Kinetic and Thermodynamic Aspects of *In Vitro* Interphase Transfer of Sulfonamides I: Influence of Methyl Group Substitution on Transfer of Unionized Sulfonamides

G. E. SCHUMACHER[x] and JANARDAN B. NAGWEKAR

Abstract □ The influence of methyl group substitution on the kinetic and thermodynamic aspects of the interphase transfer of three unionized sulfonamides was studied in a two-phase *in vitro* system composed of an aqueous pH 4.3 buffer and *n*-octanol. By applying the theory of absolute reaction rates to the interphase transfer process, the forward parameters (k_f, ΔH_f^*, and ΔS_f^*) increased but the back parameters (k_b, ΔH_b^*, and ΔS_b^*) decreased as the lipophilic nature of the sulfonamides increased. In terms of the net thermodynamic parameters for the process, both ΔH and ΔS increased as the lipophilicity increased. The entropic energy contribution ($T\Delta S$) dominated the ΔH contribution, however. Thus, the observed increase in the ratio of k_f/k_b with increased lipophilicity appeared to be due to an increase in ΔS for transfer from aqueous to alcohol phases resulting from substitution of the methyl group. Based upon these kinetic and thermodynamic parameters, possible mechanisms for the interphase transfer of unionized sulfonamides were proposed.

Keyphrases □ Sulfonamides (sulfadiazine, sulfamerazine, and sulfamethazine)—effect of pyrimidine ring methyl on interphase transfer, water-*n*-octanol system □ Transfer of unionized sulfonamides (sulfadiazine, sulfamerazine, and sulfamethazine)—effect of pyrimidine ring methyl on interphase transfer □ Thermodynamic parameters—interphase transfer of unionized sulfonamides (sulfadiazine, sulfamerazine, and sulfamethazine), water-*n*-octanol system

In recent years, several investigators developed the application of *in vitro* models in the study of the transfer of solutes across immiscible phases (1–8). These studies have been valuable in constructing models and developing kinetic equations to evaluate the influence of variables such as partition coefficient, dissociation constant, pH, phase polarity, and phase constituents on the diffusion rates of solutes. The thermodynamics and mechanisms of interphase transfer, however, do not appear to have been examined in pharmaceutical systems.

The purpose of this investigation was to determine in *in vitro* systems the kinetic and thermodynamic parameters for the interphase transfer (aqueous ↔ octanol) of sulfadiazine and its homologs, sulfamerazine and sulfamethazine, and to use these parameters to gain insight into possible mechanisms for the interphase transfer of these compounds at the molecular level. These three sulfonamides are considered to be suitable compounds for this investigation, because they differ from each other only in the hydrophobic nature of the pyrimidine aromatic moiety and because they are ampholytes which exist in cationic, unionized, and anionic forms over the physiological pH range encountered during GI absorption. Thus, in support of the objectives of this study, the manner in which factors such as the partition coefficient, interface composition, solute structure and charged form, and thermodynamic parameters contribute to the interphase transfer characteristics of sulfonamides can be studied in two-phase systems composed of various aqueous buffer and alcohol phases. The differences in interphase transfer rates demonstrated by the homologs and their charged forms may be attributed to differences in activation entropies and enthalpies resulting from variations in intermolecular forces between solute and solvent.

This portion of the study examines the effect on the kinetic and thermodynamic parameters of the interphase transfer of sulfonamides resulting from methyl group substitution on the pyrimidine moiety of the unionized sulfonamide nucleus. These results may reveal the possible role of the hydrophobic interaction between a drug molecule and solvent while crossing the interface and they may provide an additional dimension to the understanding of the mechanisms responsible for the transfer of drugs across biological membranes.

EXPERIMENTAL[1]

Sulfadiazine, sulfamerazine, and sulfamethazine were specially synthesized commercially, purified, and analyzed by differential scanning calorimetry[2]. The following reagents were also used in the highest quality obtainable: *n*-octanol, acetic acid, potassium chloride, and hydrochloric acid.

Diffusion Experiments—All aqueous buffer solutions and organic solvents were mutually saturated prior to beginning the diffusion experiments. To approximate the ionic strength of the GI tract (9), all aqueous buffer solutions were adjusted to 0.15 with potassium chloride. To study the diffusion of the unionized form of the sulfonamides, 4×10^{-4} *M* solutions of each sulfonamide were prepared in an aqueous acetate buffer solution[3] adjusted to pH 4.3.

A suitable glass cell capable of containing two immiscible solvents and a stirring apparatus were used for conducting the diffusion experiments. The glass cell consisted of a 120-ml (4-oz) square, wide-mouth prescription-type bottle which presented a cross-sectional interfacial area of 25 cm^2. The cap of the bottle was perforated to allow insertion of a double-bladed, glass stirring shaft. The loss of organic solvent that occurred due to the perfo-

[1] Diffusion experiments were conducted with the aid of a Phipps and Bird six-unit stirrer (Phipps and Bird, Inc., Richmond, Va.) containing a speed controller, a water bath equipped with a thermostatic control, glass diffusion cells, and specially prepared glass stirrers. The quantitative analysis of sulfonamides in solution was performed with a Beckman model DU UV spectrophotometer (Beckman Instruments, Fullerton, Calif.). All pH determinations were made on a Corning model 12 research pH meter (Corning Scientific Instruments, Corning, N.Y.).

[2] Matheson, Coleman and Bell, Norwood, Ohio.

[3] The acetate buffer solution contained 0.02 *M* acetic acid, 0.124 *M* potassium chloride, 0.006 *M* sodium hydroxide, and distilled water.

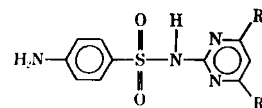


Table I—Structures and Physical Data for the Sulfonamides

Sulfonamide	Adjusted Literature[a] pK$_1$	Adjusted Literature[a] pK$_2$	R$_1$	R$_2$	pI Range[b]	Apparent Partition Coefficient[c]
Sulfadiazine	1.86	6.34	H	H	3.86–4.34	0.91
Sulfamerazine	2.12	6.92	CH_3	H	4.12–4.92	1.45
Sulfamethazine	2.22	7.24	CH_3	CH_3	4.22–5.24	2.09

[a] Adjusted values obtained by applying the Debye–Hückel equation for ionic strength of 0.15 to the literature values. [b] pH range in which the sulfonamide is more than 99% in the unionized form. [c] Expressed in terms of the ratio of solute concentrations in octanol–aqueous pH 4.3 acetate buffer phases, as obtained from interphase transfer experiments, at 36°.

ration was negligible, if any. One of the 2.0-cm blades was positioned at the midheight of each immiscible phase. The stirring blades were rotated at a constant speed of 48 rpm by using the six-unit stirrer which allowed six simultaneous experiments to be run at any one temperature. The studies at 24° were performed in a temperature-controlled room, while those at 30 or 36° were performed in a water bath maintained at the desired temperature ±0.5°.

For experiments involving the net transfer of solute from an aqueous to an organic phase, 50 ml of a sulfonamide-containing aqueous pH 4.3 buffer solution was pipeted into the glass cell; at pH 4.3 the sulfonamides are essentially in an unionized form. The stirring blades were clamped into place prior to pipeting 50 ml of *n*-octanol gently over the sulfonamide solution. A blank composed of the aqueous buffer solution and organic solvent was prepared in the same manner. Four 1-ml samples of organic phase were removed from the diffusion cells containing the sulfonamide at 15–30-min intervals, depending upon the rate of transfer, by using 1-ml tuberculin syringes. Samples of organic phase were also obtained from the diffusion cell containing the blank at the corresponding time. To maintain an equal volume of both phases in the system, a 1-ml sample of aqueous buffer phase was removed at the time the organic phase was sampled using a different tuberculin syringe. To measure the partition coefficient, diffusion was allowed to proceed to equilibrium, which required 5–8 hr depending upon the rate of transfer. The final sample was then taken from the organic phase and the blank. All samples of the organic phase were diluted to 10 ml with ethanol, their absorbance was measured at 270 nm using a UV spectrophotometer, and the concentration was determined from a previously prepared Beer's law plot for the sulfonamide. The procedure for studying the net diffusion of solute from the organic phase to the aqueous phase was the same as already described, except that the sulfonamide was initially contained in the organic phase.

Determination of Partition Coefficients of Sulfonamides—Apparent partition coefficients for the unionized form of the sulfonamides were determined at 24, 30, and 36° by measuring the concentration of sulfonamide in the organic phase at equilibrium. The partition coefficient was expressed as the ratio of equilibrium concentrations in the organic–aqueous phases.

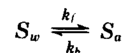
Determination of Dissociation Constants and pH for Studying Unionized Form of Sulfonamides—The dissociation constants of the sulfonamides were determined by a titrimetric procedure at 30°. They showed a close approximation to the values obtained from the literature by using the Debye-Hückel equation to compensate for the ionic strength of 0.15 of the solutions used in the study (10–12). By ignoring activity coefficients, since they were unavailable, adjusted literature values, pK$_1$ and pK$_2$, were taken to represent the pH values at half-protonation and half-dissociation of the sulfonamides, respectively. The pH range in which these amphoteric compounds were present as essentially unionized species was obtained by adding 2 units to pK$_1$ and subtracting 2 units from pK$_2$.

RESULTS

Dissociation Constants and Partition Coefficients of Sulfonamides—The structures of the three sulfonamides, their adjusted dissociation constants, and the pH range in which the compounds are more than 99% present in their unionized form are summarized in Table I. Based on the pI range of the compounds, pH 4.3 was chosen as a suitable value for the aqueous buffer phase for studying the unionized form of the three sulfonamides.

The apparent partition coefficients of the sulfonamides in the pH 4.3 acetate buffer–*n*-octanol system are also included in Table I. The partition coefficient increased as the number of methyl groups substituted on the pyrimidine moiety of the sulfonamides increased. Since the partition coefficient has long been recognized as a significant factor in membrane penetration and interphase transfer (1, 13–17), this property was expected to play a role in the interpretation of the experimental interphase transfer data.

Kinetic and Thermodynamic Data—Sulfadiazine, sulfamerazine, and sulfamethazine were used to examine the influence of methyl group substitution in these molecules (Table I) on their interphase transfer characteristics. The interphase transfer of sulfonamide in the experimental two-phase system was described by a reversible kinetic scheme (Scheme I).



$$S_w \underset{k_b}{\overset{k_f}{\rightleftharpoons}} S_a$$

Scheme I

In this scheme, S_w and S_a represent the amounts of sulfonamide in the aqueous buffer phase and alcohol phase, respectively, and k_f and k_b are the apparent first-order rate constants for forward and back transfer, respectively.

For graphical presentation, the integrated rate equation (18) describing the interphase transfer denoted in Scheme I, when the sulfonamide is initially present in the aqueous phase, is given as Eq. 1:

$$\log [(Sa)\text{eq} - (Sa)] = \log (Sa)\text{eq} - \frac{(k_f + k_b)t}{2.3} \quad \text{(Eq. 1)}$$

In this equation, (Sa)eq is the concentration of sulfonamide in the

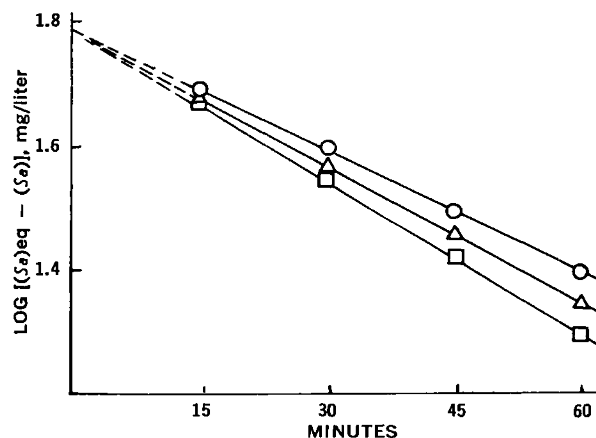


Figure 1—*Transfer of sulfamethazine from an aqueous pH 4.3 buffer to* n-*octanol. Data are the average of four experiments at each temperature. Key:* ○, *25°;* △, *30°; and* □, *36°.*

Table II—Kinetic and Thermodynamic Parameters of Activation for the Interphase Transfer of Unionized Sulfonamides in a Two-Phase System at 36°

	k, hr^{-1}		ΔH^*, cal/mole		ΔS^*, cal/mole-deg		ΔF^*, cal/mole		Ea, cal/mole	
Sulfonamide	k_f	k_b	ΔH_f^*	ΔH_b^*	ΔS_f^*	ΔS_b^*	ΔF_f^*	ΔF_b^*	Ea_f	Ea_b
Sulfadiazine	0.473	0.518	4099	4145	−46.8	−46.5	18,574	18,515	4713	4759
Sulfamerazine	0.672	0.456	4374	3147	−45.2	−50.0	18,355	18,590	4988	3761
Sulfamethazine	0.896	0.428	5060	2379	−42.4	−52.6	18,174	18,639	5674	2993

octanol phase at equilibrium, and (Sa) is the concentration in that phase at the time of sampling, t. A typical plot of experimental data using Eq. 1 is shown in Fig. 1. The slope of the line, as obtained by the method of least squares, is $(k_f + k_b)/2.3$.

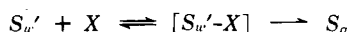
The method for obtaining the k_f and k_b values, as well as the energy of activation for the forward (Ea_f) and back (Ea_b) reactions, was described (18). Accordingly, k_f and k_b are calculated from the following equations:

$$k_f = \frac{(Sa)\text{eq}}{(Sw)_0}(k_f + k_b) \quad \text{(Eq. 2)}$$

$$k_b = (k_f + k_b) - k_f \quad \text{(Eq. 3)}$$

where $(Sw)_0$ is the initial concentration of sulfonamide in the aqueous buffer phase.

The thermodynamic parameters of activation for the interphase transfer process noted in Scheme I were obtained by applying the theory of absolute reaction rates to the diffusion process, as depicted in Scheme II (19), where S_w' and X represent a sulfonamide molecule and solvent molecule(s) of octanol, respectively. This scheme provides for the inclusion of an intermediate state composed of a transient association of reacting molecules, S_w' and X, which is termed an "activated complex" $[S_w'\text{-}X]$, prior to the diffusion of the solute to a new equilibrium position. Assuming that transfer across the interface is rate limiting (2, 4, 8), the formation of the activated complex is considered to be the rate-limiting step for the diffusion process across the interface.



Scheme II

A summary of the kinetic and thermodynamic parameters for the interphase transfer of the three sulfonamides at 36° is shown in Table II.

The ΔF^* for the forward or back transfer was obtained from Eq. 4 (18):

$$k = \frac{RT}{Nh} e^{-\Delta F^*/RT} \quad \text{(Eq. 4)}$$

where R, T, N, and h have the usual meanings. The ΔH^* for the forward or back transfer was obtained from Eq. 5 (18):

$$\Delta H^* = Ea - RT \quad \text{(Eq. 5)}$$

where Ea is the energy of activation; Ea is obtained from the slope of the Arrhenius plot of log k *versus* $1/T$. These plots for the interphase transfers are shown in Figs. 2 and 3. Since these plots yielded reasonable least-squares lines, the ΔH^* is considered to be constant over the temperature range of 24–36°. As noted in Table III, the forward parameters $(k_f$, ΔH_f^*, and $\Delta S_f^*)$ increased but the back parameters $(k_b$, ΔH_b^*, and $\Delta S_b^*)$ decreased as the lipophilic nature of the three sulfonamides increased.

Davies (1) developed the concept of partition coefficient energy in interpreting interphase transfer data. He considered the difference in free energy of activation for forward and back transfer $(\Delta F_f^* - \Delta F_b^*)$ to represent the net free energy of transfer (ΔF) of solute across an interface. He related the partition coefficient, rate constants, and the net free energy of interphase transfer as follows:

$$K_w^0 = \frac{k_f}{k_b} = \frac{e^{-\Delta F_f^*/RT}}{e^{-\Delta F_b^*/RT}} = e^{\Delta F/RT} \quad \text{(Eq. 6)}$$

$$K_w^0 = \frac{k_f}{k_b} = e^{(\Delta H/RT - \Delta S/R)} \quad \text{(Eq. 7)}$$

The relationships between the rate constants, net thermodynamic parameters, and partition coefficients (K_w^0) for the interphase transfer of the three sulfonamides are recorded in Table III.

Thermodynamic Contributions of Methyl Group Substitution to Interphase Transfer of Sulfonamides—To assess the role of the methyl group in altering the net thermodynamic parameters for interphase transfer, the thermodynamic contributions resulting from the systematic addition of methyl groups to sulfadiazine are recorded in Table IV. Since sulfamerazine differs from sulfadiazine and sulfamethazine differs from sulfamerazine only

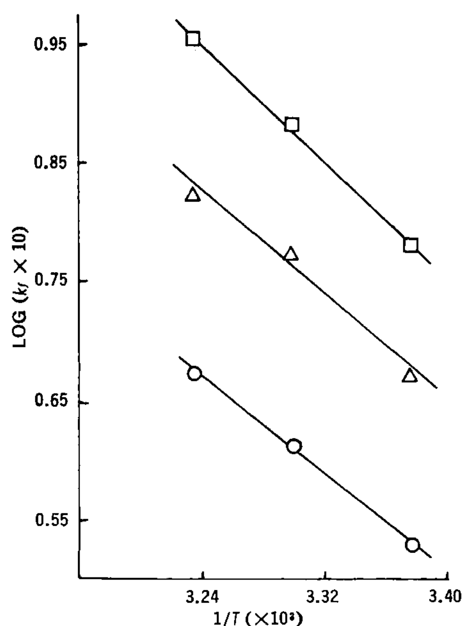


Figure 2—*Arrhenius plots of the transfer of sulfonamides from an aqueous pH 4.3 buffer to* n-*octanol. Key:* ○, *sulfadiazine;* △, *sulfamerazine; and* □, *sulfamethazine.*

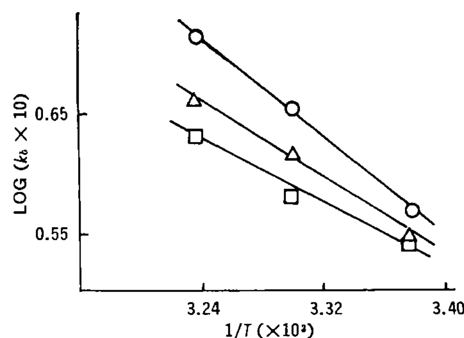


Figure 3—*Arrhenius plots of the transfer of sulfonamides from* n-*octanol to an aqueous pH 4.3 buffer. Key:* ○, *sulfadiazine;* △, *sulfamerazine; and* □, *sulfamethazine.*

Table III—Kinetic Parameters, Net Thermodynamic Parameters, and Apparent Partition Coefficients for the Interphase Transfer of Three Unionized Sulfonamides in a Two-Phase System at 36°

Sulfonamide	k_f/k_b[a] or K_w^0	ΔH[b], cal/mole	ΔS[b], cal/mole-deg	$T\,\Delta S$[b], cal/mole	ΔF[b], cal/mole
Sulfadiazine	0.91	−46	−0.3	−93	59
Sulfamerazine	1.45	1227	4.8	1483	−245
Sulfamethazine	2.09	2681	10.2	3152	−465

[a] As defined by Eqs. 6 and 7. [b] Net values representing the difference between activation parameters for forward transfer minus back transfer. Values are calculated from the data in Table II.

Table IV—Contribution of Methyl Groups to Net Thermodynamic Parameters for the Interphase Transfer of Unionized Sulfonamides at 36°

ΔH, cal/mole		ΔS, cal/mole-deg		$T\,\Delta S$, cal/mole		ΔF, cal/mole	
SMR[a] minus SD	SMT[b] minus SMR	SMR[a] minus SD	SMT[b] minus SMR	SMR[a] minus SD	SMT[b] minus SMR	SMR[a] minus SD	SMT[b] minus SMR
1273	1454	5.1	5.4	1576	1669	−294	−230

[a] The difference in net values between sulfamerazine (SMR) and sulfadiazine (SD). [b] The difference in net values between sulfamethazine (SMT) and sulfamerazine (SMR).

in the addition of a single methyl group, the difference in any given thermodynamic value between these two sets is considered to result from the contribution of the methyl group.

DISCUSSION

As observed in Table II, the large free energy of activation (ΔF_f* or ΔF_b*) for interphase transfer of the sulfonamides, approximately 18 kcal/mole, suggests that the energy barrier for transfer across the interface is great. Values of this magnitude were also observed (1, 4) in studying the diffusion of inorganic ions across an interface composed of water and various organic phases. This value is considerably higher than the ΔF* values for ordinary bulk diffusion, which generally fall within the range of 2–3 kcal/mole (19).

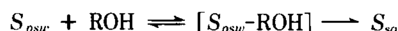
The negative entropy of activation (ΔS_f* or ΔS_b*) for interphase transfer (Table II) was also observed by others (1, 4). Since most substances diffuse in homogeneous bulk solutions with ΔS* values within a range of −5 to +5 eu (19), the large negative ΔS* values observed for crossing the interface appear to influence interphase transfer rates and ΔF* values significantly.

Based upon the kinetic and thermodynamic parameters presented in this and the following paper (20), it is possible to consider a model of the activated complex formed for interphase transfer. Neither the nature of the activated complex nor the number of solvate molecules interacting with the solute during formation of the activated complex for diffusion has been clarified in the literature, however. Conway (21) suggested that it is difficult to ascribe a unique set of initial and final states to the formation and cleavage of the activated complex because the process probably includes not only the rearrangement of the solvent structure around the solute but also the movement of the solute into the rearranged region. Others suggested that a number of hydrogen bonds are broken during formation of the activated complex (19, 22).

For these reasons, the possibility of the interaction of more than one solvate molecule with the sulfonamide molecule is considered in Schemes III and IV. To interpret the data in Table II, as well as the experimental evidence on the role of the escaping tendency of solvate molecules into the interface, presented more extensively in the next paper (20), these schemes are postulated as possible mechanisms for the interphase transfer of unionized sulfonamides. S_{sw} and S_{sa} represent the solvated sulfonamide molecule in the aqueous and alcohol phases, respectively; S_{psw} and S_{psa} represent the partially desolvated sulfonamide molecule in the aqueous and alcohol phases, respectively, at the interface; ROH and HOH represent alcohol and water molecules in the interface, respectively; and [S_{psw}-ROH] and [S_{psa}-HOH] represent the activated complex for the forward and back transfer, respectively, at the interface.

As depicted in Scheme III and as discussed more completely in the following paper (20), an interaction between a partially desolvated sulfonamide molecule and alcohol molecules during the formation of the activated complex for forward transfer occurs as a result of two types of intermolecular forces. Alcohol molecules are assumed to associate with the sulfonamide molecule primarily through hydrogen bonding with some of the several possible sites, including the sulfamyl oxygen(s) and the nitrogen and hydrogen(s) of the *para*-amino group, and secondarily through hydrophobic interaction between the hydrocarbon chain of the alcohol and the nonpolar groups of the sulfonamide. However, since the three sulfonamides do not differ in substitution on the phenyl group (Table I), the contribution to ΔH_f* and ΔS_f* due to hydrogen bonding by alcohol molecules at the *para*-amino group and the hydrophobic interaction at the phenyl moiety is not expected to differ significantly for the three homologs. But the sulfonamides do differ in the number of methyl groups substituted on the pyrimidine ring. Sulfamerazine, with the addition of one methyl group, should be more solvated by water molecules than sulfadiazine, which contains no methyl group, due to the greater iceberg formation (23) induced by the methyl group. It has been recognized for some time that the structural order of water increases near nonpolar solutes in aqueous phases (23–26). Therefore, it is conceivable that the association of sulfonamide and alcohol molecules through hydrogen bonding at the sulfamyl oxygens and hydrophobic interaction with the pyrimidine moiety may result in releasing more water molecules upon desolvation in the case of sulfamerazine as compared to sulfadiazine. The addition of two methyl groups for sulfamethazine should result in even greater solvation, with the subsequent release of water molecules, than is suggested for sulfamerazine. For back transfer, as discussed previously for Scheme IV, it is assumed that water molecules associate with the partially desolvated sulfonamide molecule through hydrogen bonding with some of the several possible sites, including the sulfamyl oxygen(s), pyrimidine nitrogen(s), and the nitrogen and hydrogen(s) of the *para*-amino group. In addition, icebergs may form around the nonpolar groups during transfer of solute from alcohol to aqueous phases. This formation is expected to be greatest for sulfamethazine, due to the presence of two methyl groups on the pyrimidine moiety, and least for sulfadiazine, with no methyl group substitution.

These schemes may explain the variations in ΔH* and ΔS*



Scheme III—Transfer from water to alcohol

Scheme IV—Transfer from alcohol to water

values observed in Table II. The increase in ΔH_f^* and ΔS_f^* values with increased lipophilicity of the solute may be attributed to the increasingly positive enthalpy and entropy contributions that can be expected to arise from the release of water molecules upon hydrophobic interaction between the nonpolar group of the octanol molecules and the pyrimidine moiety of the sulfonamides as the lipophilic nature of the homologs increased. For back transfer, ΔH_b^* and ΔS_b^* values decreased as the lipophilicity of the three sulfonamides increased. This may be attributed to the increasingly negative enthalpy and entropy contributions expected to result from increasing iceberg formation around the methyl groups of the sulfonamides.

These considerations may also suggest an explanation for the observation that the ΔH_f^* and ΔS_f^* values in Table II for sulfamerazine and sulfamethazine are greater than the corresponding ΔH_b^* and ΔS_b^* values. It is possible that the number of water molecules released in forming the activated complex for forward transfer is greater than the number of alcohol molecules displaced in forming the activated complex for back transfer. Furthermore, it is possible that the association of water molecules with the solute during the back-transfer process is greater than the association of alcohol molecules with the solute during the forward-transfer process. For sulfadiazine, however, which lacks a methyl group, the thermodynamic parameters for forward and back transfer are similar.

In terms of the kinetic data and the thermodynamic parameters for interphase transfer (Tables III and IV), increasing the lipophilicity of the sulfonamide by methyl group substitution resulted in an increase in the forward rate constant and a decrease in the backward rate constant due to an increase in the apparent partition coefficient of the unionized sulfonamides. Although increases in lipophilicity of the solute were accompanied by increases in both the net enthalpy and entropy, the entropy contribution and, consequently, the entropic energy $(T\ \Delta S)$ dominated the enthalpy contribution. Thus, as predicted by Eqs. 6 and 7, the ratio of forward to backward rate constants (k_f/k_b) increased with increased lipophilicity due to increases in the entropy for transfer from aqueous to alcohol phases resulting from substitution of the methyl group. This resulted in decreases in the net free energy of interphase transfer as the lipophilicity and apparent partition coefficient of the unionized sulfonamides increased. This pattern relating increases in lipophilicity and partition coefficient to decreases in the free energy of transfer from polar to nonpolar phases was observed by other investigators (13, 15, 17).

These observations are consistent with the proposal for the formation of the activated complex discussed in Schemes III and IV. The increased lipophilicity of the sulfonamides was associated with an increased liberation of water molecules upon hydrophobic interaction during formation of the activated complex for forward transfer and an increased association, or restriction, of water molecules upon formation of the activated complex for back transfer. This should result in a net positive enthalpy and entropy for interphase transfer, as observed in Tables III and IV. The data corroborate the common observation that there is a relationship between interphase transfer rates and the partition coefficient. Since the partition coefficient reflects the net gain in enthalpy and entropy during transfer, variations in interphase transfer rates are related to variations in the degree of interaction of solute and solvate molecules during formation of the activated complex for forward and back transfer.

It is recognized that the octanol phase used in the simple model system employed in this study does not simulate the complexity of biological membranes composed of proteins, phospholipids, cholesterol, water, and other constituents. However, as inferred by Diamond and Wright (17), it appears that the intermolecular forces governing the permeation of solutes through cell membranes are the same forces governing the partitioning of solutes between immiscible phases. Thus, these results and conclusions are expected to provide some insight into the mechanisms for the passive transfer of solutes across aqueous-membrane interfaces.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 25, 1973, from the *College of Pharmacy, Wayne State University, Detroit, MI 48202*

Accepted for publication September 24, 1973.

Abstracted in part from a dissertation submitted by G. E. Schumacher to Wayne State University in partial fulfillment of the Doctor of Philosophy degree requirements. Some of the studies were performed by G. E. Schumacher in the Physical Pharmacy Laboratories, University of Toledo, Toledo, Ohio.

[x]To whom inquiries should be directed.