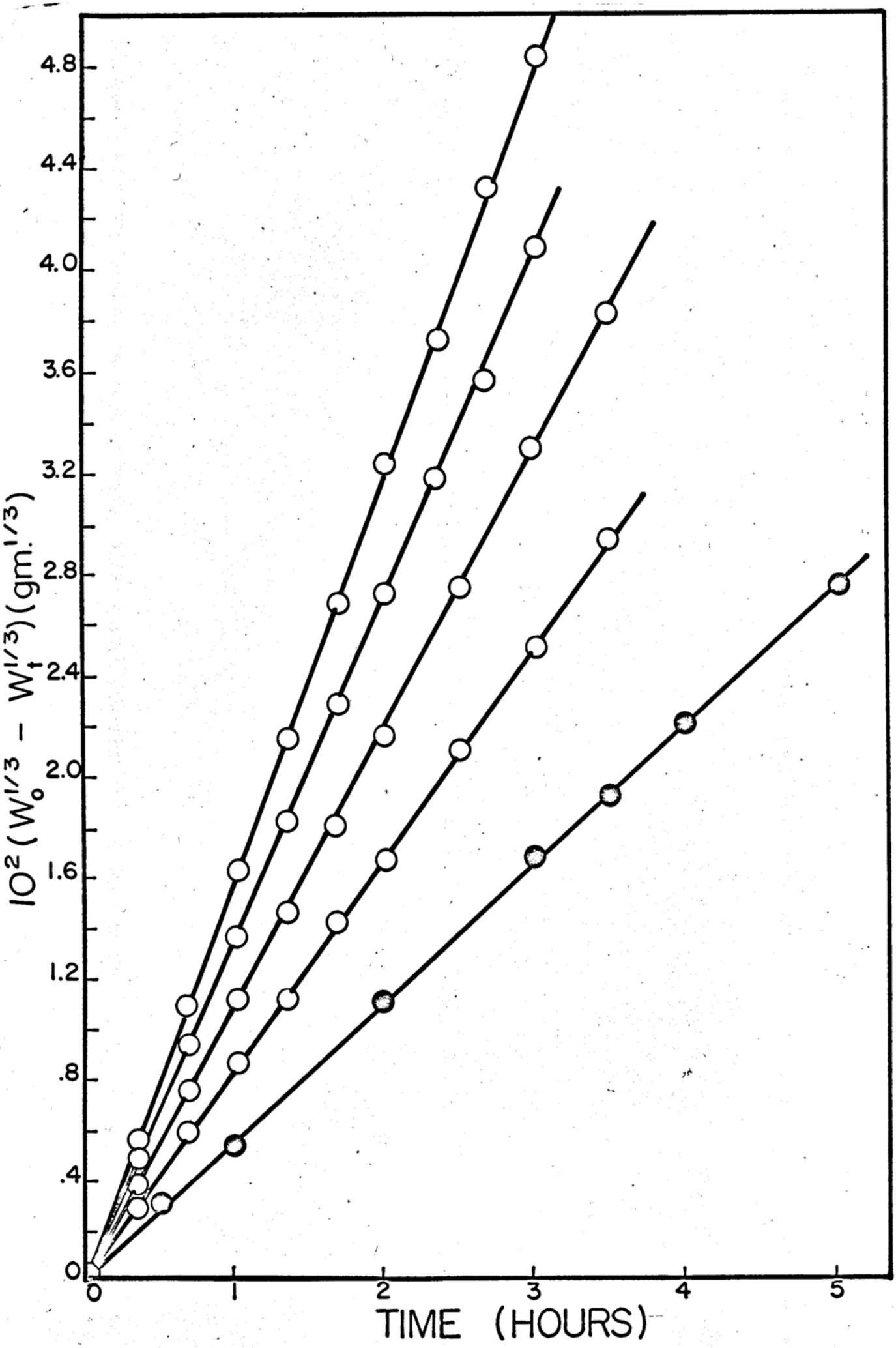


Fig. 15. Hixson-Crowell Plot. ◎ Dissolution in distilled water. ○ Dissolution in 2,3-dihydroxynaphthalene 6-sulfonic acid, sodium salt solutions of increasing concentrations, .01, .02, .03, and .04 molar.


4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
1.2
.8
.4
0
$10^2 (W_o^{1/3} - W_t^{1/3})$ (gm.$^{1/3}$)
0
1
2
3
4
5
TIME (HOURS)

layer between the free and solubilized solute. The equation resulting from these assumptions is the following:

$$G = \frac{1}{h}(D_o C_o + \sum_i D_i C_i) \qquad \text{(Eq. 1)}$$

Here G is the initial dissolution rate per cm^2 for the solid in the medium containing the solubilizing agent, D_o is the diffusion coefficient of the free solute molecule in solution, C_o is the equilibrium solubility of solute in the pure solvent, D_i is the diffusion coefficient for species, i, and C_i is the increase in solubility due to species i. This equation reduces to

$$G = \frac{1}{h}(D_o C_o + D_x C_x) \qquad \text{(Eq. 2)}$$

when the solubilization involves only a single species, x. Such would be the case if the solubilizing agent was a complexing agent that formed an apparent 1:1 complex with the solute. Since this was apparently the situation in the present study, the dissolution-solubility data was treated according to equation 2, the modified diffusion layer theory. The resulting graphs of G vs. C_x are given in Figures 17-21 with the corresponding data given in Tables 2-6. The data fit equation 2 very well over a solubility range of twice to almost four times the normal solubility of prednisolone. The diffusion coefficient of prednisolone in pure solvent (D_o) was

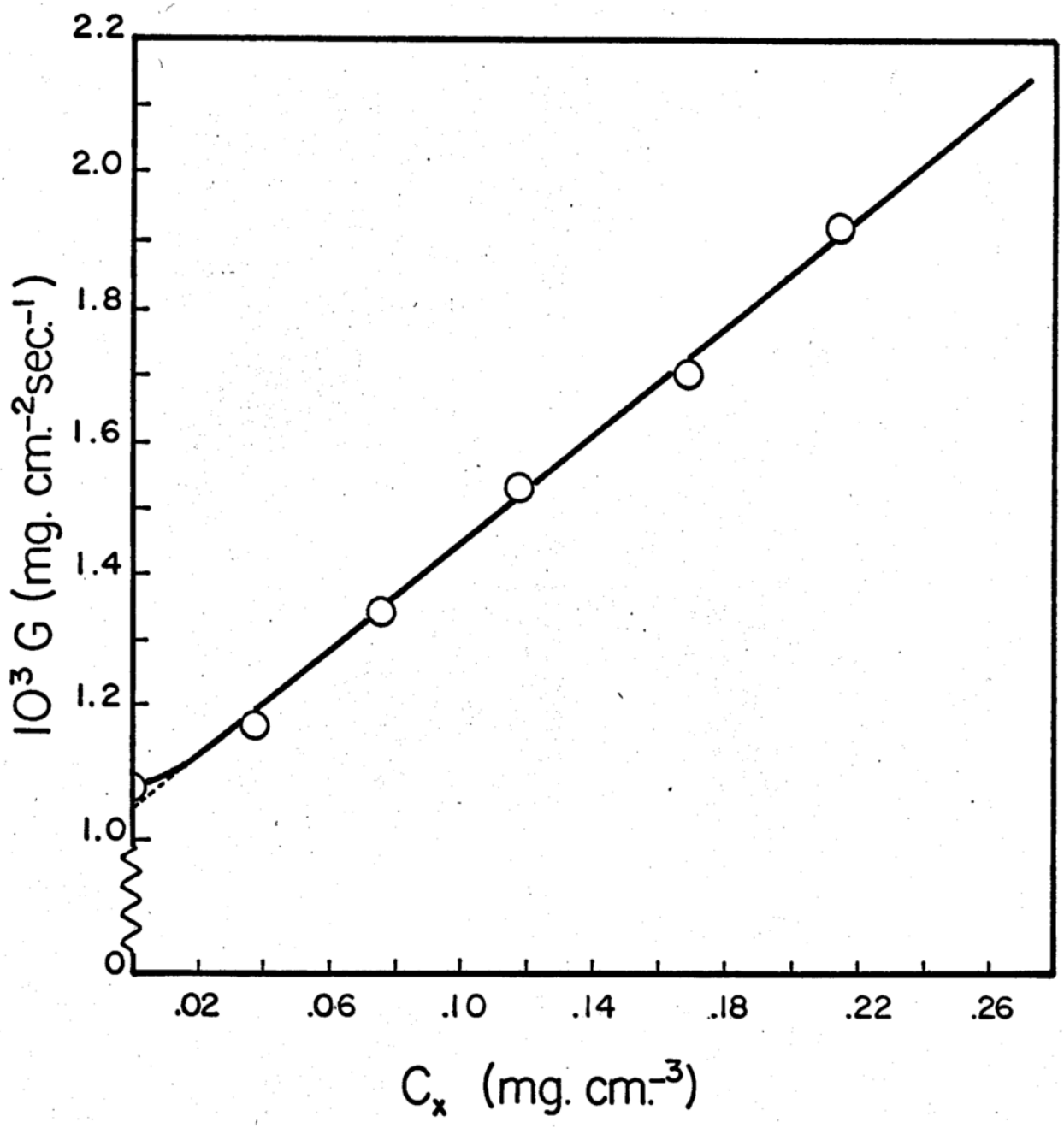


Fig. 17. At various concentrations of 2-naphthalene sulfonic acid, the dissolution rate vs. the increase in concentration of prednisolone.

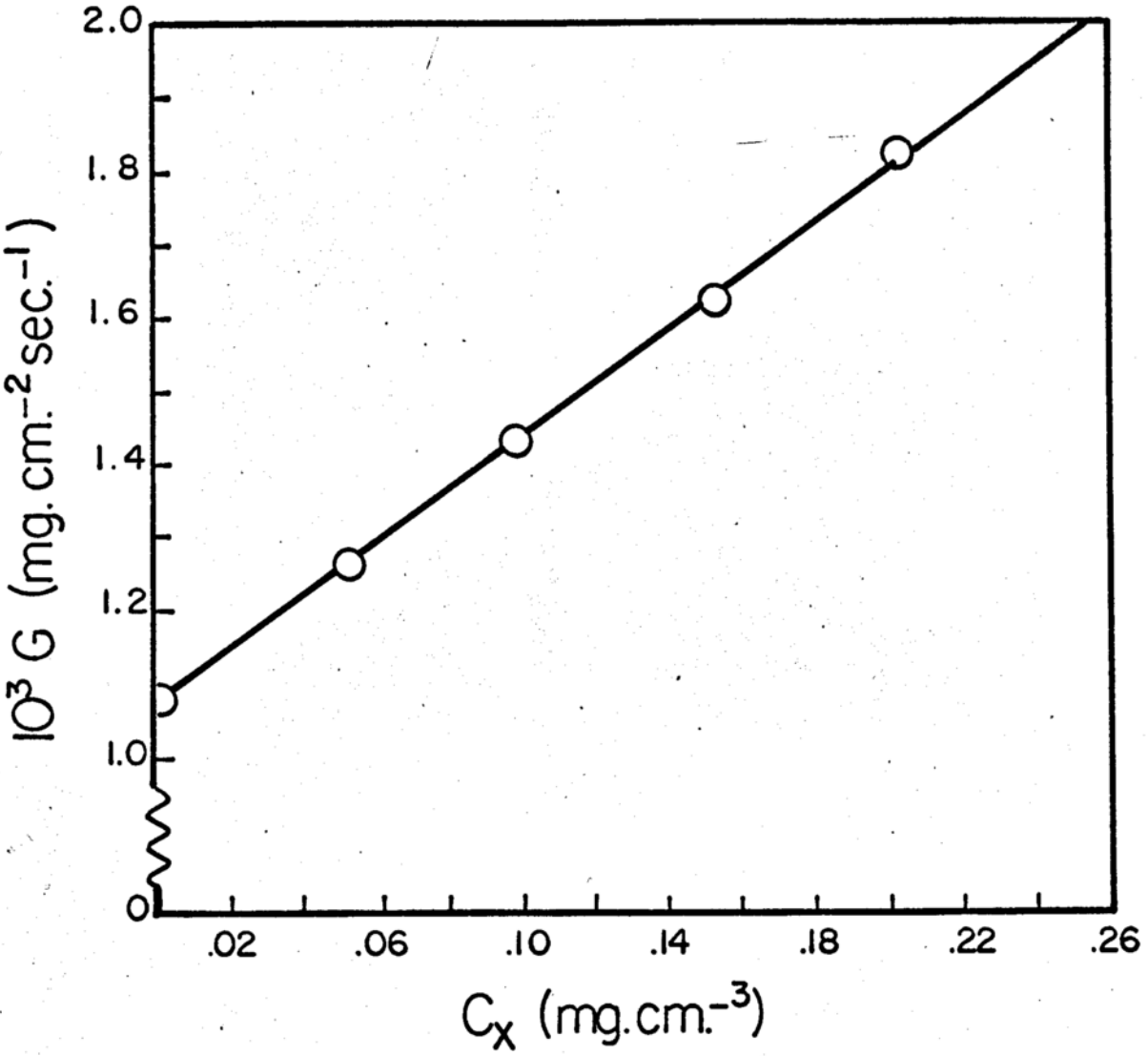


Fig. 18. At various concentrations of 2-naphthol-3, 6-disulfonic acid, disodium salt, the dissolution rate vs. the increase in concentration of prednisolone.

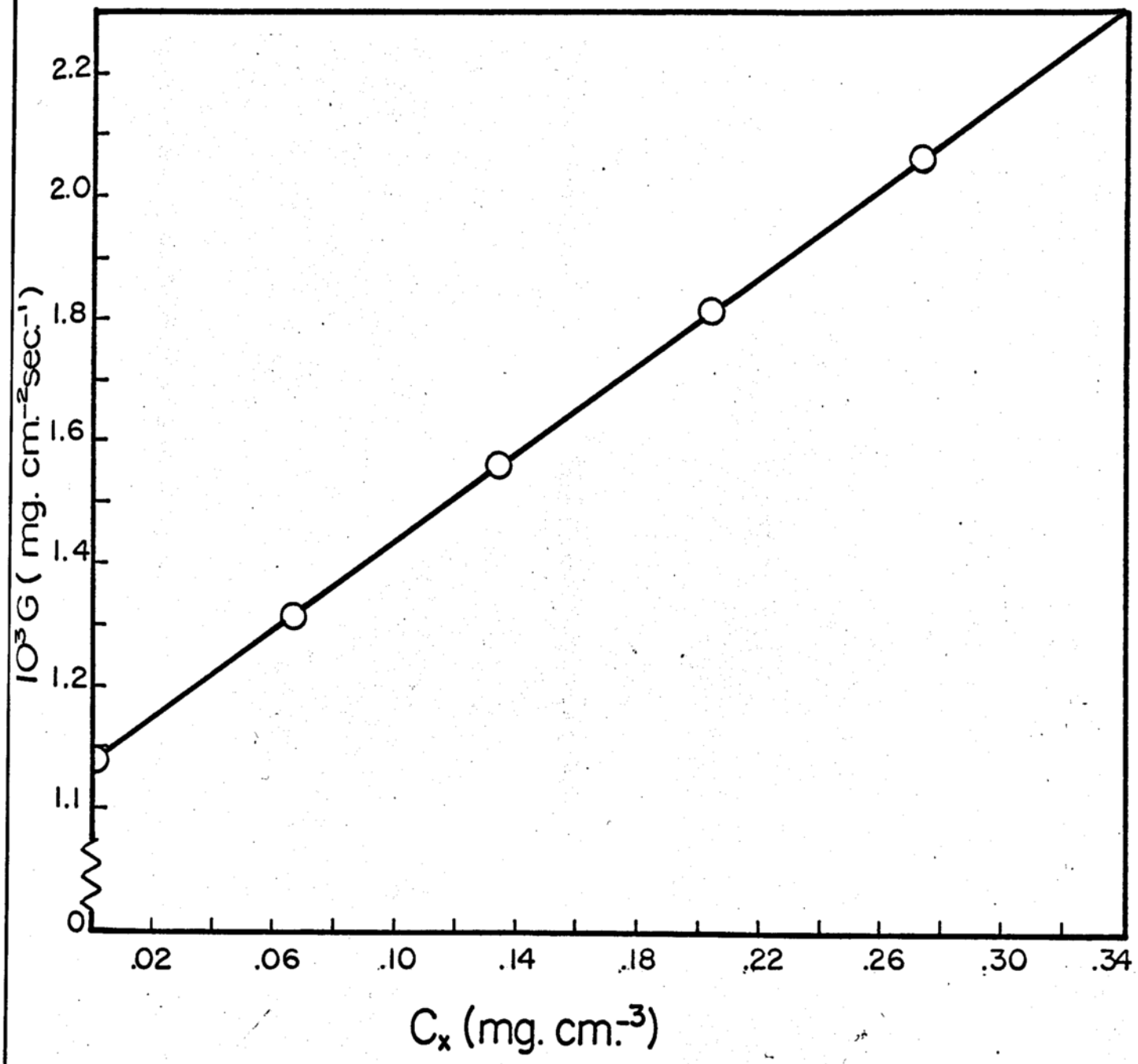


Fig. 19. At various concentrations of 4,5-dihydroxynaphthalene-2,7-disulfonic acid, disodium salt, the dissolution rate vs. the increase in concentration of prednisolone.

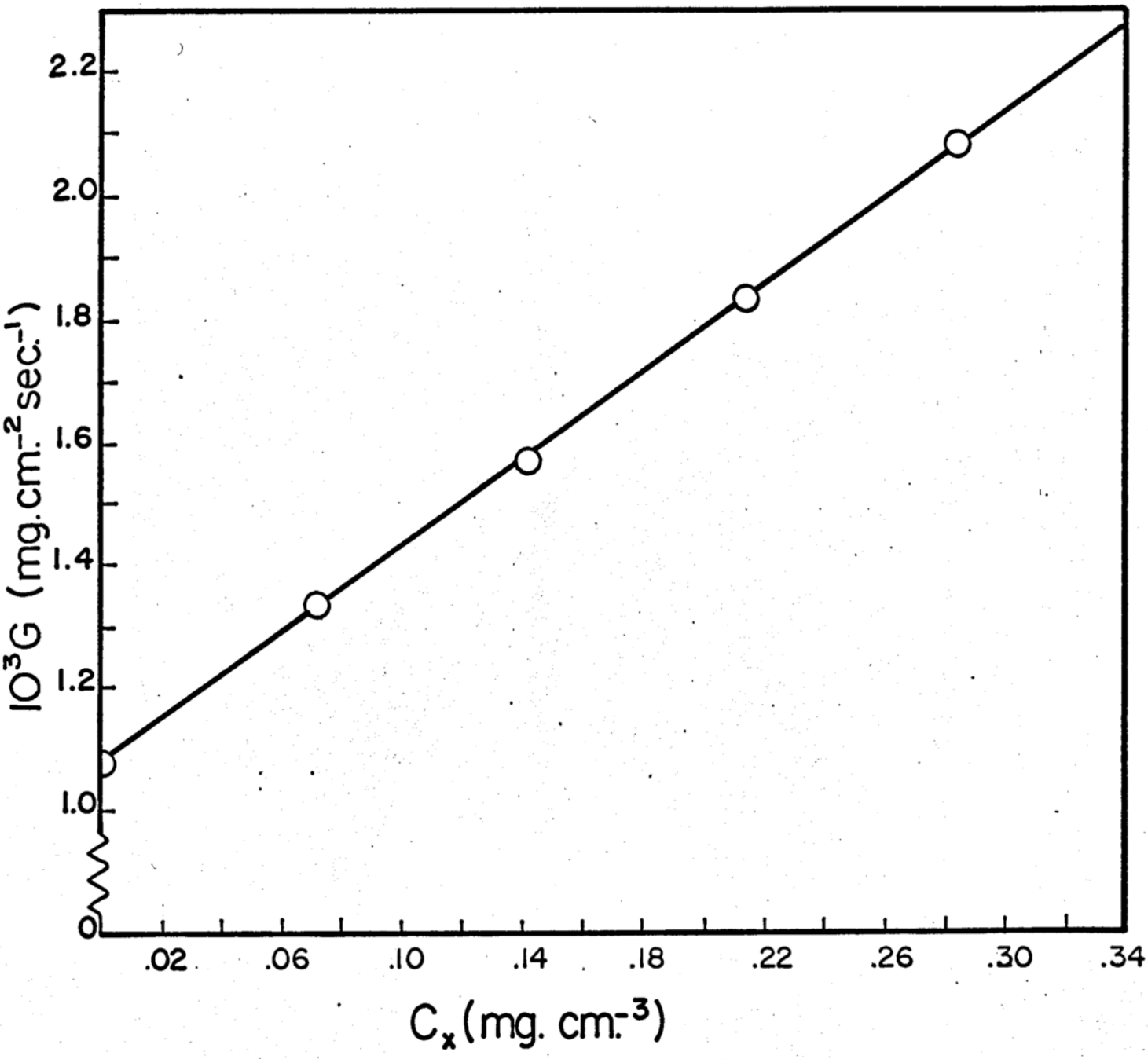


Fig. 20. At various concentrations of 2,3-dihydroxynaphthalene-6-sulfonic acid, sodium salt, the dissolution rate vs. the increase in concentration of prednisolone.

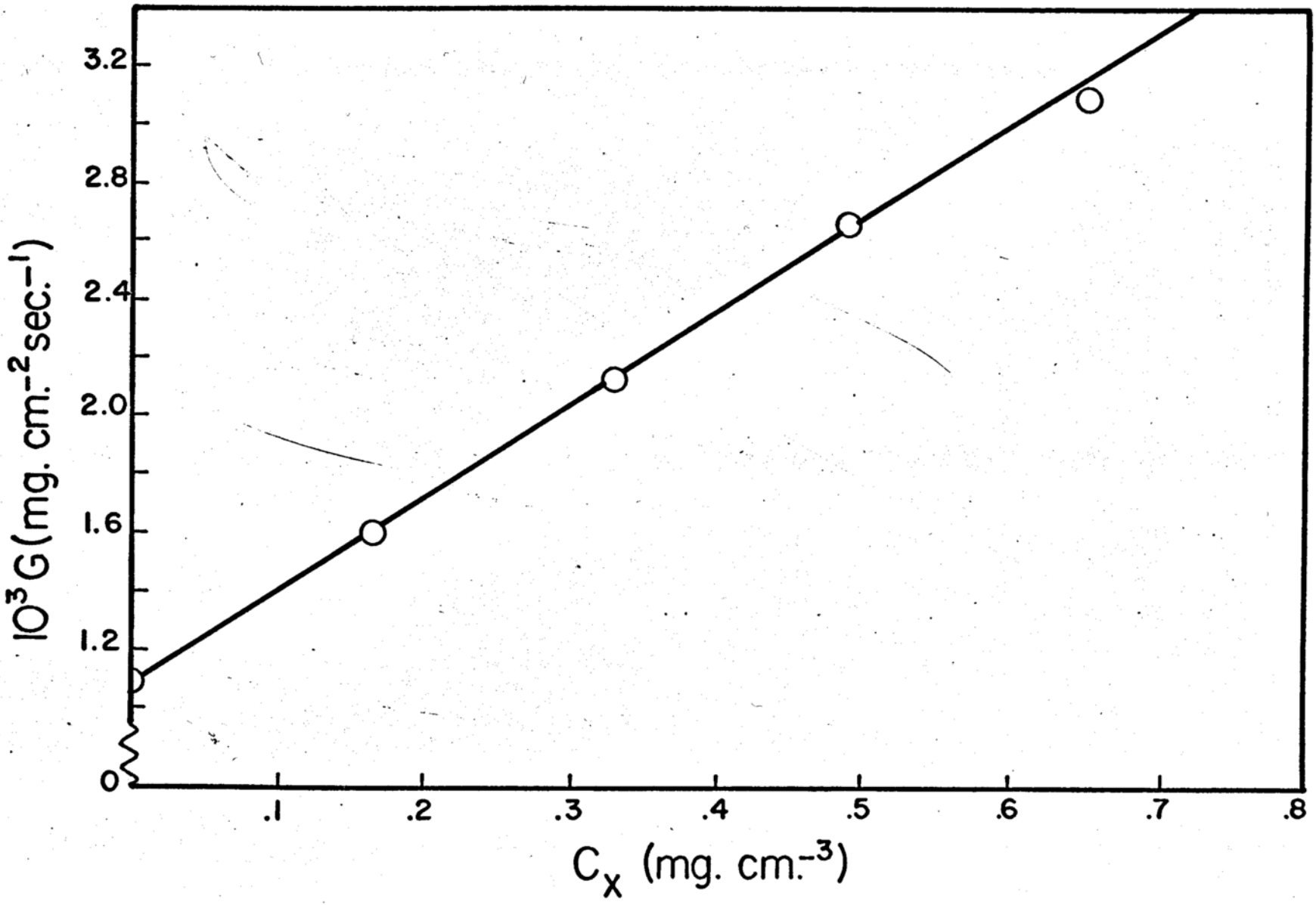


Fig. 21. At various concentrations of 5,5'-methylenedisalicylic acid, disodium salt, the dissolution rate vs. the increase in concentration of prednisolone.

Table 2

Dissolution and Solubility Data from 2-Naphthalene Sulfonic Acid Experiments

Ligand added (M)	Dissolution rate (G) $(mg\ cm^{-2} sec^{-1}) \times 10^{3}$	Total solubility $C_t (mg\ cm^{-3})$	Change in solubility $C_x (mg\ cm^{-3})$
0	1.08	.242	0
.01	1.17	.279	.037
.02	1.34	.318	.076
.03	1.53	.360	.118
.04	1.70	.411	.169
.05	1.92	.457	.215

$D_x/D_o = .90$

$D_x = 5.2 \times 10^{-6}\ cm^2\ sec^{-1}$

$h = 1.3 \times 10^{-3}\ cm.$

Table 3

Dissolution and Solubility Data from
2-Naphthol-3,6-Disulfonic Acid,
Disodium Salt Experiments

Ligand added (M)	Dissolution rate (G) $(mg\ cm^{-2} sec^{-1}) \times 10^3$	Total solubility $C_t (mg\ cm^{-3})$	Change in solubility $C_x (mg\ cm^{-3})$
0	1.08	.242	0
.01	1.26	.295	.053
.02	1.43	.341	.099
.03	1.62	.395	.153
.04	1.82	.446	.203

$D_x/D_o = 0.81$

$D_x = 4.7 \times 10^{-6}\ cm^2 sec^{-1}$

$h = 1.3 \times 10^{-3}\ cm$

Table 4

Dissolution and Solubility Data from 4,5-Dihydroxy-naphthalene-2,7-disulfonic Acid, Disodium Salt Experiments

Ligand added (M)	Dissolution rate (G) $(mg\ cm^{-2} sec^{-1}) \times 10^3$	Total solubility $C_t (mg\ cm^{-3})$	Change in solubility $C_x (mg\ cm^{-3})$
0	1.08	.242	0
.01	1.31	.308	.066
.02	1.56	.376	.134
.03	1.81	.446	.204
.04	2.06	.516	.274

$D_x/D_o = 0.81$

$D_x = 4.7 \times 10^{-6}\ cm^2 sec^{-1}$

$h = 1.3 \times 10^{-3}$ cm.

Table 5

Dissolution and Solubility Data from 2,3-Dihydroxy-naphthalene-6-sulfonic Acid, Sodium Salt Experiments

Ligand added (M)	Dissolution rate (G) $(mg\ cm^{-2} sec^{-1}) \times 10^3$	Total solubility $C_t (mg\ cm^{-3})$	Change in solubility $C_x (mg\ cm^{-3})$
0	1.08	.242	0
.01	1.33	.314	.072
.02	1.57	.384	.142
.03	1.83	.457	.215
.04	2.08	.527	.285

$D_x/D_o = 0.78$

$D_x = 4.5 \times 10^{-6}\ cm^2 sec^{-1}$

$h = 1.3 \times 10^{-3}\ cm.$

Table 6

Dissolution and Solubility Data from 5,5'-Methylene-disalicylic Acid, Disodium Salt Experiments

Ligand added (M)	Dissolution rate (G) $(mg\ cm^{-2} sec^{-1}) \times 10^{3}$	Total solubility $C_t (mg\ cm^{-3})$	Change in solubility $C_x (mg\ cm^{-3})$
0	1.08	.242	0
.01	1.60	.407	.165
.02	2.13	.572	.330
.03	2.65	.731	.489
.04	3.08	.895	.653

$D_x/D_o = 0.72$

$D_x = 4.2 \times 10^{-6}\ cm^2 sec^{-1}$

$h = 1.3 \times 10^{-3}\ cm.$

equal to 5.8×10^{-6} $cm^2 sec^{-1}$ as calculated previously (84) from the Stokes-Einstein equation. This value appears acceptable since it is comparable to other diffusion coefficients used previously (56,57,89). Using this value for D_o plus the slope and intercept from the graphs, the values for D_x/D_o, D_x, and h were calculated and are given in Tables 2-6. The value for the diffusion layer thickness, h, was the same in all cases as expected, since the ordinate intercepts were all equal. The values of D_x/D_o, which are directly proportional to the slope, range from 0.72 to 0.90. The resulting values for D_x are approximately what would be predicted using the Stokes-Einstein equation where the diffusion coefficient is proportional to $(M)^{-1/3}$, with M the molecular weight of the diffusing species.

In previous work by Wurster and Taylor (5) the dissolution process of prednisolone was described by the following equation

$$G = \left(\frac{k_R k_D}{k_R + k_D}\right)(C_o - C) \qquad \text{(Eq. 3)}$$

where k_D equals D_o/h, k_R is the rate constant for the surface reaction, and C is the concentration in the bulk solution. Substituting for k_D, and since $C_o >> C$, C may be canceled, equation 3 becomes

$$G = \left(\frac{k_R D_o}{hk_R + D_o}\right) C_o \qquad \text{(Eq. 4)}$$

The results given previously (85) for hydrous prednisolone show that $hk_R >> D_o$ such that equation 4 reduces to the Noyes-Whitney equation.

$$G = \frac{D_o}{h} C_o \qquad \text{(Eq. 5)}$$

The resulting value for h in the present study equals 1.3×10^{-3} cm compared to 1.5×10^{-3} cm found earlier (84). The similarity in these two results would be expected as the result of the above equations.

To compare the data fit of the modified diffusion layer theory to that of the Noyes-Whitney (6) and Danckwerts' (64) theories, it is useful to use the relationships derived previously (56,57). The Noyes-Whitney relationship is given by

$$G = \frac{D_o}{h} C_o \qquad \text{(Eq. 6)}$$

If D_o and h remain constant during dissolution in a solution of ligand, then the ratio of the dissolution rate in complexing solution to that in pure solvent is

$$R = \frac{C_T}{C_o} \qquad \text{(Eq. 7)}$$

where C_T is total concentration of solute in solution.

Applying the same procedure to the modified diffusion layer theory (equation 2), the diffusion rate ratio is

$$R = \frac{D_o C_o + D_x C_x}{D_o C_o} \qquad \text{(Eq. 8)}$$

Then, by defining an effective diffusion coefficient, D_e,

$$D_e = \frac{D_o C_o + D_x C_x}{C_o + C_x} \qquad \text{(Eq. 9)}$$

Equation 8 becomes

$$R = \frac{D_e C_T}{D_o C_o} \qquad \text{(Eq. 10)}$$

Continuing this approach to Danckwerts' theory

$$G = S^{1/2}[(C_o + C_x)(D_o C_o + D_x C_x)]^{1/2} \qquad \text{(Eq. 11)}$$

where S is the mean rate of production of fresh surface, the diffusion rate ratio is

$$R = \frac{[(C_o + C_x)(D_o C_o + D_x C_x)]^{1/2}}{D_o^{1/2} C_o} \qquad \text{(Eq. 12)}$$

Then, with the substitution of D_e, equation 12 becomes

$$R = \left[\frac{D_e}{D_o}\right]^{1/2} \frac{C_T}{C_o} \qquad \text{(Eq. 13)}$$

Table 7

Theories	Ratio Rate Equations	
Noyes-Whitney	$R = \frac{C_T}{C_o}$	(Eq. 7)
Modified Diffusion Layer	$R = \frac{D_e\ C_T}{D_o\ C_o}$	(Eq. 10)
Danckwerts'	$R = [\frac{D_e}{D_o}]^{1/2}\ \frac{C_T}{C_o}$	(Eq. 13)
with D_e =	$\frac{D_oC_o + D_xC_x}{C_o + C_x}$	

Since the results of this study fit the modified diffusion layer theory, it will be readily apparent how the other theories deviate from this theory. By comparing the slopes from a graph of R vs. C_T in all three cases the deviations can be seen. Equating the slopes, in the order equation 7, 13, and 10, and multiplying by the common term gives the following result

$$1 = (\frac{D_e}{D_o})^{1/2} = \frac{D_e}{D_o} \qquad \text{(Eq. 14)}$$

It is obvious that the equality does not hold, but in order to find the order of the inequality, the value of D_e/D_o must be examined.

$$\frac{D_e}{D_o} = \frac{C_o + \left(\frac{D_x}{D_o}\right) C_x}{C_o + C_x} \qquad \text{(Eq. 15)}$$

Since D_x/D_o is less than one, the value of D_e/D_o is also less than one. Therefore, the square root of D_e/D_o is greater than D_e/D_o, but also less than one. So then the following relationship is established

$$1 > \left(\frac{D_e}{D_o}\right)^{1/2} > \frac{D_e}{D_o} \qquad \text{(Eq. 16)}$$

In summary, then, the Danckwerts' theory shows a positive deviation from the modified diffusion layer theory, but the Noyes-Whitney theory shows the largest positive deviation.

SUMMARY

The dissolution rate of the hydrous form of prednisolone has been studied as a function of a changing equilibrium solubility. The change in equilibrium solubility was accomplished by using various chemicals that formed a soluble complex with prednisolone.

The extent of complex formation, or the increase in the apparent saturation solubility, was determined by adding increasing amounts of a ligand to an excess of prednisolone in water. After equilibration, the suspension was filtered and the filtrate extracted with chloroform. An aliquot of the chloroform solution was dried and then a specific volume of ethanol added. An ultraviolet analysis was used to determine the concentration of prednisolone present. The extraction procedure was necessary since the ligands present interfered with the spectrophotometric analysis.

The pH of these solutions and those in the dissolution experiments were adjusted to be less than 8 so that degradation was negligible and therefore a specific colorimetric analysis was unnecessary. Nine compounds were found to be active as ligands forming a soluble complex with prednisolone. Eight of these compounds were naphthalene sulfonic acid derivatives and the other was the salt of 5,5'-methylenedisalicylic

acid. By comparing ligand structures and their resulting apparent 1:1 stability constants, and utilizing the results of a complexing experiment which used hydrocortisone as the substrate, it was postulated that the interaction between prednisolone and the ligands was a hydrophobic interaction involving the alpha surface of the steroid and the flat ring surface of the ligands.

The dissolution rate of hydrous prednisolone was determined in the presence of various concentrations of the above ligands. An essentially spherical pellet of hydrous prednisolone was used in a free rotational dissolution system. Due to the spectrophotometric interference of the ligands present in the dissolution medium, its analysis was determined by liquid scintillation using tritium-labeled prednisolone. By studying the dissolution rate over an extended range of equilibrium solubilities and with various ligands, the factors controlling the dissolution process could be examined. It was found that when the various ligands were added to the dissolution medium in increasing concentrations, the resulting dissolution rates remained a linear function of the change in solubility due to the presence of ligand. These results fit the modified diffusion layer theory of the dissolution process. By using the calculated diffusion coefficient for free prednisolone and the graphical data, the diffusion

layer thickness, h, and the diffusion coefficients for the complexed species of prednisolone were calculated. The resulting values were in agreement with theoretical predictions. It was also shown why other dissolution theories did not fit this system.

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APPENDIX

Table 8

Change in Total Solubility of Hydrous Prednisolone in the Presence of 2-Naphthalene Sulfonic Acid. pH = 2.2-1.5

Ligand added (molar)	Total solubility of hydrous prednisolone ($M \times 10^3$)
0	.63
.02	.82
.04	1.06
.06	1.32
.08	1.60
.10	1.89

$K_{1:1} = 22$

Table 9

Change in Total Solubility of Hydrous Prednisolone in the Presence of 1-Naphthol-2-sulfonic Acid; Potassium Salt pH = 7.3-6.8

Ligand added (molar)	Total solubility of hydrous prednisolone ($M \times 10^3$)
0	.63
.01	.73
.02	.87
.04	1.16
.06	1.51
.08	1.91

$K_{1:1} = 28$

Table 10

Change in Total Solubility of Hydrous Prednisolone in the Presence of 2,6-Naphthalene Disulfonic Acid, Disodium Salt

pH = 7.0

Ligand added (molar)	Total solubility of hydrous prednisolone ($M \times 10^3$)
0	.63
.01	.72
.02	.80
.04	.99
.06	1.16
.08	1.32
.10	1.47

$K_{1:1} = 14$

Table 11

Change in Total Solubility of Hydrous Prednisolone in the Presence of 2-Naphthol-3,6-disulfonic Acid, Disodium Salt

pH = 7.6

Ligand added (molar)	Total solubility of hydrous prednisolone ($M \times 10^3$)
0	.63
.01	.76
.02	.88
.04	1.15
.06	1.41
.08	1.67
.10	1.94

$K_{1:1} = 21$

Table 12

Change in Total Solubility of Hydrous Prednisolone in the Presence of 2-Naphthol-6,8-Disulfonic Acid, Dipotassium Salt. pH = 6.1

Ligand added (molar)	Total solubility of hydrous prednisolone ($M \times 10^3$)
0	.63
.01	.69
.02	.76
.04	.90
.06	1.05
.08	1.20
.10	1.37

$K_{1:1} = 13$

Table 13

Change in Total Solubility of Hydrous Prednisolone in the Presence of 4,5-Dihydroxynaphthalene-2,7-Disulfonic Acid, Disodium Salt. pH = 4.1-3.6

Ligand added (molar)	Total solubility of hydrous prednisolone ($M \times 10^3$)
0	.63
.01	.78
.02	.97
.04	1.32
.06	1.69
.08	2.07
.10	2.46

$K_{1:1} = 29$

Table 14

Change in the Total Solubility of Hydrous Prednisolone in the Presence of 2,7-Dihydroxynaphthalene-3,6-Disulfonic Acid, Disodium Salt. pH = 3.2-4.1

Ligand added (molar)	Total solubility of hydrous prednisolone ($M \times 10^3$)
0	.63
.01	.77
.02	.93
.04	1.26
.06	1.58

$K_{1:1} = 26$

Table 15

Change in Total Solubility of Hydrous Prednisolone in the Presence of 2,3-Dihydroxynaphthalene-6-sulfonic acid, Sodium Salt. pH = 6.0-5.5

Ligand added (molar)	Total solubility of hydrous prednisolone ($M \times 10^3$)
0	.63
.01	.81
.02	.99
.04	1.35
.06	1.74

$K_{1:1} = 30$

Table 16

Change in Total Solubility of Hydrous Prednisolone in the Presence of 5,5'-Methylenedisalicylic Acid, Disodium Salt

pH = 6.2

Ligand added (molar)	Total solubility of hydrous prednisolone ($M \times 10^3$)
0	.63
.01	1.05
.02	1.49
.04	2.29
.06	3.11
.08	3.97

$K_{1:1} = 63$

Table 17

Change in Total Solubility of Hydrocortisone in the Presence of 2,3-Dihydroxynaphthalene-6-sulfonic Acid, Sodium Salt

Ligand added (molar)	Total solubility of hydrocortisone ($M \times 10^3$)
0	.87
.01	1.16
.02	1.46
.03	1.77
.04	2.06

$K_{1:1} = 35$

Table 18

Dissolution of Hydrous Prednisolone in the Presence of 2-Naphthalene Sulfonic Acid

Tablet number	Ligand added (M)	Tablet weight (gms x 10^3)	Tablet volume (in cc)	a = $4.85/d^{2/3}$	Slope = K_a ($gm^{1/3}/hr$)	Dissolution rate (mg $cm^{-2}hr^{-1}$) Individual	Average
20	.01	21.78	.01800	4.27	.00602	4.23	
21	.01	21.42	.01763	4.26	.00597	4.20	4.22
22	.02	21.49	.01770	4.26	.00690	4.83	
23	.02	21.15	.01740	4.26	.00687	4.83	4.83
24	.03	21.98	.01812	4.27	.00795	5.58	
25	.03	21.36	.01771	4.28	.00780	5.46	5.52
26	.04	21.48	.01761	4.25	.00876	6.18	
38	.04	22.00	.01847	4.33	.00881	6.09	
39	.04	22.00	.01844	4.33	.00880	6.09	6.12
36	.05	21.67	.01826	4.33	.0100	6.90	
37	.05	21.93	.01833	4.29	.0100	6.99	6.95

Table 19

Dissolution of Hydrous Prednisolone in the Presence of 2-Naphthol-3,6-Disulfonic Acid, Disodium Salt

Tablet number	Ligand added (M)	Tablet weight (gms x 10^3)	Tablet volume (in cc)	$a = 4.85/d^{2/3}$	Slope = K_a ($gm^{1/3}/hr$)	Dissolution rate ($mg\ cm^{-2}hr^{-1}$) Individual	Average
40	.01	22.19	.01859	4.33	.00650	4.50	
41	.01	21.85	.01837	4.33	.00660	4.56	4.53
42	.02	21.93	.01837	4.33	.00743	5.16	
43	.02	21.60	.01811	4.33	.00743	5.16	5.16
44	.03	21.59	.01821	4.33	.00842	5.82	
45	.03	21.89	.01843	4.33	.00843	5.85	5.84
46	.04	21.83	.01835	4.33	.00945	6.54	
47	.04	21.81	.01851	4.33	.00943	6.54	6.54

Table 20

Dissolution of Hydrous Prednisolone in the Presence of 4,5-Dihydroxynaphthalene-2,7-Disulfonic Acid, Disodium Salt

Tablet number	Ligand added (M)	Tablet weight (gms x 10^3)	Tablet volume (in cc)	$a = 4.85/d^{2/3}$	Slope = K_a ($gm^{1/3}/hr$)	Dissolution rate ($mg\ cm^{-2} hr^{-1}$) Individual	Average
48	.01	22.12	.01853	4.33	.00690	4.77	
49	.01	21.81	.01837	4.33	.00674	4.68	4.73
50	.02	21.95	.01843	4.33	.00808	5.61	
51	.02	22.10	.01851	4.33	.00808	5.61	5.61
53	.03	21.87	.01831	4.33	.00933	6.45	
54	.03	22.18	.01865	4.33	.00945	6.54	6.50
55	.04	21.98	.01831	4.29	.0106	7.41	
56	.04	22.18	.01853	4.29	.0106	7.41	7.41

Table 21

Dissolution of Hydrous Prednisolone in the Presence of 2,3-Dihydroxynaphthalene-6-sulfonic Acid, Sodium Salt

Tablet number	Ligand added (M)	Tablet weight (gms x 10^3)	Tablet volume (in cc)	$a = 4.85/d^{2/3}$	Slope = K_a ($gm^{1/3}/hr$)	Dissolution rate ($mg\ cm^{-2} hr^{-1}$) Individual	Average
12	0	21.37	.01754	4.25	.00561	3.93	
11	0	21.34	.01774	4.27	.00550	3.84	3.88
7	.01	21.77	.01800	4.27	.00662	4.65	
8	.01	21.85	.01800	4.25	.00687	4.86	4.76
10	.02	21.49	.01767	4.25	.00800	5.64	
13	.02	21.80	.01823	4.28	.00813	5.67	5.65
18	.03	21.95	.01823	4.28	.00953	6.66	
19	.03	21.90	.01808	4.27	.00926	6.48	6.57
16	.04	22.00	.01834	4.30	.0106	7.41	
17	.04	22.53	.01867	4.28	.0108	7.56	7.48

Table 22

Dissolution of Hydrous Prednisolone in the Presence of 5,5'-Methylene Disalicylic Acid, Disodium Salt

Tablet number	Ligand added (M)	Tablet weight (gms x 10^3)	Tablet volume (in cc)	$a = 4.85/d^{2/3}$	Slope = K_a ($gm^{1/3}/hr$)	Dissolution rate ($mg\ cm^{-2} hr^{-1}$) Individual	Average
28	.01	21.78	.01833	4.33	.00830	5.76	
29	.01	21.94	.01850	4.33	.00830	5.76	5.76
30	.02	21.31	.01792	4.32	.0109	7.56	
31	.02	21.55	.01810	4.32	.0112	7.77	7.66
32	.03	21.93	.01832	4.30	.0135	9.42	
33	.03	21.83	.01823	4.30	.0138	9.63	9.53
34	.04	22.17	.01855	4.30	.0160	1.12	
35	.04	21.79	.01833	4.32	.0159	1.10	1.11

EFFECT OF COMPLEXING AGENTS ON THE DISSOLUTION KINETICS OF PREDNISOLONE

by JOHN SCOTT KENT

(Under the supervision of Professor Dale E. Wurster)

The absorption of a biologically active drug with poor water solubility is dependent in some manner on its dissolution rate. With a drug such as this, it is important then to maximize the dissolution rate to obtain the best absorption and hence the greatest effect per milligram of drug. In striving to find systems that increase the dissolution rate of a drug, it is important to understand the mechanism involved in the dissolution process.

The dissolution rate of the hydrous form of prednisolone has been studied as a function of a changing equilibrium solubility. The change in equilibrium solubility was accomplished by using various chemicals that formed a soluble complex with prednisolone.

The extent of complex formation, or the increase in the apparent saturation solubility, was determined by adding increasing amounts of a ligand to an excess of prednisolone in water. After equilibration, the suspension was filtered and the filtrate extracted with chloroform. An aliquot of the chloroform solution was dried and then a specific volume of ethanol added. An

ultraviolet analysis was used to determine the concentration of prednisolone present. The extraction procedure was necessary since the ligands present interfered with the spectrophotometric analysis.

The pH of these solutions and those in the dissolution experiments were adjusted to be less than 8 so that degradation was negligible and therefore a specific colorimètric analysis was unnecessary.

Nine compounds were found to be active as ligands forming a soluble complex with prednisolone. Eight of these compounds were naphthalene sulfonic acid derivatives and the other was the salt of 5,5'-methylene-disalicylic acid. By comparing ligand structures and their resulting apparent 1:1 stability constants, and utilizing the results of a complexing experiment which used hydrocortisone as the substrate, it was postulated that the interaction between prednisolone and the ligands was a hydrophobic interaction involving the alpha surface of the steroid and the flat Pi ring surface of the ligands.

The dissolution rate of hydrous prednisolone was determined in the presence of various concentrations of the above ligands. An essentially spherical pellet of hydrous prednisolone was used in a free rotational dissolution system. Due to the spectrophotometric interference of the ligands present in the dissolution

medium, its analysis was determined by liquid scintillation using tritium-labeled prednisolone. By studying the dissolution rate over a range of two to four times the equilibrium solubility of prednisolone using various ligands, the factors controlling the dissolution process could be examined. It was found that when the various ligands were added to the dissolution medium in increasing concentrations, the resulting dissolution rates remained a linear function of the change in solubility due to the presence of ligand. These results fit the modified diffusion layer theory of the dissolution process.

By using the calculated diffusion coefficient for free prednisolone ($D_o = 5.8 \times 10^{-6}$ $cm^2 sec^{-1}$) and the graphical data, the diffusion layer thickness ($h = 1.3 \times 10^{-3}$ cm) and the diffusion coefficients for the complexed species of prednisolone ($D_x = 4.2\text{-}5.2 \times 10^{-6}$ $cm^2 sec^{-1}$) were calculated. These results were in agreement with theoretical predictions. It was also shown why other dissolution theories did not fit this system.

APPROVED Dale E. Kurster

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