Drug Transport Through Model Membranes and Its Correlation with Solubility Parameters

By SAID A. KHALIL* and ALFRED N. MARTIN†

The kinetics of drug transport through lipoidal barriers was studied using a series of nonpolar liquids as models of living membranes. The nonpolar liquids were selected to represent a range of different solubility parameters (Hildebrand δ values), which varied between 7.1 and 10.7. Carboxyl salicylic acid-^{14}C was used as the drug molecule, the solubility parameter of which was found to have a δ value of approximately 10.8. The rate of drug transfer was studied from layer *a*, an aqueous buffer solution of pH 2, representing the stomach, through layer *b*, a liquid lipoidal barrier representing the gastric mucosal barrier, to layer *c*, an aqueous solution buffered at pH 7.4, representing the blood serum. The rate constants for the drug transport were obtained using an analog computer. The distribution of the drug between the three layers can be represented by a mathematical expression from which drug concentrations in the layers at various times can be calculated. It was found that the closer the δ value of the drug molecule to that of the lipoidal barrier, the faster was the disappearance of the drug from layer *a* and the slower its appearance in layer *c*. The results provided an approach for estimating the desired chemical characteristics of drug molecules required for optimum membrane penetration.

THE PASSAGE of drug molecules across living membranes has been the subject of many studies. Mullins (2), in his review of the physical mechanisms involved in narcosis, postulated that the membrane acceptance of a narcotic molecule depends upon its having a cohesive energy density (Hildebrand solubility parameter) appropriate to that of the membrane, and that the membrane acceptance is related to the ideal partition coefficient of the narcotic drug. Brodie and his associates (3–10) reported that the absorption of drug molecules from the gastrointestinal tract depends on their ability to penetrate a lipoidal barrier, and that the transport of most drugs is accomplished by the passive diffusion of their unionized species. The importance of the physicochemical characteristics of drug molecules, their solubility as well as partition coefficients between aqueous media and lipoidal barriers, has received much attention since the start of this century (2, 9–20).

Hansch and his co-workers (21), employed a mathematical treatment to correlate the molecular structure of a series of chemically related compounds with biological activity. They considered the partition coefficient to be an important factor in the equation. Recently, Swintosky and his associates (22–24) reviewed the importance of partition coefficients in biological and pharmaceutical systems. They studied drug partitioning between aqueous solutions of different pH values representing the gastrointestinal contents, a nonpolar solvent representing the lipoidal barrier, and a buffer solution of pH 7.4, corresponding to the blood serum. They used a rocking Y-tube apparatus for their studies. The various possibilities of drug transfer between the three compartments were also reported. Schulman (25) had previously suggested a cell of different design for such studies, and Perrin (26) recently reported on the application of this apparatus for the study of drug absorption.

Factors such as pKa, pH (3–6), binding to plasma proteins (6, 27–32), and the existence of active transport mechanisms (33) have been investigated. No attempts, however, have reportedly been made to evaluate the characteristics of the different lipoidal barriers and to correlate the solubility properties of various drug molecules with the characteristics of lipoidal membranes. Since the early work of Meyer and Overton (11), the partition coefficient of drug molecules between water and immiscible nonpolar liquids has been determined. Yet, the selection of the specific nonpolar liquid in

Received April 14, 1967, from the School of Pharmacy, Purdue University, Lafayette, IN 47907, and the † Laboratory of Physical Medicinal Chemistry, School of Pharmacy, Medical College of Virginia, Richmond, VA 23219
Accepted for publication June 21, 1967.
Presented to the Basic Pharmaceutics Section, A.PH.A. Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.
* Present address: Faculty of Pharmacy, Alexandria University, Alexandria, Egypt, U.A.R.

such studies has not usually been made on a rational basis.

INTRODUCTION

In the present investigation, the Hildebrand solubility theory (1) is used to describe in a quantitative way a series of nonpolar liquids representing models of biological membranes. The values obtained can then be employed to correlate the structures and solubilities of drug molecules with ability to pass through different membranes. Work along similar lines has been reported by Mullins (2, 34) in his studies on narcosis and olfaction. Dikstein (35, 36) also used the solubility parameter as an index of drug action. It is proposed that Mullins' approach might serve as the primary step toward characterizing biological membranes relative to drug penetrability.

In vitro experiments were carried out to correlate the Hildebrand solubility parameters (δ values) of selected lipoidal barriers with the δ values of drug molecules passing through the barriers. This *in vitro* method was used to simulate *in vivo* transport of drugs through biological membranes. It was accomplished by the use of an apparatus essentially the same as that described by Doluisio and Swintosky (23), which consisted of a slow rocking bar to which a set of inverted Y-shaped tubes were fixed. The two arms of each Y-tube contained aqueous layers, and the two aqueous layers were separated by a nonpolar liquid that was immiscible with them. The liquid interface expanded and contracted with the rocking motion of the tubes, simulating movement of the gastrointestinal tract. A series of nonpolar liquids, having δ values which varied between 7.1 and 10.7, were employed. Carboxyl salicylic acid-^{14}C was used to represent the drug molecule, the δ value of which was determined using previously established techniques (37, 38). The rate of drug transfer, as well as equilibrium drug distribution in the different lipoidal barriers, was determined by measuring the radioactivity of the drug in samples of each of the three layers at various time intervals, using a liquid scintillation counter. Plots of the radioactivity *versus* time were made. The equilibrium concentrations in the three phases were read from the graphs, and the rate constants for the transfer of salicylic acid through the various lipoidal barriers were determined from the graphs using an analog computer.

The present kinetic method, developed by Doluisio and Swintosky (23) for determining the partitioning of drugs between various phases, is a more informative technique than usual partition coefficient measurements. Rate constants of both forward and reverse transfer, as well as partition coefficients, can be obtained by this method. Furthermore, a system consisting of two aqueous phases of definite pH and an intervening lipid phase more nearly simulates absorption conditions in some biological processes. Since absorption and drug action depend upon penetration of lipoidal barriers, this *in vitro* model appears to be suitable for studies on transport and action of drugs and has been adopted for the present study.

This report describes the rate of drug transfer through different lipoidal barriers having variable solubility parameters (δ values). An attempt was made to correlate the rate of drug transfer with the Hildebrand δ values of both the drug and the liquid lipoidal barrier, through which it passed. From the preliminary *in vitro* results, as well as those under investigation, it is hoped to correlate *in vitro* results with *in vivo* findings reported in the literature, using a specific drug molecule. By such a means, it should be possible to specify roughly the region of drug penetration and rate of transport. The site of absorption of the gastrointestinal tract and other biological barriers could then be assigned δ values, or similar parameters, which measure the polarity of the membranes.

The correlation of solubility properties of nonaqueous systems with a single parameter such as the δ value or the dielectric constant has been criticized, because it assumes the solvent phase to be a continuum; more emphasis should be placed on such factors as the solute–solvent–cosolvent interactions (39). Furthermore, biological membranes are complex structures, and it is not likely that a single parameter, adapted to express the polar nature of solvents, could be highly successful in characterizing a living membrane. The Hildebrand δ value is used here because it has a precise meaning and can be expressed in a quantitative manner. At a later point in this program, it is planned to introduce modified parameters or combinations of parameters to express in a more satisfactory way the polar character of complex living membranes.

THEORY AND CALCULATION

The system tested may be represented by the model:

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C \qquad \text{(Eq. 1)}$$

The kinetics of this system is expressed by the following equations:

$$V_a \frac{dA}{dt} = -V_a k_1 A + V_b k_{-1} B \qquad \text{(Eq. 2)}$$

$$V_b \frac{dB}{dt} = V_a k_1 A - V_b k_{-1} B - V_b k_2 B + V_c k_{-2} C \qquad \text{(Eq. 3)}$$

$$V_c \frac{dC}{dt} = V_b k_2 B - V_c k_{-2} C \qquad \text{(Eq. 4)}$$

Where V_a, V_b, V_c, are the volumes and A, B, C, are the concentrations of the drug at any instant in the three layers a, b, and c, respectively. The symbols k_1 and k_2 represent the apparent rate constants for forward drug transfer from a to b and from b to c; and k_{-1} and k_{-2} represent the apparent rate constants of the reverse drug transfer from b to a, and from c to b, respectively. A_0 is the initial concentration present in layer a at time t = 0, and:

$$A_0 = A + B + C \qquad \text{(Eq. 5)}$$

The volumes V_a, V_b, and V_c were in the ratios of 1:2:1. (See under *Experimental.*) In order to keep this ratio constant throughout the experiment, the sample volume withdrawn from layer b was double the volumes withdrawn from layers a

and c. The volume terms may therefore be neglected and Eqs. 2, 3, and 4 reduce to Eqs. 6, 7, and 8:

$$\frac{dA}{dt} = -k_1A + k_{-1}B \quad \text{(Eq. 6)}$$

$$\frac{dB}{dt} = k_1A - k_{-1}B - k_2B + k_{-2}C \quad \text{(Eq. 7)}$$

$$\frac{dC}{dt} = k_2B - k_{-2}C \quad \text{(Eq. 8)}$$

To calculate the true transfer rate constants, pH-partition effects must be taken into consideration by assuming that only the unionized portion of the drug molecule passes through the lipoidal membrane. The true rate constant k_1' is related to the apparent rate constant reported in this study, k_1, for the forward step from a to b of Eq. 1 by:

$$k_1' = \frac{k_1}{(1 - \alpha)} \quad \text{(Eq. 9)}$$

where α is the degree of ionization $[I/(U + I)]$ of the drug at the specified pH. The true rate constant may be defined (23) as:

$$k_1' = \frac{(U + I)}{U} k_1 \quad \text{(Eq. 10)}$$

where U and I are the unionized and ionized species of the drug molecule, respectively. In the present study, only the apparent rate constant is considered.

EXPERIMENTAL

Reagents—The solvents and their sources are given as follows: *n*-pentane, technical grade (b.p. 36.1°), *n*-hexane (b.p. 68.5–69°), and *n*-hexyl alcohol (b.p. 157–158°) from Eastman Organic Chemicals; *n*-octyl alcohol from Matheson Coleman & Bell (b.p. 193.5–195.1°); benzene from Baker & Adamson (b.p. 79.8–80.2°); toluene, Baker analyzed reagent (b.p. 110.1–110.7°); cyclohexane, Phillips (b.p. 80.5–82.0°). The reagents were redistilled, and the first and the last portions of the distillate were rejected. Distillation was continued until gas chromatography indicated that they were pure.

Karl Fischer reagent was obtained from Mallinckrodt Chemical Works; naphthalene, *p*-dioxane, and 2-ethoxyethanol were obtained from Eastman Organic Chemicals; 2,5-diphenyloxazole (PPO) and 1,4-bis-2-(4-methyl-5-phenyloxazolyl) benzene (dimethyl POPOP) were products of the Packard Instrument Co.

Carboxyl salicylic acid-^{14}C (17.5 μc./mg.) was synthesized in the laboratories of the Bionucleonics Department, Purdue University, Lafayette, Ind.[1] Its chemical purity was established by thin-layer chromatography. A sample of salicylic acid, Fischer certified reagent grade, which has been recrystallized from chloroform, was used as a reference standard. The radio-purity of carboxyl salicylic acid-^{14}C was determined by autoradiography.

Potassium chloride, monobasic sodium phosphate, sodium hydroxide, and hydrochloric acid were all of reagent grade.

Apparatus—The rocking device and Y-shaped tubes described by Doluisio and Swintosky (23) were used for the model membrane penetration experiment; a Beckman model 72 pH meter; Autoprep, model A 700 Aerograph; Wilkens-Anderson Lo-Temp constant-temperature bath; Packard Tri-Carb liquid scintillation spectrometer model 3003; and A. D. analog computer model 2-24 PB (Applied Dynamics, Inc.) were also employed in the study.

Procedure—Experiments were first conducted to determine the solubility of water (from the buffer solutions) in the nonpolar liquid phase. The drug, salicylic acid, was not added to the acid solution in these preliminary experiments. Inverted Y-shaped Pyrex glass cells were filled with the appropriate liquid phases. Into one arm was introduced 40.0 ml. of a KCl–HCl buffer solution of pH 2, and into the other arm 40.0 ml. of a phosphate buffer of pH 7.4. Then 80.0 ml. of a nonpolar liquid was carefully introduced into the cell over the two aqueous layers. A series of nonpolar liquids having different Hildebrand δ values (1) were used. These included *n*-pentane (δ = 7.1), *n*-hexane (δ = 7.3), cyclohexane (δ = 8.2), toluene (δ = 8.9), benzene (δ = 9.2), *n*-octyl alcohol (δ = 10.3), and *n*-hexyl alcohol (δ = 10.7). The rocking apparatus with its tubes was submerged in a thermostatically controlled water bath at 25 ± 0.1°. The apparatus was slowly rocked at a rate of one stroke per minute for a period of 24 hr. Then samples from the nonpolar liquids were taken and left in a separator for 24 hr. to allow any suspended water droplets to separate. The supernatant was analyzed for its water content using the Karl Fischer method.

The experiments were repeated substituting an aqueous pH 2 buffer solution of carboxyl salicylic acid-^{14}C (33.25×10^{-5} moles/L.) for the pH 2 buffer solution alone. The nonpolar liquids, *n*-octyl alcohol and *n*-hexyl alcohol, were presaturated with the aqueous buffer layers for 24 hr. as described above. The other solvents did not dissolve water sufficiently to require presaturation. On introducing the nonpolar liquid over the aqueous layers in each tube, care was taken to minimize any turbulence or mixing. The apparatus was rocked as described above, and samples were withdrawn from each of the three layers in each Y-tube at various intervals. Each sample was injected into a liquid scintillation spectrometer vial containing 15.0 ml. of liquid scintillator. The liquid scintillator consisted of 8.0% w/v naphthalene, 1.0% w/v of 2,5-diphenyloxazole (PPO), and 0.05% w/v of 1,4-bis-2-(4-methyl-5-phenyloxazolyl) benzene (dimethyl POPOP), in a mixture of toluene, *p*-dioxane, and 2-ethoxyethanol in the ratio of 1:3:3 parts by volume.

A blank for each experiment was carried out at the time, using the same procedure, but without the radioactive salicylic acid. The activity obtained from each sample of the blank experiment was considered as the background activity for its respective sample, and was subtracted from its activity when recording the results. The samples

[1] The authors wish to acknowledge the assistance of Dr. Wayne Kessler and Dr. A. Noujaim, Department of Bionucleonics, Purdue University, for their assistance in the radioactive analysis conducted in this study. Dr. A. M. Knevel, Department of Medicinal Chemistry, assisted in determining the identity and purity of the solvents.

TABLE I—APPARENT RATE CONSTANTS FOR THE TRANSFER OF SALICYLIC ACID THROUGH THE DIFFERENT LIPOIDAL BARRIERS

Nonpolar Liquid Used as Barrier	δ Value of Liquid Barrier	Adjusted δ Value of Barrier	∇[a]	Apparent Rate Constants (as Obtained from Analog Computer) × 10^4 sec.$^{-1}$ k_1	k_{-1}	k_2	k_{-2}
n-Pentane	7.1	7.1	3.7	0.024	0.003	0.650	0.003
n-Hexane	7.3	7.4	3.4	0.032	0.028	0.570	0.002
Cyclohexane	8.2	8.3	2.5	0.018	0.107	0.250	0.002
Toluene	8.9	8.9	1.9	0.126	0.008	0.335	0.000
Benzene	9.2	9.2	1.6	0.107	0.019	0.330	0.000
n-Octyl alcohol	10.3	10.8	0.0	0.230	0.003	0.019	0.000
n-Hexyl alcohol	10.7	11.4	0.6	0.452	0.005	0.042	0.008

[a] $\nabla = |\delta_D - \delta_B|$, where δ_D is the δ value of salicylic acid taken as 10.8, and δ_B is the δ value of the liquid lipoidal barrier.

were counted in a model 3003 Tri-Carb liquid scintillation spectrometer. Five 1-min. counts were taken and their average recorded.

An internal standard, carboxyl benzoic acid-^{14}C standard solution, was added to each sample and the sample was recounted so that the efficiency of the counting instrument, as well as the existence of any quenching effect due to the different samples in the liquid scintillator, could be determined.

The solubility parameter of the salicylic acid was determined using already established techniques (37, 38).

RESULTS AND DISCUSSION

From the Karl Fischer titration results, it was obvious that under the condition of the experiment the nonpolar layer became saturated with the aqueous layers, which resulted in a change in the δ values in some cases. From the estimation of water content, the δ values of the resulting nonpolar layers were calculated as described by Chertkoff and Martin (37). The results are summarized in Table I.

The water saturation effect was quite apparent in the case of *n*-octyl and *n*-hexyl alcohol resulting in an increase in their δ values of 0.5 and 0.7 unit, respectively. Because of this fact, it was important to presaturate these two liquids before the rate of drug transfer through them was determined. Presaturation was not required for the other liquids, as their water saturation capacity was very small, and their δ values were not changed significantly by the addition of water.

The solubility of the nonpolar phase in both aqueous layers no doubt affects the rate constant to a small extent. Only apparent rate constants are reported. It is more probable that this effect does not significantly alter the conclusion drawn from a consideration of the δ value of the lipoidal phase in relation to drug transport, which is the main concern.

The δ value of salicylic acid was found to be approximately 10.8. This value agrees with that given by Paruta *et al.* (40). They reported a dielectric constant requirement for salicylic acid of 15, possibly another of 25. The equation relating the dielectric constant ε and the delta value δ in pharmaceutical solvents, *i.e.*, alcohols, glycols, and water, reported also by Paruta *et al.* (41) is:

$$\delta = 0.22\,\epsilon + 7.5$$

The δ value for salicylic acid can thus be calculated:

$$\delta = 0.22 \times 15 + 7.5 = 10.8$$

Typical results obtained by determining the concentration of radioactive salicylic acid in the three different layers at various time intervals are shown in Figs. 1–4, where drug concentrations in each of the three layers as measured by radioactivity in c.p.m. *versus* time were plotted.

A consecutive first-order rate of transfer was expected from the results obtained. Curves were drawn to fit the experimental points using an *x–y* recorder attached to an analog computer. The analog computer was programmed to represent a reversible consecutive first-order transfer rate, as shown in Fig. 5. This model was quite suitable for the cases studied as shown by the fit of the computed curves to the experimental points. Apparent rate constants were obtained from the computer potentiometer settings for the best fitting curves, as shown in Table I.[2] From Table I, it is observed that a relation exists between the apparent rate of transfer of salicylic acid from a buffer solution of pH 2, layer *a* to the liquid lipoidal barrier, layer *b*. The results suggest that the closer the δ value of the liquid lipoidal barrier to the δ value of the drug molecule, the greater the rate of drug transfer or disappearance from layer *a*. This fact could also be shown if the logarithm of the concentration of salicylic acid in layer *a* was plotted *versus* time for all cases studied. Such curves for the different nonpolar liquids are found in Fig. 6. Straight lines (in most cases) with negative slopes were obtained. It was possible to relate the slopes of the linear portions of the lines to the δ values of the liquid lipoidal barriers used. The slopes increased as the δ values of the liquid lipoidal barriers increased.

Some of the results did not coincide exactly with those expected from the hypothesis connecting the slope or the apparent rate of transfer with the δ value of the nonpolar liquid layers, and these discrepancies are not easily accounted for. Cyclohexane has a δ value higher than *n*-pentane and *n*-hexane, and it should have produced a slope greater than the slopes for *n*-pentane and *n*-hexane. Yet it has the smallest slope of all tested nonpolar liquids. The reverse transfer rate constant of salicylic acid from *b* to *a* is significant in this case, namely 0.107 ×

[2] The dependability of the analog computer results as well as the *x–y* recorder were checked with an IBM 7094 digital computer. The rate constants calculated by use of the analog computer were fed to a digital computer to give the theoretically expected curves. The curves obtained by use of the digital computer fitted those produced on the *x–y* recorder by the analog computer. The digital program is not reported here, but may be obtained by contacting one of the authors.

10^{-3} sec.$^{-1}$. This finding has been reported previously in the literature (24). Similarly the rate of transfer of salicylic acid through benzene should be higher than through toluene, but the reverse was found. Again the reverse specific rate of transfer from *b* to *a* for benzene is higher than for toluene,

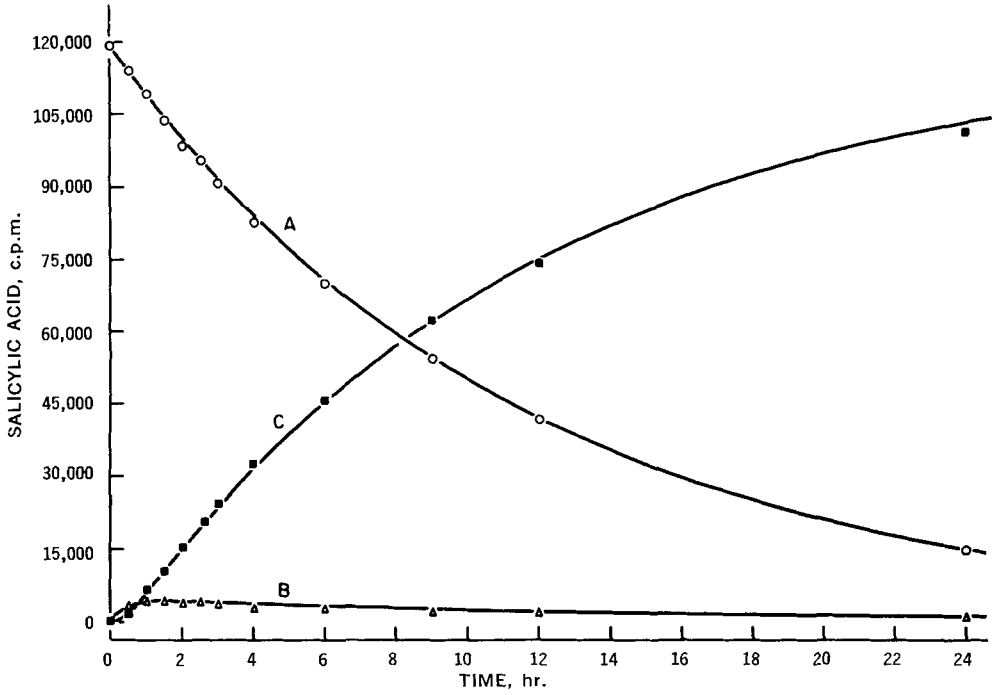

Fig. 1—The transfer of salicylic acid from an aqueous pH 2.0 buffer (layer a*) through* n*-pentane barrier (layer* b*) to an aqueous pH 7.4 buffer (layer* c*). The points are experimental and the lines are theoretical. Key:* O, *pH 2.0 layer* a; Δ, n*-pentane layer* b; ■, *pH 7.4 layer* c.

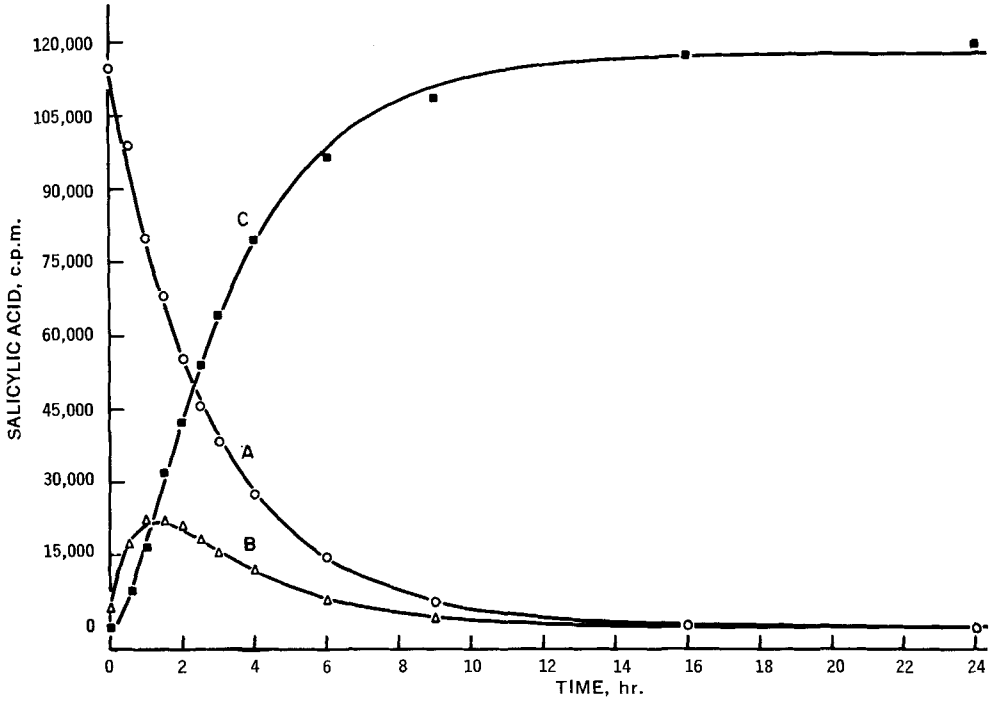

Fig. 2—The transfer of salicylic acid from an aqueous pH 2.0 buffer (layer a*) through a benzene barrier (layer* b*) to an aqueous pH 7.4 buffer (layer* c*). The points are experimental and the lines are theoretical. Key:* O, *pH 2.0 layer* a; Δ, *benzene layer* b; ■, *pH 7.4 layer* c.

as shown in Table I. All other cases followed the expected correlation between the rate of drug transfer and the δ value of the lipoidal barrier through which the drug is transferred. It should be noted from Fig. 6 that the rate of transfer of salicylic acid through the rather polar liquids,

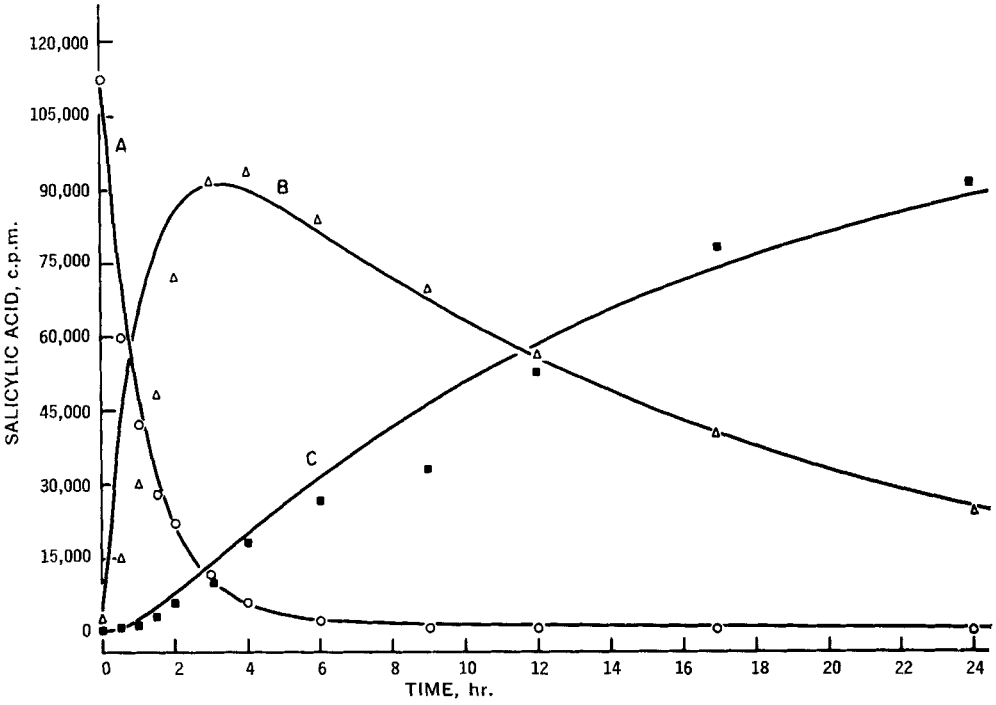

Fig. 3—The transfer of salicylic acid from an aqueous pH 2.0 buffer (layer a) *through a* n-*octyl alcohol barrier (layer* b) *to an aqueous pH 7.4 buffer (layer* c). *The points are experimental and the lines are theoretical. Key:* O, *pH 2.0 layer* a; Δ, n-*octyl alcohol layer* b; ■, *pH 7.4 layer* c.

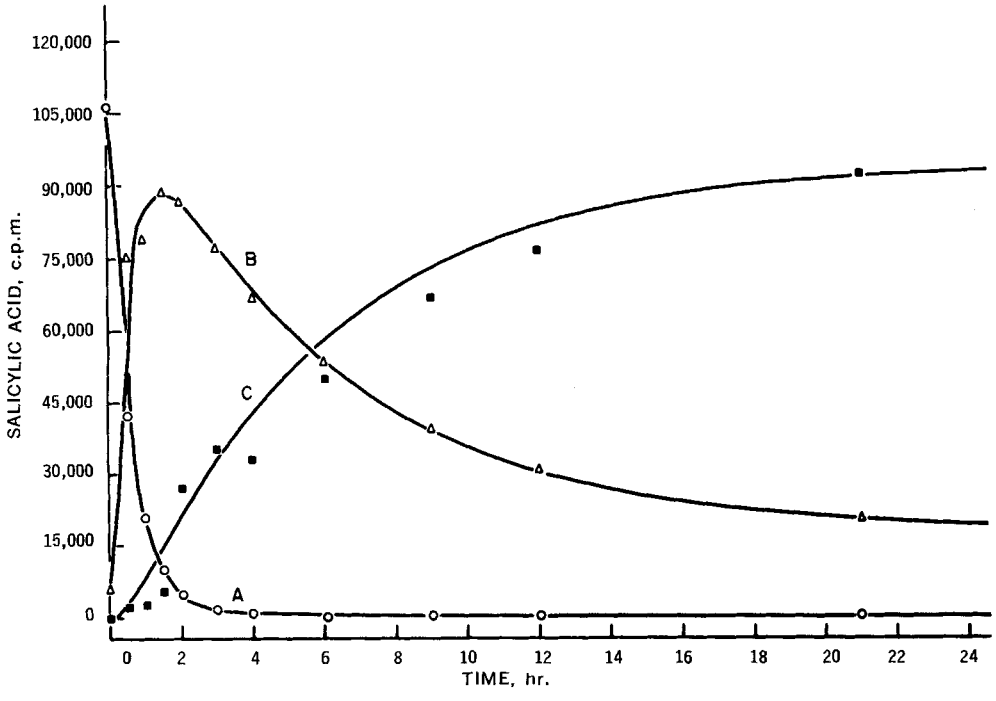

Fig. 4—The transfer of salicylic acid from an aqueous pH 2.0 buffer (layer a) *through a* n-*hexyl alcohol barrier (layer* b) *to an aqueous pH 7.4 buffer (layer* c). *The points are experimental and the lines are theoretical. Key:* O, *pH 2.0 layer* a; Δ, n-*hexyl alcohol layer* b; ■, *pH 7.4 layer* c.

n-octyl alcohol and *n*-hexyl alcohol, followed a first-order transfer in the first 3 to 4 hr., then began to disappear from *a* at a reduced rate, as can be seen by their curvilinear plots. This is probably due to the rapid onset of equilibrium between layers *a* and *b*. Such equilibrium requires longer periods of time to be reached in the relatively nonpolar barriers used.

In the case of *n*-octyl alcohol (Fig. 3) the analog computer curves representing layer *a* and *c* fitted the experimental data quite well, while in layer *b* the sample concentrations withdrawn in the early hours of the experiment were less than the expected theoretical concentrations. This is explained by the high rate of transfer from *a* to *b* with insufficient time for equilibration in layer *b*, and the concentration of the salicylic acid in the interface during the time that samples were taken from the bulk of the nonpolar layer. The same reasoning could explain the relatively lower concentration of salicylic acid in layer *c* as compared with the expected value when hexyl alcohol was used as the lipoidal barrier, as seen in Fig. 4. Doluisio and Swintosky (24) suggested that deviations in solvents, such as octyl alcohol, are possibly due to hydrogen bonding.

The second observation which can be made from Table I is that the apparent rate constant, k_2, of transfer of salicylic acid from the liquid lipoidal barrier, layer *b*, to layer *c*, decreased with the increase in the δ value of the liquid lipoidal barrier. The reverse rates of transfer k_{-1} and k_{-2} are considered to be small in most cases and their effects are negligible. Consequently, a plot of the forward rate constants, k_1 and k_2, can be made *versus* the δ value of the liquid lipoidal barrier, as shown in Fig. 7. Although the points do not lie well along the lines, it is observed that k_1 increases and k_2 declines with an increase in the δ values of the organic solvents. Theoretically, k_1 should reach a maximum and then fall off, whereas k_2 should reach a minimum and then rise. The expected maximum and minimum values should be reached at a δ value of about 10.8, the δ value of salicylic acid. Such a maximum or minimum could not be obtained experimentally in this work due to the failure to find a nonpolar liquid that was immiscible with water and also had a δ value higher than 10.7.

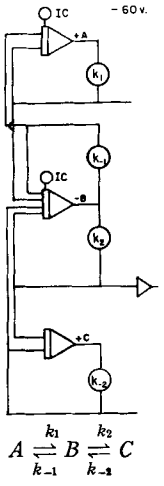

Fig. 5—Analog computer program for determining the rate constants for the system A ⇌ B ⇌ C *by obtaining the best fitting line to the experimental points.*

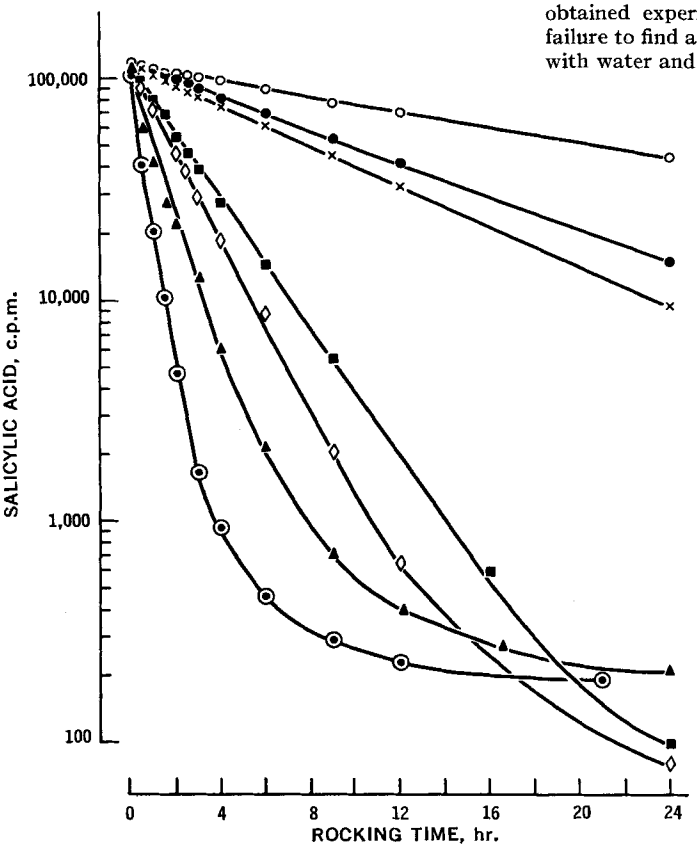

Fig. 6—A semilogarithmic plot showing the rate of salicylic acid disappearance from layer a *to different liquid lipoidal barriers (layer* b*). Key:* ○, *cyclohexane;* ●, n-*pentane;* ×, n-*hexane;* ■, *benzene;* ◇, *toluene;* ▲, n-*octyl alcohol;* ⊙, n-*hexyl alcohol.*

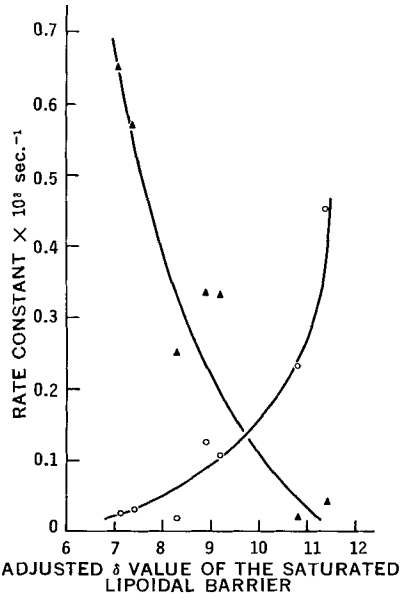

Fig. 7—Apparent rate constants for the transfer of salicylic acid from layer a *to layer* b, k_1 *and from layer* b *to layer* c, k_2, vs. *the adjusted* δ *values of the liquid lipoidal barrier layer* b. *Key:* ○, *rate of transfer from* a *to* b, k_1; ▲, *rate of transfer from* b *to* c, k_2.

If liquids could be found to provide a broader spectrum of δ values, and at the same time immiscible with the buffer solution, a maximum might be reached in the rate of drug transfer from *a* to *b* and a minimum from *b* to *c*. These points should then correspond to the δ value of the drug used.

In general, although only one compound, salicylic acid, was used as a solute in this work, the results suggested that the apparent rate constant, k_1, of drug disappearance from layer *a* to the liquid lipoidal barrier *b*, would increase with a decrease of the difference, ∇, in the δ values between the drug and the lipoidal barrier:

$$\nabla = |\delta_D - \delta_B|$$

where δ_D is the δ value of the drug molecule and δ_B is the δ value of the lipoidal barrier. The apparent rate constant, k_2, of drug release from the lipoidal layer to the aqueous layer *c* should decrease with the decrease in ∇.

The trend of ∇ values with k_1 and k_2 is observed in Table I. Thus, it might be said that as the δ value of the drug molecule approaches that of the lipoidal barrier, the rate of transfer of the drug to the lipoidal barrier increases and the rate of release of the drug from the lipoidal barrier decreases. The lipoidal barrier would tend to act as a storage compartment for the drug molecules with a prolonged release time. An optimum rate of passage of the drug from one aqueous compartment to another through a lipoidal barrier should occur when the δ value of the drug was somewhat different from that of the barrier. As seen in Fig. 7, the curves for k_1 and k_2 intersect at δ = 9.7. This should be the optimum δ value of the simulated membrane for the most rapid penetration of a drug with a δ value of 10.8. The principle might also be applied to the sustained release of drugs from tissue depots. Here one would desire a δ value of the drug relative to that of the tissue such that the drug penetrates rapidly into the tissue yet is released at a slow rate over a prolonged period of time.

The kinetics of the transfer of salicylic acid through the different lipoidal barriers studied can be an *in vitro* model for some of the theoretically possible kinetics cases suggested by Doluisio and Swintosky (24). From the values of the apparent rate constants found in Table I, as well as the concentration of drug at various times as seen in Figs. 1 through 4, the following cases are observed.

The transfer of the drug through *n*-pentane can be considered to represent kinetics of the type $a \rightarrow c$. This is possible because the concentration of the drug in layer *b* is relatively small and does not accumulate (see Fig. 1), and the reverse transfer rates, k_{-1} and k_{-2}, are also small and can be considered negligible (see Table I). Using cyclohexane as the lipoidal barrier, the process can be simulated by kinetics of the type $a \rightleftharpoons b \rightarrow c$. This is due to the relatively large rate of reverse transfer from *b* to *a*, and the relatively fast rate of forward drug transfer from *b* to *c*. Drug transfer through *n*-octyl alcohol can represent the kinetics of the type $a \rightarrow b \rightarrow c$. The drug builds up in layer *b*, and the reverse rate constants are very small and can be considered negligible. The results of the present study are summarized in Fig. 8, where the length of the arrows represent the relative rates of forward and reverse processes.

The concept of using δ values as one of the parameters that may explain the relative rates of drug transport across biological membranes and subsequent equilibrium concentrations can be applied to some of the experimental data reported by Brodie *et al.* (6). They reported that salicylic acid and barbital exist mainly in the stomach in their unionized form; yet the absorption of salicylic acid was quite high, while that of barbital was very poor. This fact can perhaps be explained by saying that the δ value of salicylic acid (δ = 10.8) is closer to the supposed δ value of the gastric lipoidal barrier (δ = 10) than that of barbital with a δ value of about 13.5. The δ values of salicylic acid and barbital were obtained by the method of Chertkoff and Martin (37), and the results are shown in Fig. 9.

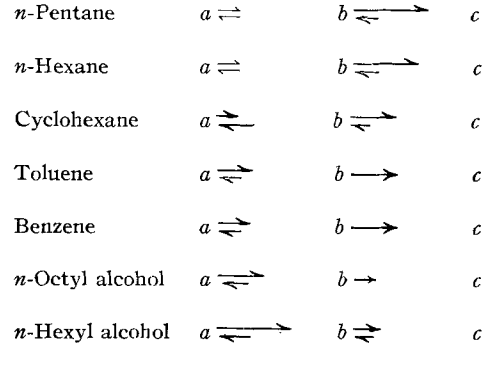

Fig. 8—Representation of the system A ⇌ B ⇌ C, *where the length of the line signifies the relative magnitudes of the rate constants.*

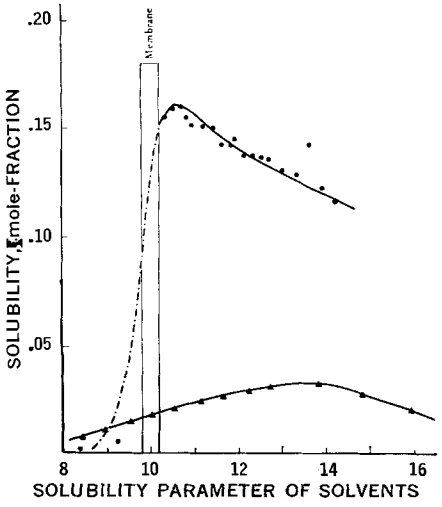

Fig. 9—Determination of the solubility parameter of salicylic acid and barbital at 25°. Key: ●, salicylic acid; ▲, barbital.

One observes from Fig. 9 that the suggested δ value for optimum penetration into the lipoidal membrane is about 10. Salicylic acid with a δ value of 10.8 being close to the δ value of the membrane will easily cross the lipoidal barrier. Barbital has a δ value of about 13.5,[8] well beyond the δ value of the membrane and would not be expected to show marked membrane penetrability.

SUMMARY AND CONCLUSIONS

The rate of transfer of carboxyl salicylic acid-^{14}C through different liquid lipoidal barriers was studied and the rate constants were determined using an analog computer. The liquid lipoidal barriers used represented a range of different solubility parameters expressed as Hildebrand δ values. A correlation between the δ value of the liquid lipoidal barrier, the δ value of the drug model, salicylic acid, and the rate of transfer of the drug through the lipoidal barrier has been presented. It is hypothesized that the smaller the difference between the δ value of a drug molecule that exhibits significant lipid solubility, and the δ value of the liquid lipoidal barrier, the faster would be the transfer across the barrier and into the lipoidal layer, and the slower the drug would be released from the lipoidal layer into the aqueous buffer phase. This suggests that a quantity ∇ could perhaps be used to express the optimum difference in δ values of the drug and membrane for transport and penetration by the drug. The results of the study seem to bear out this principle, but a number of drugs and liquids of varying δ values must be tested before the hypothesis can be accepted.

The δ value concept may also be valuable in relating partition coefficients to drug action. The proper choice of the nonpolar liquid in partition coefficient experiments may be arrived at through a knowledge of δ values, and the authors intend to present the results of a study dealing with this suggestion at a later time.

The goal is to be able to correlate *in vitro* with *in vivo* results and suggest molecular structures which can facilitate drug transfer across membranes, and drug release from tissue depots in the body. The region of absorption and drug release at the lipoidal barriers in the gastrointestinal tract and other membranes and tissues could be assigned δ values, or more acceptable polarity parameters, which would account for the complex nature of these biological structures.

[8] Barbital has no sharp maximum point of solubility in the solvents studied, and it is difficult to assign it a definite δ value. The solubility of barbital over the whole range of δ values from 7 to 16 is seen to be low and accordingly the drug is not expected to show marked solubility in the simulated membranes.

REFERENCES

(1) Hildebrand, J. H., and Scott, R. L., "The Solubility of Nonelectrolytes," 3rd ed., American Chemical Society Monograph No. 17, Reinhold Publishing Corp., New York, N. Y., 1950; Hildebrand, J. H., and Scott, R. L., "Regular Solutions," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1962.
(2) Mullins, L. J., *Chem. Rev.*, **45**, 289(1954).
(3) Shore, P. A., Brodie, B. B., and Hogben, C. A. M., *J. Pharmacol. Exptl. Therap.*, **119**, 361(1957).
(4) Schanker, L. S., Shore, P. A., Brodie, B. B., and Hogben, C. A. M., *ibid.*, **120**, 528(1957).
(5) Hogben, C. A. M., Schanker, L. S., Tocco, D. J., and Brodie, B. B., *ibid.*, **120**, 540(1957).
(6) Brodie, B. B., and Hogben, C. A. M., *J. Pharm. Pharmacol.*, **9**, 345(1957).
(7) Schanker, L. S., Brodie, B. B., and Hogben, C. A. M., *J. Pharmacol. Exptl. Therap.*, **122**, 66A(1958).
(8) Schanker, L. S., Tocco, D. J., Brodie, B. B., and Hogben, C. A. M., *ibid.*, **123**, 81(1958).
(9) Hogben, C. A. M., Tocco, D. J., Brodie, B. B., and Schanker, L. S., *ibid.*, **125**, 275(1959).
(10) Schanker, L. S., *ibid.*, **126**, 283(1959).
(11) Meyer, H., *Arch. Exptl. Pathol. Pharmacol.*, **42**, 109(1899); Overton, E., *Vierteljahrsschr. Naturforsch. Ges. Zürich*, **44**, 88(1899).
(12) Ferguson, J., *Proc. Royal Soc. (London)*, **B127**, 387 (1939).
(13) Butler, T. C., *J. Pharmacol. Exptl. Therap.*, **74**, 118(1942).
(14) Gladtke, E., and Liss, E., *Biochem. Z.*, **331**, 65(1959).
(15) Schanker, L. S., *J. Med. Pharm. Chem.*, **2**, 343(1960).
(16) McMahon, R. E., *ibid.*, **4**, 67(1961).
(17) Schanker, L. S., *Pharmacol. Rev.*, **14**, 501(1962).
(18) Rall, D. P., and Zubrod, C. G., *Ann. Rev. Pharmacol.*, **2**, 109(1962).
(19) Quintana, R. P., *J. Pharm. Sci.*, **54**, 462(1965).
(20) Katz, M., and Shaikh, Z. I., *ibid.*, **54**, 591(1965).
(21) Hansch, C., Muir, R. M., Fujita, T., Maloney, P. P., Geiger, F., and Streich, M., *J. Am. Chem. Soc.*, **85**, 2817 (1963).
(22) Reese, D. R., Irwin, G. M., Dittert, L. W., Chong, C. W., and Swintosky, J. V., *J. Pharm. Sci.*, **53**, 591(1964).
(23) Doluisio, J. T., and Swintosky, J. V., *ibid.*, **53**, 597(1964).
(24) *Ibid.*, **54**, 1594(1965).
(25) Rosano, H. L., Duby, P., and Schulman, J. H., *J. Phys. Chem.*, **65**, 1704(1961).
(26) Perrin, J., *J. Pharm. Pharmacol.*, **19**, 25(1967).
(27) Goldstein, A., *Pharmacol. Rev.*, **1**, 102(1949).
(28) Goldbaum, L. R., and Smith, P. K., *J. Pharmacol. Exptl. Therap.*, **111**, 197(1954).
(29) Lindenbaum, A., and Schubert, J., *J. Phys. Chem.*, **60**, 1663(1956).
(30) Anton, A. H., *J. Pharmacol. Exptl. Therap.*, **129**, 282(1960).
(31) Eichman, M. L., Guttman, D. E., Van Winkle, Q., and Guth, E. P., *J. Pharm. Sci.*, **51**, 66(1962).
(32) Klotz, I. M., Urquhart, J. M., and Weber, W. W., *Arch. Biochem.*, **26**, 420(1950).
(33) Schanker, L. S., and Tocco, D. J., *J. Pharmacol. Exptl. Therap.*, **128**, 115(1960).
(34) Mullins, L. J., *Ann. N. Y. Acad. Sci.*, **62**, 247(1955).
(35) Dikstein, S., "Quantitative Methods in Pharmacology," de Jonge, H., ed., Interscience Publishers, Inc., New York, N. Y., 1961, p. 312.
(36) Dikstein, S., "Biophysics of Physiological and Pharmacological Actions," Shanes, A. M., ed., American Association for the Advancement of Science, Washington, D. C., 1961, p. 49.
(37) Chertkoff, M. J., and Martin, A. N., *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 444(1960).
(38) Restaino, F. A., and Martin, A. N., *J. Pharm. Sci.*, **53**, 636(1964).
(39) Higuchi, T., Finger, K. F., and Higuchi, W. I., "Annual Reports Medicinal Chemistry," Cain, C. K., ed., Academic Press Inc., New York, N. Y., 1965, p. 331.
(40) Paruta, A. N., Sciarrone, B. J., and Lordi, N. G., *J. Pharm. Sci.*, **53**, 1349(1964).
(41) *Ibid.*, **51**, 704(1962).