The model used in fitting the data predicts a lag time before absorption begins and a single absorption phase that abruptly ends before absorption ceases. Accordingly, the use of HFCM equations yields positive values for both t_1 and t_2 and a value for the single absorption rate constant, k_{a1}, as observed in column 2 of Table IV. The proposed method in this case provides estimates of the same parameters, and there is good agreement between the estimates given in columns 2 and 3. The close-fitting plot obtained using NONLIN is given in Fig. 3.

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Kinetics and Thermodynamics of Interfacial Transfer

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Received January 13, 1981, from the **Department of Pharmaceutical Chemistry, The School of Pharmacy, University of London, London, WC1N 1AX, UK.* and the ‡*Department of Pharmacy, University of Nottingham, University Park, Nottingham, NG7 2RD, UK.* Accepted for publication March 25, 1982. §Present address: School of Pharmacy, University of California, San Francisco, CA 94143.

Abstract □ The kinetic barrier against the transport of methyl and ethyl nicotinates across the water–isopropyl myristate interface has been studied as a function of temperature using a rotating diffusion cell. The temperature dependence of the interfacial transfer kinetics has enabled calculation of the thermodynamic parameters for the process. It is evident from the results that, for the transferring solutes considered, the activation energy barrier is enthalpic, because there is a large positive entropy for transfer into the interfacial region.

Keyphrases □ Interfacial transfer—kinetics and thermodynamics, water–isopropyl myristate interface, methyl and ethyl nicotinates □ Kinetics—interfacial transfer thermodynamics, water–isopropyl myristate interface, methyl and ethyl nicotinates □ Thermodynamics—interfacial transfer kinetics, water–isopropyl myristate interface, methyl and ethyl nicotinates

An important physical process, common to all systems in which a solute transports from a high concentration aqueous phase across an organic membrane barrier into a low concentration aqueous phase, is the interfacial transfer of the substrate at the aqueous–organic and organic–aqueous interfaces. Few investigations into the kinetics and thermodynamics of interfacial transfer have been made, and the contribution of the phenomenon to overall membrane permeation has generally been assumed insignificant. However, recent studies have shown that transfer across the interfacial barrier can require a significant free energy input (1–3), and it is possible to identify circumstances for which the rate of interfacial transfer becomes the rate-determining step in membrane transport. For example, in the simplest case, consider the transport of drug molecules from an aqueous reservoir across an organic membrane into a perfect sink. Assuming that there is no stagnant diffusion layer in the aqueous reservoir phase, then the drug molecules must overcome two barriers so as to reach the sink on the far side of the membrane. These barriers are present due to interfacial transfer at the aqueous phase–membrane interface and due to diffusion through the organic membrane. The interfacial transfer is characterized by a heterogeneous rate constant k_{-1} (m/sec), which is related to the aqueous–organic partition coefficient of the drug (K) by the rate constant k_1 for interfacial transfer in the opposite direction (organic → aqueous), $K = k_1/k_{-1}$. Diffusion through the membrane is dependent upon the thickness of the membrane (l) and the diffusion coefficient of the drug in the membrane (D_{org}). Both processes also depend upon the cross-sectional area of the membrane. The relative contributions of the two components of the barrier may be compared by their reciprocal permeabilities [or resistivities (4)] and for interfacial transfer kinetics to have a significant effect on the overall rate of transport therefore requires:

$$1/Kk_{-1} \geq l/D_{org} \qquad \text{(Eq. 1)}$$

For certain small organic drug molecules, Kk_{-1} has been shown (1–3) to be $\sim 10^{-6}$ m/sec, and, taking a typical D_{org} of 10^{-10} m^2/sec, the inequality (Eq. 1) is satisfied by $l \leq 100$ μm. This degree of thickness is relevant not only to many biological membranes but also to emulsion systems and sustained-release formulations. Therefore, in neglecting slow interfacial transfer, it is possible that a major contribution to the transport rate-determining process in these systems is being ignored.

In this study, the kinetic barrier against interfacial transfer was investigated as a function of temperature. The

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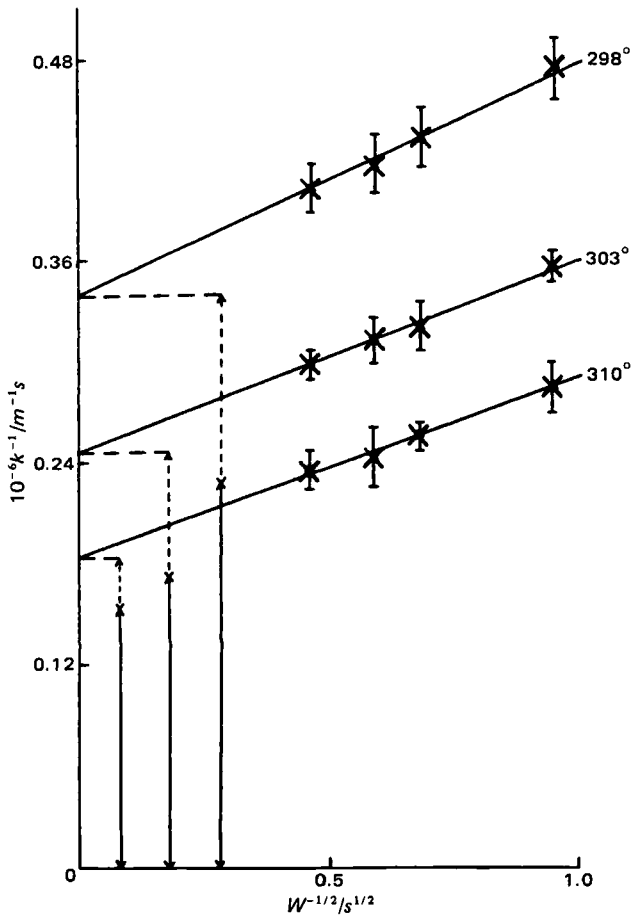

Figure 1—*Methyl nicotinate: Plots of* k^{-1} *as a function of rotation speed at the three temperatures (°K) indicated. Each experimental point is the mean of at least 10 separate determinations; the error bars indicate the standard deviations about the mean. The lines through the data are the theoretical gradients calculated from the Levich equation (Eq. 5) and given in Table I. The contributions to the intercepts of interfacial transfer* ($I_t = 2/a'k_{-1}$) *and diffusion through the filter* ($D_f = Kl/a'D_{org}$) *are indicated. Key: (⟷) D_f; (←→) I_t.*

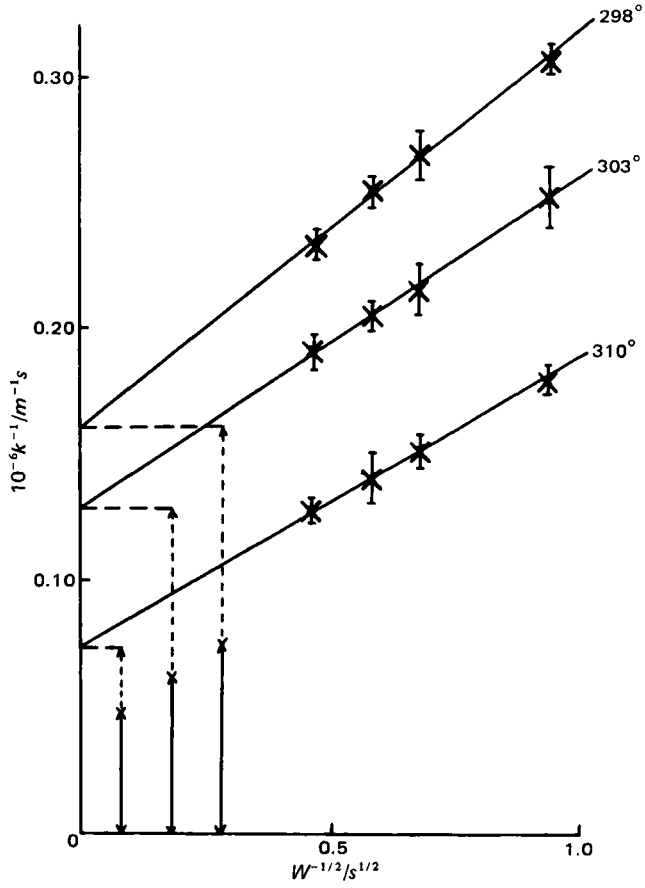

Figure 2—*Ethyl nicotinate: The corresponding plots for the ethyl ester. Temperature in °K. Key: (⟷) D_f; (←→) I_t.*

transport of the methyl and ethyl esters of nicotinic acid across the water–isopropyl myristate (I) interface has been followed using a rotating diffusion cell (1). This cell uses the hydrodynamics of the rotating disk system (5) to impose a known pattern of convective diffusion on either side of a filter[1]. The rotation of the cell produces a stagnant diffusion layer of known thickness on both sides of the filter. In the experiments reported here, two interfaces were established with the aqueous phase above and below the filter which was saturated with the organic phase. The choice of I as the organic liquid reflected the suggestion by several workers that it is a good model compound for skin lipids (6). The rate constants for interfacial transfer were determined at three temperatures and converted to free energies of activation. An Arrhenius relationship has enabled the enthalpic contribution to the energy barrier to be found and the entropic component was obtained by difference. The data indicate that the free energy barrier to transfer is essentially enthalpic, there being a large positive entropy for transfer into the interfacial region. The results show the same pattern as that recently found for salicylic acid crossing the same aqueous–organic interface (3). Finally, the thermodynamic parameters for interfacial transfer are compared with those corresponding to solute transfer between the bulk IPM and bulk aqueous phases (the values being determined from the temperature dependence of the partition coefficient), and the marked differences are discussed.

[1] Millipore Corp., Bedford, Mass.

EXPERIMENTAL

Comprehensive descriptions of the rotating diffusion cell and its method of operation have been given previously (1, 2, 7). The transport of methyl and ethyl nicotinates at 25, 30, and 37° was followed from an aqueous inner compartment across a filter[1] saturated with I into a larger aqueous outer compartment. The flux of ester into the receptor phase was determined as a function of rotation speed by periodically sampling the outer compartment and analyzing the nicotinate concentration using UV spectrophotometry.

Partition coefficients were found by continuously shaking an aqueous solution of nicotinate with an equal volume of I for a period of ~48 hr and then analyzing for the substrate spectrophotometrically.

Diffusion coefficients for the two nicotinates in water and in I were determined at 25° using the Goüy interferometric technique. The results for methyl nicotinate were found to be in good agreement with the published values (1). Diffusion coefficients at the higher temperatures were obtained using the Stokes–Einstein relation and a ratio technique previously described (1–3, 7).

All chemicals were supplied commercially at least 99% pure and were used without further purification. Solutions were prepared with distilled water from an all-glass apparatus.

THEORETICAL

For the experiments described in this paper, the flux (J/mole/sec) of diffusing species from the inner compartment of the rotating diffusion cell to the outer is given by

$$J = kA(C_I - C_O) \qquad \text{(Eq. 2)}$$

Table I—Experimental Results from Figs. 1 and 2 and the Associated Solute Diffusion Coefficients [a]

°K	$10^9 D_{aq}$/ $m^2 s^{-1}$	$10^9 D_{org}$/ $m^2 s^{-1}$	10^{-6}Gradient[b]/ $s^{1/2} m^{-1}$	10^{-6}Intercept/ $m^{-1} s$
		Methyl Nicotinate		
298	0.88	0.41	0.137	0.341
303	1.13	0.48	0.114	0.246
310	1.20	0.51	0.107	0.184
		Ethyl Nicotinate		
298	0.76	0.37	0.151	0.161
303	0.89	0.42	0.134	0.129
310	1.06	0.46	0.116	0.074

[a] Diffusion coefficient values at 298°K were measured experimentally using a high precision Goüy diffusiometer (Ref. 9). The Stokes–Einstein relationship and a ratio technique were used to determine the values at the two higher temperatures. [b] These values were calculated using the corresponding aqueous diffusion coefficients and kinematic viscosities (Ref. 10). The gradients have then been forced through the experimental points in Figs. 1 and 2 to obtain the intercepts given in the final columns of this table.

where A is the area of the filter and C_I and C_O are the bulk concentrations in the inner and outer compartments, respectively. Detailed treatment of this expression has been presented previously (1) and the variation of the concentrations with time was shown to be:

$$[(C_{O,t} - C_{O,0})(1 + V_O/V_I)]/(C_{I,0} - C_{O,0}) = 1 - \exp[-kA(V_I^{-1} + V_O^{-1})t] \quad \text{(Eq. 3)}$$

where V_I and V_O refer to the respective volumes of the inner and outer compartments and the second subscripts on C refer to time. Furthermore, analysis of the flux equations for the double interface systems of this study indicates that the rate constant k be interpreted as follows (1):

$$k^{-1} = 2Z_D/D_{aq} + Kl/a'D_{org} + 2/a'k_{-1} \quad \text{(Eq. 4)}$$

In this equation, $2Z_D/D_{aq}$ describes the diffusion through the aqueous stagnant diffusion layers established on either side of the filter by the rotating disk hydrodynamics. The thickness of these layers (Z_D) is given by the equation (8):

$$Z_D = 0.643\, \upsilon^{1/6} D_{aq}^{1/3} W^{-1/2} \quad \text{(Eq. 5)}$$

where υ is the kinematic viscosity of water, D_{aq} the aqueous diffusion coefficient of the solute, and $W(s^{-1})$ the rotation speed of the filter. The second term in Eq. 4 describes the diffusion of the solute through the organic liquid filled filter of length l; K is the aqueous–organic partition coefficient of the substrate, and D_{org} its diffusion coefficient in the organic phase. The factor a' is the area of the pores of the filter divided by A. The final term $2/a'k_{-1}$ describes the interfacial transfer of the solute, the factor of two arising because there are two interfaces. For transfer of a substrate M, the forward and backward interfacial transfer rate constants (k_1 and k_{-1}) have the following significance:

$$M_{org} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} M_{aq}: \qquad K = k_1/k_{-1} \quad \text{(Eq. 6)}$$

The largest of the three terms in Eq. 4 wil be the most important in determining the rate of the overall transfer process.

RESULTS AND DISCUSSION

The samples periodically removed from the outer compartment of the rotating diffusion cell enable values of k^{-1} to be calculated using Eq. 3. Figures 1 and 2 show that the linear relationship, predicted by Eqs. 4 and 5, between k^{-1} and $W^{-1/2}$ is experimentally verified for both methyl and ethyl nicotinates at each of the three temperatures considered. In these figures, the theoretical gradients calculated using Eq. 5 are forced through the experimental points to obtain the intercepts on the k^{-1} axis. Experimental data lie very close to the theoretical slopes, indicating that the correct hydrodynamics are indeed set up by the rotation of the diffusion cell. The aqueous diffusion coefficients and theoretical gradients together with the derived intercepts at $W^{-1/2} = 0$ are given in Table I for both nicotinic acid esters.

The intercepts in Table I and Figs. 1 and 2 correspond to the flux at infinite rotation speed when the Z_D term in Eq. 4 is zero. The remaining two terms describing diffusion through the filter and interfacial transfer may be separated using known values of K, D_{org}, l, and a': the partition coefficients for both esters at the three temperatures were determined and are presented in Table II; values for D_{org} were also found and are given in Table I; and the parameters[2] l and a' are 150 μm and 0.75, respectively, for the 0.22-μm pore size filters used. Independent verifications of the values of l and a' have been reported (11, 12). Hence, the intercepts provide direct measurements of k_{-1} for both esters at three temperatures. These rate constants, and the corresponding k_1 values calculated from Eq. 6, are given in Table II, and the interfacial transfer contributions to the intercepts are shown in Figs. 1 and 2. Furthermore, in Table II, the kinetic terms have been converted to free energy barriers using Eq. 7 (1)

Table II—Interfacial Transfer Parameters

°K	K	$10^6 k_1$/ m/sec	$10^6 k_{-1}$/ m/sec	$\Delta G°_{1,\#}$/kJ mole^{-1}	$\Delta G°_{-1,\#}$/kJ mole^{-1}
			Methyl Nicotinate		
298	0.45	9.9	22	39.7	37.8
303	0.42	16	38	39.4	37.2
310	0.39	34	86	38.4	36.0
			Ethyl Nicotinate		
298	0.14	4.4	31	42.0	37.1
303	0.13	5.2	40	42.2	37.1
310	0.11	11	102	41.3	35.5

$$\Delta G°_{\pm 1,\#} = -RT \ln(k_{\pm 1}/Z) \quad \text{(Eq. 7)}$$

which includes a frequency factor (Z) of 10^2 m/sec (13).

Because the interfacial transfer rate constants have been determined as a function of temperature, the enthalpy of transfer into the interfacial region may be estimated using an Arrhenius relation:

$$\ln k_{\pm 1} = \text{constant} - \Delta H°_{\pm 1,\#}/RT \quad \text{(Eq. 8)}$$

Plots of the natural logarithm of the $k_{\pm 1}$ values in Table II against $1/T$ were constructed and the enthalpy changes obtained from the gradients are given in the first columns of Tables III and IV for methyl and ethyl nicotinates, respectively. The magnitude of the entropy changes for interfacial transfer may then be calculated by difference using:

$$\Delta S°_{\pm 1,\#} = (\Delta H°_{\pm 1,\#} - \Delta G°_{\pm 1,\#})/T \quad \text{(Eq. 9)}$$

The results obtained for the two nicotinates at 298°K are again given in the left-hand columns of Tables III and IV.

The thermodynamic parameters for solute transfer between the bulk phases, *i.e.*, the energy difference between molecules in the bulk I and in the bulk aqueous phase, have been calculated from the partition coefficients in Table II. The results at 298°K are summarized in the second columns of Tables III and IV for methyl and ethyl nicotinates, respectively.

Consideration of the thermodynamic data in Tables II–IV provides the following observations:

1. The free energy of activation for interfacial transfer in either direction (organic ⇌ aqueous) is always in the region of 39 kJ/mole. The free energy differences between the molecules in the bulk phases, however, are comparatively small at 298°K.
2. For interfacial transfer in both directions, there is a reasonably large positive enthalpy of activation. The temperature dependence of the nicotinates water–I partition coefficients, though, indicates that transfer from the bulk I phase to the bulk aqueous phase is an exothermic process $\Delta H \simeq$ 10–15 kJ/mole. The transfer between the bulk phases in the opposite direction has a correspondingly positive ΔH.
3. For both solutes, in either direction, there is a large significant positive entropy for transfer into the interfacial region. This implies that the free energy barrier to interfacial transfer discussed above is essentially enthalpic rather than entropic. For solute transfer from the bulk I to the bulk aqueous phase, on the other hand, ΔS is negative. Furthermore, in this situation, the negative entropy changes are responsible for the positive free energy changes calculated from the partition coefficients.

The constancy of the interfacial transfer free energy of activation has been reported previously (1, 3), and the results of this study are in good agreement with the data in the literature. The values also compare favorably with a result for $\Delta G°_{\#}$ determined using a Stokes cell (14). In

[2] Millipore Corp., Bedford, Mass., Cat. no. MC 179/u, pp. 3–4, 13.

Table III—Methyl Nicotinate: Thermodynamic Values at 298°K

I → Water

	I (interface) $\xrightarrow{k_1}$ Water (interface)	I (bulk) $\xrightarrow{K}$ Water (bulk)[a]
$\Delta G/kJ$ mole^{-1}	39.7	2.0
$\Delta H/kJ$ mole^{-1}	75.9	−9.1
$\Delta S/J$ mole$^{-1}K^{-1}$	121	−37

Water → I

	Water (interface) $\xrightarrow{k_{-1}}$ I (interface)	Water (bulk) $\xrightarrow{1/K}$ I (bulk)[b]
$\Delta G/kJ$ mole^{-1}	37.8	−2.0
$\Delta H/kJ$ mole^{-1}	85.1	9.1
$\Delta S/J$ mole$^{-1}K^{-1}$	159	37

[a] ΔG in this column is calculated using $\Delta G = -RT \ln K$, ΔH is found from the slope of an Arrhenius plot of ln K *versus* $1/T$, and ΔS is determined by difference. [b] In this case, $\Delta G = +RT \ln K$, ΔH is found by plotting ln K^{-1} against $1/T$, and ΔS is again determined by difference.

Table IV—Ethyl Nicotinate: Thermodynamic Values at 298°K

I → Water

	I (interface) $\xrightarrow{k_1}$ Water (interface)	I (bulk $\xrightarrow{K}$ Water (bulk)[a]
$\Delta G/kJ$ mole^{-1}	42.0	4.9
$\Delta H/kJ$ mole^{-1}	67.2	−15.6
$\Delta S/J$ mole$^{-1}K^{-1}$	85	−69

Water → I

	Water (interface) $\xrightarrow{k_{-1}}$ I (interface)	Water (bulk) $\xrightarrow{1/K}$ I (bulk)[b]
$\Delta G/kJ$ mole^{-1}	37.1	−4.9
$\Delta H/kJ$ mole^{-1}	84.1	15.6
$\Delta S/J$ mole$^{-1}K^{-1}$	158	69

[a] ΔG in this column is calculated using $\Delta G = -RT \ln K$, ΔH is found from the slope of an Arrhenius plot of ln K *versus* $1/T$, and ΔS is determined by difference. [b] In this case, $\Delta G = +RT \ln K$, ΔH is found by plotting ln K^{-1} against $1/T$, and ΔS is again determined by difference.

this case, the system contained only one interface (set up on the surface of the sinter of the cell) between I and water, and the transferring substrate was *p*-methyl benzyl chloride. It seems unlikely that the technique of this earlier determination and the rotating diffusion cell suffer from the same experimental errors or artifacts. The good agreement between the two sets of results is believed (1), therefore, to provide confirmation of both the existence of the interfacial transfer process and of the reliability of the rotating diffusion cell.

Investigations of the temperature dependence of the interfacial transfer process have produced somewhat disparate results. For example, the interfacial barrier for *p*-methyl benzyl chloride crossing the water–I interface (14) was found to be almost totally enthalpic, with little or no entropic contribution. However, an earlier investigation of methyl nicotinate traversing the same interface (1), indicated that the interfacial transfer rate constants passed through a minimum as the temperature was raised from 11 to 37°. The data obtained at 21 and 37° support the trend in values found in this work. The discrepancy arises because of the enhanced rate of transfer measured at 11°, for which there appears to be no straightforward explanation. Most recently, the transfer of salicylic acid across the water–I interface has been considered (3), and substantially the same pattern of results was obtained as reported for the nicotinates in this paper; *i.e.*, the entropy of transfer across the interfacial region acts so as to reduce the overall free energy barrier, to which there exists a large positive enthalpic contribution.

The large positive entropy of activation found for interfacial transfer in either direction warrants further consideration. For both nicotinates [and salicylic acid (3)], transfer from the bulk I to the bulk aqueous phase involves a negative entropy change. This seems reasonable, since it is undoubtedly true that the solvation of the solute molecules will be more efficient in water than in I. The transfer from bulk I to bulk water will, therefore, produce an increase in the order of the system. However, this is not true in the region of the interface where nicotinate transfer causes a large increase in disorder. It is possible that this observation reflects the absence of any solvation sheath around the solutes as they traverse the interfacial regions. Alternatively it seems reasonable to suggest that a I–water interface possesses a well-ordered structure in which the ester groups of the I moieties will be oriented toward and solvated by the adjacent water molecules. The transport of a solute molecule through this rather ordered structure must destroy the I–water interactions, thereby contributing toward a positive entropy charge.

Further conclusions from the kinetic and thermodynamic parameters reported here cannot be drawn until more experiments are performed in which the nature of the solutes and solvents used are systematically varied. Like most two-phase and solvation phenomena, a variety of behavior may be expected. However, it has been demonstrated that the role of interfacial transfer in the permeation of organic barriers by the solutes described in this and other work should be considered significant to the overall transport process taking place in these systems.

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