# Effect of Complex Formation on Drug Absorption XIII: Effect of Constant Concentrations of *N,N*-Di-*n*-propylpropionamide on Prednisolone Absorption from the Rat Small Intestine

WILLIAM L. HAYTON* and GERHARD LEVY▲

**Abstract** □ Previous studies in this laboratory showed that *N,N*-dialkylpropionamides complex with prednisone and prednisolone in an organic solvent and enhance significantly the intestinal absorption of these steroids in rats. A kinetic analysis of the absorption data was complicated by the rapid decrease in amide concentration during the experiments. Therefore, a new approach was developed which involves the perfusion of a continuously recirculating solution of the steroid and amide through a small intestine segment of the anesthetized rat. An aqueous solution of amide is infused into this system at a constant rate to replace the amide absorbed from the intestine. Variability between experiments is minimized by concomitant use of butanol as an internal standard. Absorption rate constants for prednisolone were determined as a function of the concentration of *N,N*-di-*n*-propylpropionamide in the intestinal solution. Comparison of these data with the results of parallel *in vitro* studies shows that the intestine does not act like a simple lipoid barrier. Computer simulations indicate that the effect of the amide on steroid absorption can be rationalized by assuming that the intestine functions like two or more barriers in series with respect to the steroid, and that the permeability of one of these barriers is increased by the amide. This concept of the intestine as a series of two or more barriers with different permeability characteristics is consistent with the results of other recent studies of the permeability of the human small intestine, the human red cell, and the toad bladder.

**Keyphrases** □ Drug absorption, complex formation—effect of *N,N*-di-*n*-propylpropionamide on prednisolone absorption, rat small intestine □ Prednisolone absorption—effect of *N,N*-di-*n*-propylpropionamide, rat small intestine □ *N,N*-Di-*n*-propylpropionamide—effect on prednisolone absorption, rat small intestine □ Absorption, intestinal—effect of complex formation, prednisolone, rats

The more lipophilic members of a homologous series of *N,N*-dialkylpropionamides significantly enhance the absorption of prednisone and prednisolone from the *in situ* small intestine of the rat (1). This appears to be due to complex formation between the steroid and the amide within the intestinal barrier(s), similar to that observed in model studies on artificial lipoid barriers (2). The rapid decrease in the amide concentration of the intestinal drug solutions due to absorption of the amides precluded a rigorous kinetic analysis of their absorption-enhancing effect. To overcome this problem, a new method was developed whereby the absorption rates of drugs can be determined in the presence of a *constant* concentration of additive. The effect of constant concentrations of *N,N*-di-*n*-propylpropionamide on the absorption of prednisolone from the *in situ* rat intestine was investigated by this method and the results of this and of parallel *in vitro* studies are presented here.

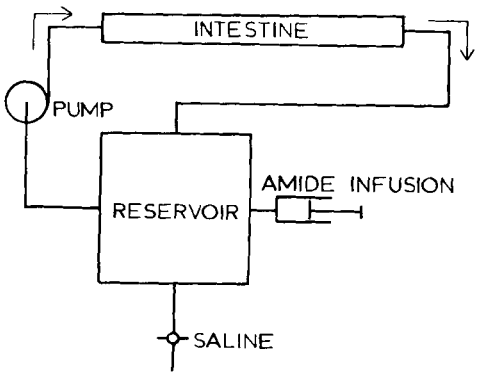


**Figure 1**—*Schematic diagram of the system used to study the absorption of prednisolone from the* in situ *rat intestine in the presence of constant concentrations of amide.*

## EXPERIMENTAL

**Materials**—Tritium-labeled prednisolone[1] and $^{14}$C-butanol[2] were used as received. The sources and methods of purification of other chemicals used in this study were reported previously (1).

**Drug Solutions**—For the absorption studies, 0.5 m*M* prednisolone, 1 m*M* butanol, and 0–22 m*M* *N,N*-di-*n*-propylpropionamide were dissolved in 0.9% NaCl solution. Sufficient $^{3}$H-prednisolone and $^{14}$C-butanol were added to make the activity of each label approximately $5 \times 10^5$ d.p.m./ml. For the lipoid barrier experiments, prednisolone (0.5 m*M*) and amide (when present) were dissolved in water.

**Prednisolone Absorption from Rat Intestine**—Male Sprague-Dawley rats, weighing 220–310 g. and fasted 14–22 hr., were anesthetized with ethyl carbamate, 1.3 g./kg. i.p. The abdomen of each rat was opened by a midline incision, and 5 ml. of 0.9% NaCl solution at 37° was instilled into the peritoneal cavity. A stainless steel cannula[3] was inserted through a small transverse incision in the intestine approximately 10 cm. distal to the stomach and tied in place with a silk suture. A second cannula, constructed from polyethylene tubing[4], was placed approximately 20 cm. distal to the first cannula.

The intestine was washed as described previously (1), and the rat was placed on a heating pad. The temperature of the rat, monitored throughout the absorption experiment, was maintained at 35–37°. The stainless steel cannula was connected with polyethylene tubing[5] to the outlet of a perfusion pump[6], and the polyethylene cannula was connected to a 5-ml. reservoir[7] containing a magnetic stirring bar (Fig. 1). The inlet of the perfusion pump, the outlet of a 10-ml. buret containing a solution of 0.9% NaCl, and the outlet of an infusion pump[8] (when the amide was present) were also connected to the reservoir with polyethylene tubing[5]. When the amide was not present in the drug solution, the unused opening to the reservoir was tightly sealed with a polyethylene cap. The drug solution was placed in the reservoir, and the infusion pump was adjusted to deliver an aqueous solution of the amide into the reservoir at a rate of 0.0216 ml./min. The rate of infusion of the amide required to maintain the

[1] Amersham/Searle, Des Plaines, IL 60018. Specific activity 1.4 mc./mg.; labeled radiochemical purity > 98%.
[2] New England Nuclear, Boston, MA 02118. Specific activity 3.7 mc./mmole.
[3] The cannula was a 21-gauge disposable hypodermic needle without the plastic hub; the hub end of the needle was inserted into the intestine.
[4] Intramedic polyethylene tubing, PE 320, 2.7 mm. i.d.
[5] Intramedic, PE 60, 0.76 mm. i.d.
[6] Beckman solution metering pump, model 746.
[7] The reservoir was constructed from a 5-ml. volumetric flask by adding four 1.5-cm. pieces of 3-mm. o.d. glass tubing at equally spaced distances around the body of the flask.
[8] Harvard Apparatus Co., syringe pump model 940.

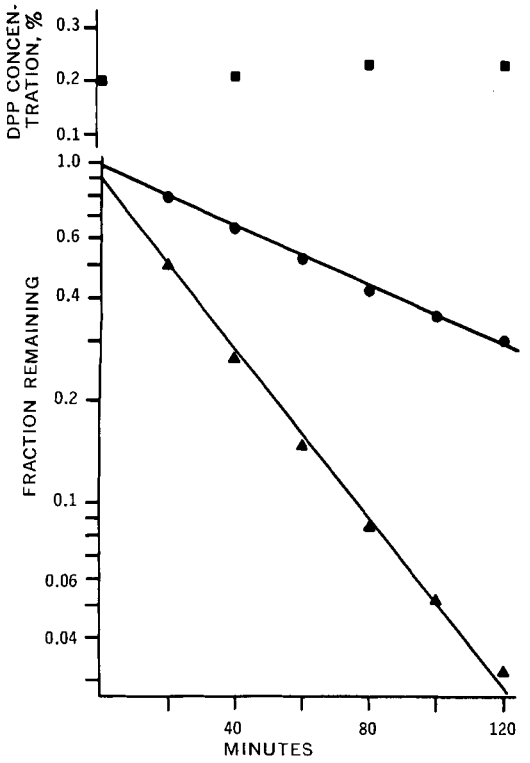


**Figure 2**—*Concentrations of* N,N-*di*-n-*propylpropionamide* (*DPP*) (■), *prednisolone* (●), *and butanol* (▲) *as a function of time in a typical intestinal absorption experiment.*

initial concentration in the intestinal solution was calculated from its absorption rate constant as determined by preliminary experiments.

The steady-state concentration of the amide in the intestinal solution was varied by changing its concentration in the solution infused into the reservoir. The perfusion and infusion pumps were started simultaneously; additional drug solution was then added to the reservoir, which was immersed in a 37° water bath, until the system (pump, rat intestine, reservoir, and tubing) was filled to capacity (approximately 9 ml.). The drug solution was circulated through the intestine for 5–10 min. before the "zero-time" sample was removed. From then on, 0.1-ml. samples were obtained periodically from the reservoir for subsequent assay.

Prednisolone and butanol absorption rate constants were determined from the slopes of lines fitted by least squares to semilogarithmic plots of the fraction of prednisolone or butanol remaining *versus* time[9]. The rate constants were corrected for drug removed in the samples and were converted to clearance per centimeter by multiplying the rate constant by the volume of the drug solution and dividing it by the length of intestine between the cannulas. The amide concentration reported for each experiment was the average of four determinations made throughout the experiment. A small positive hydrostatic pressure was maintained in the intestine by keeping the level of drug solution in the neck of the reservoir, which was open to the atmosphere, approximately 2 cm. above the rat. The volume of perfusate was kept constant throughout the experiment by adding solvent (0.9% NaCl solution) intermittently to the reservoir from the buret. During a 120-min. experiment, approximately 4.5 ml. (including 2.60 ml. aqueous amide solution from the infusion pump in experiments with amide) was added to the system to replace fluid loss due to sampling and water absorption from the intestine. At the end of the experiment, the segment of intestine between the cannulas was excised and its length was measured; the volumes of the drug solution in the system and the total volume of solvent added to the system during the experiment were recorded.

**Prednisolone Transfer across Lipoid Barrier**—A diffusion cell consisting of two 5-ml. capacity chambers separated by a Millipore filter[10] soaked in isopropyl myristate (2) was used. This cell was attached to the perfusion–infusion system, already described, in place of the rat. The two ports of the source chamber were connected with polyethylene tubing to the perfusion pump outlet and to the reservoir, respectively. When studying the transfer of prednisolone across the barrier in the presence of *N,N*-di-*n*-propylpropionamide, the initial concentration of the amide in the source solution was maintained constant by continuously infusing undiluted amide from a syringe pump into the reservoir at a rate equal to its transfer rate across the barrier. The amide immediately dissolved in the well-stirred drug solution in the reservoir.

The solution of prednisolone with or without amide was circulated (2 ml./min.) continuously by the perfusion pump through the source chamber and the reservoir, and water saturated with isopropyl myristate was pumped (5 ml./min.) through the sink chamber without recirculation. When amide was present, the perfusion pump was started at the same time as the infusion pump. Additional drug solution was added to the reservoir until the system (reservoir, pump, source chamber, and tubing) was filled to capacity (approximately 12 ml.). The "zero-time" sample was removed from the reservoir after the drug solution had circulated for 30 min. Except at the times when samples were removed, the neck of the reservoir was sealed with a greased ground-glass stopper. This fixed the position of the membrane in the cell, preventing its displacement by unequal hydrostatic pressures in the two compartments.

The volume of the source solution remained nearly constant throughout the experiment since no more than 4% of the volume was removed for assay and amide was replaced by constant infusion into the source solution. Therefore, no solvent was added to the source solution during these experiments. Three experiments were carried out with each lipoid barrier, and the rate constants determined from these experiments were averaged. Also averaged were the amide concentrations, each of which was the average of determinations made on samples taken at the beginning, middle,

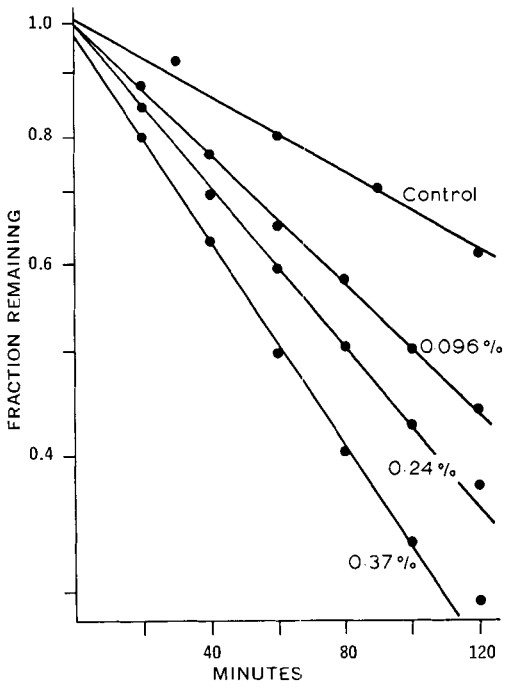


**Figure 3**—*Effect of various constant concentrations (0.096, 0.24, and 0.37%) of* N,N-*di*-n-*propylpropionamide on the absorption of prednisolone from the* in situ *rat intestine. The control experiment (without amide) was carried out for 180 min. Shown are representative data from single experiments.*

[9] Circulation of prednisolone solution with and without amide through the perfusion system without the rat (phantom perfusion) did not change the steroid concentration. Certain other steroids are, however, taken up by the tubing or adsorbed on parts of the apparatus. It is essential to carry out phantom perfusions with all drugs to prevent artifacts.

[10] Type OH (polyethylene).

**Table I**—Influence of *N,N*-Di-*n*-propylpropionamide on Butanol Clearance[a] from the Rat Small Intestine

| | Control | With 0.4% Amide |
|---|---|---|
| Mean clearance | 0.0113 | 0.0119 |
| Standard deviation | 0.00216 | 0.00150 |

[a] Milliliters per minute per centimeter of intestine; each mean value is based on 20 experiments.

and end of an experiment. Preliminary experiments showed that the transfer rate of prednisolone across the barrier was independent of the flow rate of solvent through the source chamber between 2 and 5 ml./min. and that the steady-state concentration of the amide decreased less than 6% over this range of flow rate.

**Assay Methods**—*N,N*-Di-*n*-propylpropionamide was determined by GLC as described previously (1). Prednisolone and butanol were determined by a dual-label assay method using a three-channel scintillation spectrometer[11]. The efficiencies of $^{14}C$ and tritium (approximately 70 and 30%, respectively), and the spillover of $^{14}C$ and tritium counts into the other's channel (approximately 10 and 1%, respectively) were a linear function of the ratio of the counts induced by an external gamma source in two of the channels over a range of quenching encompassing that encountered in assaying the intestinal drug solutions. During each counting period, the efficiency and spillover were checked with quenched standards, and several standards containing varying proportions of $^{14}C$ and tritium were counted. The disintegration rates in each sample of intestinal drug solution due to tritium and $^{14}C$ were determined from the total counts in the tritium and $^{14}C$ channels, the background count rate in each channel (50 and 15 c.p.m., respectively), and the channels ratio for each sample.

## RESULTS AND DISCUSSION

The initial concentration of *N,N*-di-*n*-propylpropionamide in the intestinal drug solution was maintained throughout the prednisolone absorption experiment by infusing the amide at a constant rate equal to its absorption rate (Fig. 2). The absorption of prednisolone proceeded by apparent first-order kinetics under the experimental conditions. Preliminary experiments showed that the absorption rate constant of the steroid was perfusion rate independent over a 0.5–5.0-ml./min. range. It is, therefore, unlikely that the aqueous diffusion layer at the drug solution–mucosa interface is absorption rate limiting in these studies.

To minimize rat-to-rat variability in absorption kinetics due to physiologic or technical factors, the absorption rate constant of prednisolone was determined relative to that of butanol which served as an "internal standard." The intestinal absorption of butanol was also describable by first-order kinetics (Fig. 2), and its absorption rate was not affected by the amide (Table I). When the intestinal clearances of prednisolone and butanol were determined simultaneously in 16 animals, the coefficient of variation of the *relative* clearance of prednisolone (that is, the ratio of prednisolone clearance to butanol clearance) was only 4% of the mean compared to 12% for the absolute prednisolone clearance values.

The pronounced distributive phase noted in a previous study of prednisolone absorption from the *in situ* rat intestine (1) was not apparent in the present study in which the recirculating perfusion technique was used (Figs. 2 and 3). This is probably due to the much larger volume of drug solution used in these experiments (approximately 0.45 ml./cm. of intestine as compared to 0.08 ml./cm. in the previous study) and to the fact that perfusion proceeded for 5–10 min. before removal of the "zero-time" sample.

In agreement with the results of experiments reported previously (1), *N,N*-di-*n*-propylpropionamide enhanced appreciably the absorption of prednisolone, and this effect increased with increasing concentration of the amide (Fig. 3). However, the relationship between the intestinal absorption rate constant of prednisolone and its apparent partition coefficient was not linear (Fig. 4). This is contrary to what would be anticipated on the basis of the effect of the amide

[11] Packard Tricarb model 3320, Packard Instrument Co., Downers Grove, Ill.

**Table II**—Percent Prednisolone Complexed[a] in the Intestinal Drug Solution Initially (*A*) and when 75% of the Prednisolone Is Absorbed (*B*)

| Amide Concentration, % | Percent Complexed | |
|---|---|---|
| | *A* | *B* |
| 0.096 | 2.367 | 2.371 |
| 0.240 | 5.676 | 5.684 |
| 0.370 | 8.505 | 8.517 |

[a] Theoretical calculations based on an initial prednisolone concentration of $5 \times 10^{-4}$ *M*, a stability constant of 4.5 $M^{-1}$ (2), and an assumed 1:1 stoichiometry.

on the permeability to prednisolone of a simple homogeneous lipoid barrier (2). Curves similar to those in Fig. 4 can be explained theoretically (2), but only for complexes with an association constant in aqueous solution much larger than that of the prednisolone–amide complex. The interaction of prednisolone with the amide in water is relatively weak; the fraction of the steroid complexed with amide in the intestinal perfusion solution is, therefore, very low and does not change significantly as the concentration of prednisolone declines (Table II).

There was a question whether the curvatures in Fig. 4 were due to the fact that sink conditions applied to both prednisolone and the amide in the *in vivo* experiments. The previous studies of the effect of *N,N*-di-*n*-propylpropionamide on prednisolone transfer through an artificial lipoid barrier were carried out with equal concentrations of amide in the source and receiving chambers of the diffusion cell. However, when the effect of the amide on the permeability of the artificial lipoid barrier was determined under conditions similar to those of the intestinal absorption experiments (*i.e.*, simultaneous diffusion of both prednisolone and amide from an aqueous source solution to an aqueous sink solution), a linear relationship between transfer rate constant and apparent partition coefficient was again found (Fig. 5). Thus, the concept of the rat intestine as a simple lipoid barrier appears unsuitable as the basis for

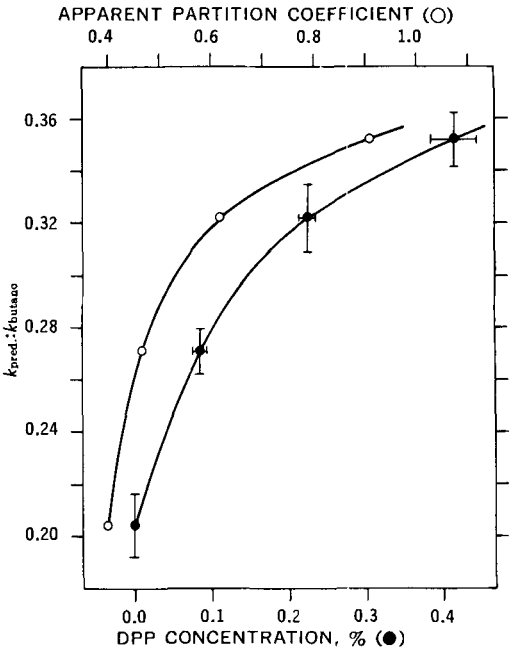


**Figure 4**—*Relationship between the intestinal absorption rate constant for prednisolone (relative to butanol) and the concentration of* N,N-*di*-n-*propylpropionamide (DPP) in the intestinal drug solution* (●). *Also shown* (○) *is the relationship between the relative intestinal absorption rate constant for prednisolone and the apparent partition coefficient of prednisolone between isopropyl myristate and water. The water phase contained the same amide concentration as the intestinal drug solution used in the various absorption experiments. Each data point represents the mean of four experiments; the bars represent the standard deviations.*

a kinetic analysis of the effect of *N,N*-di-*n*-propylpropionamide on prednisolone absorption.

Soergel *et al.* (3) pointed out that the intestinal mucosa contains several potential barriers to transepithelial movement of substances, including the fuzzy coat of the microvilli, the apical cell wall, cytoplasm, the basal and lateral cell walls, the basement membrane, the capillary endothelium, and unmixed layers of fluid on the cell surface. Experimental evidence suggests that the human small intestinal mucosa (3), the human red blood cell (4), and certain other biologic structures (5) act like two or more barriers in series, each with different permeability characteristics. This concept of the intestinal mucosa was used as a basis for theoretical explorations.

The intestinal mucosa was modeled as a series of from two to five barriers, using an analog simulation program for a digital computer (6). The inset in Fig. 6 shows schematically one such model, consisting of three barriers separating the drug solution and an infinite sink. It was assumed that the permeabilities of all of the barriers to the drug are identical in the absence of complexing agent and that the latter affects only the permeability of the first barrier to the drug. The compartments between the barriers were assumed to be homogeneous and small compared to that of the "external solution" (the drug solution on the mucosal side). The series of barriers contains only an insignificant amount of drug under these conditions, and an initial rapid loss of drug from the external solution does not occur.

The apparent rate constant ($k_{app.}$) for transfer of drug ($A$) across the composite barrier was calculated from the slope of a semilogarithmic plot of the fraction of $A$ remaining in the external solution as a function of time. When a complexing agent ($B$) was present, the rate constant ($k_1$) for transfer of $A$ across the first barrier in the series was calculated from an expression developed previously (2):

$$k_1 = k_a + k_c \cdot K' \cdot PC_b \cdot C_b/2 \qquad \text{(Eq. 1)}$$

where $k_a$ and $k_c$ are rate constants for the transfer of $A$ and complex ($C$) across the first barrier, $K'$ is the association constant for $C$ in the barrier, $PC_b$ is the barrier–water partition coefficient of $B$, and $C_b$ is the concentration of $B$ in the external solution. The concentration of $B$ in the barrier was assumed to be the average of the concentrations at each of its interfaces. Thus, the existence of a concentration gradient of complexing agent across the barrier was ignored in these calculations[12]. It was assumed that complex formation does not occur in the aqueous phase and that $k_a = 0.13$, $k_c = 0.10$, $PC_b = 5$, $K' = 10\ M^{-1}$, and $C_b$ ranges from 0 to 0.48 $M$ and remains constant with time.

The concentration of $B$ in Fig. 6 is expressed as a fraction relative to the highest (0.48 $M$) concentration used in these simulations; $k_{app.}$ is plotted as the ratio relative to the rate constant in the absence of complexing agent ($k$). The simulations show that $A$ disappears from the external solution by apparent first-order kinetics in the presence and absence of $B$. The apparent permeability of the series of barriers increases nonlinearly with an increasing concentration of $B$, as illustrated in Fig. 6 for two- and three-barrier models. The curves in the figure approach a maximum $k_{app.}:k$ ratio of 2 and 1.5, consistent with the effective removal of one barrier from a two- and three-barrier series, respectively, at high concentrations of complexing agent[13]. The data points in Fig. 6 represent the rate constants obtained in experiments with the *in situ* rat intestine; they have also been normalized ($k_{app.}:k$) so that they could be plotted on the coordinates in Fig. 6. The experimental data happen to fall exactly on the two-barrier simulation curve, although no attempt was made to "fit" the curve to the data.

In other computer simulations of the composite barrier, the complexing agent was assumed to increase the permeability of all the barriers in relation to its concentration in each barrier. As in the previous simulations, the concentration of the complexing agent was assumed to be the average concentration within each barrier. Due to the gradient of complexing agent across all the barriers, its concentration becomes progressively lower in successive barriers. In this model, the drug crosses the composite barrier by apparent first-order kinetics but the overall rate constant for transfer of the drug across the barriers is a nearly linear function of the concentration of complexing agent in the external solution and the apparent permeability of the composite barrier increases several fold. This is quite different from the observed effect of *N,N*-di-*n*-propyl-

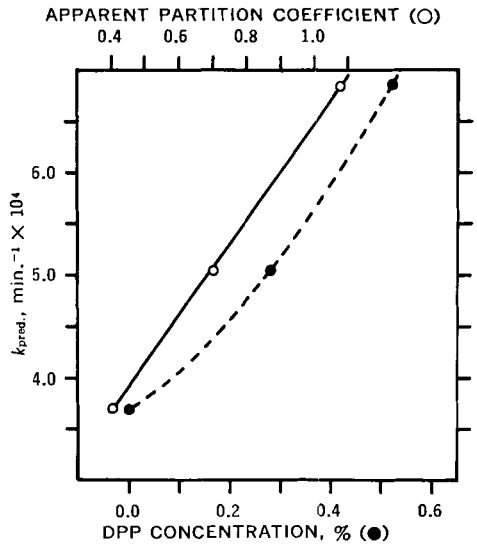


**Figure 5**—*Relationship between the rate constant for transfer of prednisolone across an artificial lipoid barrier and the apparent partition coefficient of prednisolone between isopropyl myristate and water [which contained the same concentration of* N,N-*di*-n-*propylpropionamide (DPP) as the prednisolone solutions used in the absorption experiments]. Also shown is the relationship between the rate constant for prednisolone transfer across the lipoid barrier and the concentration of amide in the drug solution. The ratio of the upper to the lower horizontal scales is the same as in Fig. 4.*

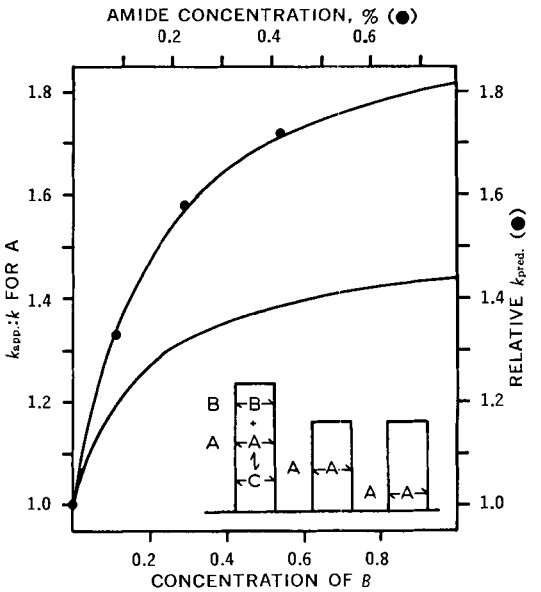


**Figure 6**—*Computer simulation of the effect of a complexing agent* (B) *on the transfer of a substance* (A) *across a series of successive barriers (depicted schematically on the lower right). The upper curve is for two barriers, the lower curve is for three. See text for additional explanations. Also shown* (●) *are the relative intestinal absorption rate constants for prednisolone at various* N,N-*di*-n-*propylpropionamide concentrations, as determined in this study.*

[12] This simplification does not seem to affect the kinetic analysis significantly. The same approach was used to calculate the effect of *N,N*-di-*n*-propylpropionamide on the permeability of the artificial lipoid barrier to prednisolone under sink conditions. The slope of the $k_{pred.}$ *versus* partition coefficient plot in Fig. 5 is very close to one-fourth the slope of a similar plot obtained when the amide concentration was equal on both sides of the barrier. This would be expected since there is a twofold difference in the average concentration of the amide in the barrier under the two conditions and the rate constant for the approach to equilibrium is twice that for unidirectional transfer to a sink (Eq. 10 in *Reference 2*).

[13] This statement applies only when each barrier has the same permeability to the drug.

propionamide on the permeability of the *in situ* rat intestine. It appears, therefore, that the nonlinear relationship between the apparent absorption rate constant of prednisolone and the concentration of *N,N*-di-*n*-propylpropionamide in the intestinal drug solution can be explained most readily if it is assumed that the intestine behaves as a series of barriers toward prednisolone and that *N,N*-di-*n*-propylpropionamide increases only the permeability of the first barrier. This could conceivably occur if the permeability of the other barriers to *N,N*-di-*n*-propylpropionamide is very high compared to that of the first barrier so that the concentration of the amide would be effectively zero beyond the first barrier. Alternatively, interaction between the steroid and *N,N*-di-*n*-propylpropionamide may occur only in the first barrier because it may differ in structure or composition from the other barriers.

It must be emphasized that what we have discussed here are functional models, which may or may not have physical reality. Such a functional approach is quite appropriate since this is how most of the present knowledge about biological membranes has been obtained. The studies described here represent a new dimension in this endeavor since they involved the use of two interacting substances, rather than single solutes, as probes to explore the characteristics of biologic barriers.

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# Rates of Hydrolysis of *N*-Chlorinated Molecules


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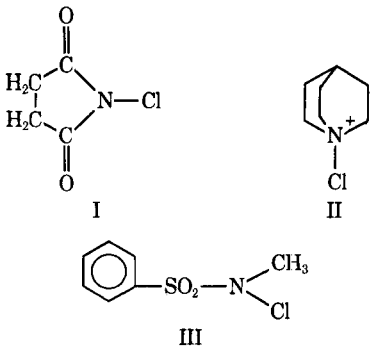
**Abstract** □ Formation and hydrolysis rate constants were calculated for *N*-chlorosuccinimide, *N*-chloroquinuclidinium ion, and *N*-chloro-*N*-methylbenzenesulfonamide in water. The rates of hydrolysis of these compounds were much slower than the rates at which they are known to transfer their active chlorine to nitrogenous bases in water. Hence, the present results confirm an earlier suggestion that chlorine transfer between nitrogenous bases in water is not mediated by hydrolysis of the *N*-chloro compounds to hypochlorous acid but involves a direct reaction between the nitrogenous chlorine donor and acceptor molecules. The kinetic results are also consistent with a postulate that the rate-determining step in the reaction between nitrogenous compounds and hypochlorous acid involves reaction between the amide and imide anions and amine neutral molecules and neutral molecules of hypochlorous acid. The rate-determining step in the hydrolysis reactions appears to involve attack of hydroxide ion on the *N*-chloro compounds.



**Keyphrases** □ *N*-Chlorosuccinimide—formation and hydrolysis rate constants in water □ *N*-Chloroquinuclidinium ion—formation and hydrolysis rate constants in water □ *N*-Chloro-*N*-methylbenzenesulfonamide—formation and hydrolysis rate constants in water □ Hydrolysis rate constants—*N*-chlorinated molecules


The bactericidal and detoxifying action of *N*-chlorinated molecules such as *N*-chloramine results from their abilities to transfer their active chlorine to other molecules. The mechanism of the chlorine transfer was postulated by Higuchi and his coworkers (1, 2) to involve a direct reaction between the organohalogenating agent and another receptor rather than *via* an intermediate forming of hypochlorous acid.

One purpose of this study was to confirm this postulation by showing that the rates of hydrolysis of *N*-chlorosuccinimide (I), *N*-chloroquinuclidinium ion (II), and *N*-chloro-*N*-methylbenzenesulfonamide (III) in water are slower by several orders of magnitude than the rates at which these molecules are known to transfer positive chlorine to other molecules. Another purpose was to obtain information about the mechanism of formation and hydrolysis of *N*-chloro compounds. Weil and Morris (3) previously showed that pH–rate profiles for formation of chloramines from hypochlorous acid and amines can be explained by either ionic ($OCl^- + R_2\overset{+}{N}H_2$) or neutral molecule ($HOCl + R_2NH$) mechanisms. Although these authors favored the neutral molecule mechanism, it was felt that more



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