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The effect of diffusion and convection on the rate of transfer of solutes across an interface

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Abstract. The transfer of substances across the interface between water and a membrane or between water and a solvent occurs in series with transport up to and away from the interface. These processes have been difficult to resolve. Recently D. M. Miller (Biochim Biophys Acta 856: 27–35, 1986) has used a moving drop technique to measure the rates of transfer of short-chain alcohols and tritiated water between water and *n*-octanol. This technique produces equivalent unstirred layers which are less than about 10 μm thick. Based on the trends in the observed rates of phase transfer, he proposes that the transfer is limited by the actual interfacial step. If so, water-oil interfacial transfer would be sufficiently slow to limit the rate of permeation of lipid membranes by these substances. It is shown here that the observed rates of phase transfer can be explained quantitatively if they are limited by convection or by diffusion across the combination of 5 – 10 μm unstirred layers both inside and outside the moving drops. For water, comparison of the observed rates with the rate of evaporation from a clean surface, suggests that the interfacial step at the water-octanol interface is not rate-limiting.

Key words: Phase transfer, water, alcohols, interfacial resistance, adsorption, unstirred layer

Introduction

Diffusion or convective transport occurs in series with adsorption or transfer across an interface in transport across lipid membranes (Dainty 1963; Everitt et al. 1969; LeBlanc 1969), electrode reactions (Vetter 1967) transfer of solutes between two fluid phases (Whitman 1923; Davies and Rideal 1963), and evaporation (Rideal 1925; Hickman 1954; Barnes 1986). In most instances the bulk phase processes have seriously obstructed attempts to measure the rates of the interfacial steps. For instance, movements of tetraphenylboron across lipid membranes produce currents that can be limited by transfer from one surface of the membrane to the other or by transport in the aqueous phases but not convincingly by interfacial transfer (Ketterer et al. 1971; Haydon and Hladky 1972; Hladky 1979; Jordan and Stark 1979). To measure the rate of desorption, Brock et al. (1981) had to choose a particularly favourable type of membrane and use current transients to assess the concentration of adsorbed ions during the first 50 ms after provoking desorption with a rapid temperature jump. Not surprisingly, the interfacial steps have not been resolved for the permeation of water or short chain alcohols across lipid membranes.

It has also proved difficult to measure the rate of the interfacial step in phase transfer between two solvents (see e.g. West et al. 1952; Lewis 1954; Blokker 1957; Davies and Rideal 1963; Ward and Quinn 1965; Davies 1972). Recently Miller (1986) has attempted to resolve the interfacial step by measuring the rates of transfer of short-chain alcohols and tritiated water between *n*-octanol and water. Based upon the trends observed in the rate constants for this series of solutes and the close agreement between the equilibrium constant and the ratio of the forward and reverse rate constants, he proposes that his moving drop technique has increased the rate of the bulk phase steps sufficiently to allow measurement of the rate constants of the actual interfacial step.

Phase transfer data for water and *n*-octanol are of interest for a combination of reasons: The equilibrium partition of small solutes between octanol and water is similar to that between membranes and water (see e.g. Seeman 1972 and Miller 1985); and the rate of interfacial transfer in this simple fluid system should provide an upper limit for the rate of interfacial transfer in the more structured environment of a lipid membrane. Miller notes that, if the interfacial steps in membrane transport are as slow as the measured phase transfer rates, then these steps will account for the water per-

Table 1. Measured permeabilities/(μs^{-1})

Solute	Red cell membranes		Water-*n*-octanol
	Dog[a]	Human[b]	Phase transfer[c]
Methanol	46	37	11
Ethanol	37	21	21
n-propanol	90	65	56
n-butanol	140	> 610	73

[a] Data of Garrick et al. (1980)
[b] Data of Brahm (1983)
[c] Data of Miller (1986)

meability of lipid bilayer membranes (reviewed by Fettiplace and Haydon 1980). Data for the permeability of lipid bilayers to the *n*-alcohols are not available because the rates of transfer are limited by the thick unstirred layers present in experiments with these membranes.

Much thinner unstirred layers have been obtained in membrane permeability studies with mammalian red blood cells (Sha'afi et al. 1967; Garrick et al. 1980; Brahm 1983). Water crosses these membranes by a hydrophilic pathway (see e.g. Sha'afi et al. 1967; Macey and Farmer 1970), and thus the water permeability is not comparable with the phasetransfer data. The membrane permeabilities to alcohols of dog and human red blood cells are compared with the phase-transfer permeabilities in Table 1. For ethanol and propanol the permeabilities are all similar as if they were limited by a common process. However, for methanol and *n*-butanol the phase transfer permeability is smaller. This comparison suggests either that interfacial transfer in red cells is faster than the measured rate of phase transfer or that methanol and *n*-butanol cross red cell membranes by a route which does not require them to move from water into oil. Brahm (1983) demonstrates that agents which greatly reduce the water permeability of mammalian red blood cells do not reduce their permeability to methanol.

It is shown here that the rates of transfer between water and *n*-octanol in the moving drop experiments vary with the solute as predicted if the phase transfer is still limited by diffusion or convection in the solutions. The rate constant for the interfacial step is likely to be much larger than the composite constant which has been measured. This conclusion is consistent with Brahm's (1983) view that the alcohols permeate via the lipid core of red cell membranes.

Theory

It is customary to treat steady-state transport up to and away from a surface as diffusion across an unstirred layer in which convection is presumed to occur only parallel to the interface. Consider transfer from the far side of the unstirred layer on the left in phase o (e.g. oil), across an interface, and on to the far side of an unstirred layer on the right in phase w (e.g. water). In the steady-state, far from the solubility limits of the diffusing species, the net flux from left to right is

$$\begin{aligned} J &= (D_o/d_o)(c_o - c') = k_{ow}c' - k_{wo}c'' \\ &= (D_w/d_w)(c'' - c_w) \\ &= \frac{(D_o/d_o)(D_w/d_w)[k_{ow}c_o - k_{wo}c_w]}{[(D_o/d_o)(D_w/d_w) + k_{wo}(D_o/d_o) + k_{ow}(D_w/d_w)]}, \end{aligned} \tag{1}$$

where c' and c'' are the concentrations just to the left and right of the interface, c_o, c_w, D_o, D_w, d_o and d_w are the concentrations, diffusion constants and equivalent unstirred layer thicknesses in phase o and w respectively, and k_{ow} and k_{wo} are the rate constants for transfer across the interface. The same equation with $d_o \to 0$ also describes adsorption to a membrane surface.

The apparent or observed rate constants for the entire system, k'_{ow} and k''_{wo}, are defined by

$$J = k'_{ow}c_o - k'_{wo}c_w. \tag{2}$$

Thus

$$\begin{aligned} k'_{ow} = {} & k_{ow}(D_o/d_o)(D_w/d_w)/[(D_o/d_o)(D_w/d_w) \\ & + k_{wo}(D_o/d_o) + k_{ow}(D_w/d_w)] \end{aligned} \tag{3}$$

and

$$\begin{aligned} k'_{wo} = {} & k_{wo}(D_o/d_o)(D_w/d_w)/[(D_o/d_o)(D_w/d_w) \\ & + k_{wo}(D_o/d_o) + k_{ow}(D_w/d_w)]. \end{aligned} \tag{4}$$

The phase transfer permeability is k'_{wo} with respect to concentrations in the water or k'_{ow} with respect to concentrations in the solvent. The ratio of the apparent rate constants k'_{wo}/k'_{ow} is equal to the equilibrium constant given by k_{wo}/k_{ow}. So long as the fluxes up to, across, and away from the interface can be described by constants, k_{ow}, k_{wo}, D_w/d_w, and D_o/d_o that are independent of concentration, this result is inevitable regardless of the physical mechanisms for transfer, because the actual processes that occur must balance at equilibrium. Equations (3) and (4) with constant, uniform unstirred layer thicknesses, the same for every solute, correspond to the 2 film model ascribed to Whitman (1923). With some reinterpretation in which the effective unstirred layer thicknesses vary with the diffusion constants, e.g. $d \propto D^{0.5}$, they also apply even when transfer up to and away from the surfaces occurs as diffusion between elements of fluid which are transiently brought very close to the interface by convection or eddys (Higbie 1935; Lewis 1954; King 1964; Szekely 1965; Davies 1972). If transfer to and from the interface occurs entirely by convection, the access permeabilities, D_w/d_w and D_o/d_o, are constant (Davies and Rideal 1963).

The maximum thicknesses of the unstirred layers that are consistent with phase-transfer data can be estimated by assuming that the actual interfacial transfer step is fast, i.e. that k_{ow} and k_{wo} are large compared to D_o/d_o or D_w/d_w in Eqs. (3) and (4). Then

$$D_w/k'_{wo} = d_w + d_o(D_w k_{ow})/(D_o k_{wo})$$

and (5)

$$D_o/k'_{ow} = d_o + d_w(D_o k_{wo})/(D_w k_{ow}) \, .$$

Application to experimental results and discussion

Miller (1986) has reported rate and equilibrium constants for transfer of tritiated water, methanol, ethanol, *n*-propanol, and *n*-butanol between water and *n*-octanol. Rate constants were measured using drops of water falling through octanol, reported as k'_{wo}, and drops of octanol rising through water, reported as k'_{ow}. The results of these experiments are plotted in Fig. 1 as D_w/k'_{wo} vs. $D_w k_{ow}/D_o/k_{wo}$ and D_o/k'_{ow} vs. $D_o k_{wo}/D_w k_{ow}$. According to the interpretation offered here, the rate constant for transfer from water to octanol, k'_{wo}, decreases as the equilibrium constant, $K_{wo} = k_{wo}/k_{ow}$, decreases, because for a given aqueous concentration the concentration of solute available for transfer away from the interface in the octanol is lower. Similarly the rate constant for transfer from octanol to water decreases as the equilibrium constant becomes larger. From Fig. 1 a and Eq. (5), the apparent unstirred layer thicknesses are $d_o = 6$ µm and $d_w = 11$ µm, while from Fig. 1 b the values are 6 µm and 9 µm respectively. The data can also be fitted (root mean square percentage deviations 10.9% for water drops and 6.6% for octanol drops) assuming constant access permeabilities, $D_o/d_o = 54$ µ/s and $D_w/d_w = 94$ µ/s from the data for water drops and 51 µ/s and 111 µ/s for octanol drops. The approximate agreement of the constants calculated from the two independent sets of experiments implies similar rate limiting processes.

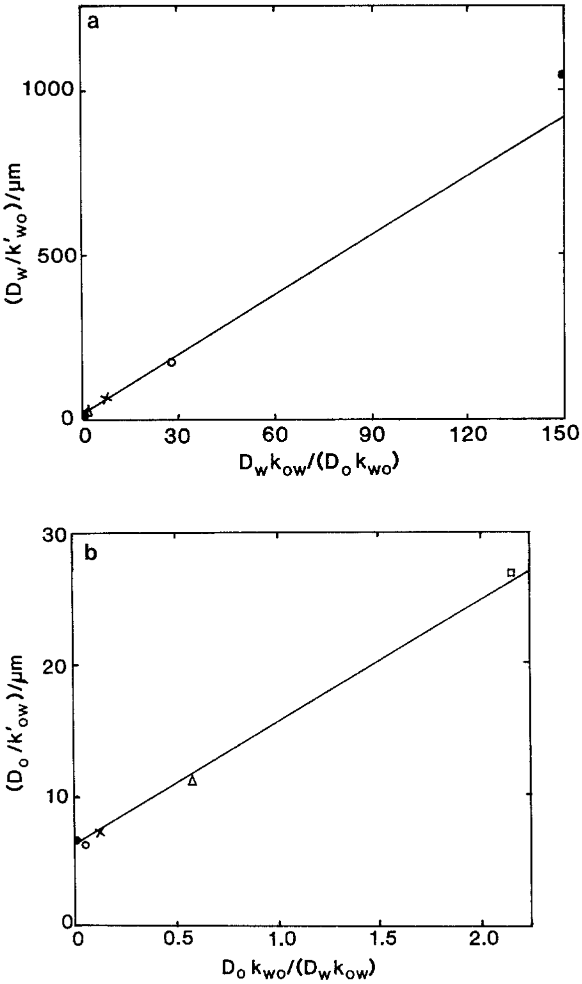

Fig. 1. The relation between the observed rate constants for transfer between water and octanol, k'_{wo} *and* k'_{ow}. The diffusion constants, D_w and D_o, and the equilibrium constant, k_{wo}/k_{ow}. The experimental rate constants and equilibrium constants are taken from Miller (1986). The aqueous diffusion constants, taken from Gary-Bobo and Weber (1969), are listed in the following as $D_w/10^{-5}$ cm^2 s^{-1}: *n*-butanol, 1.00, □; *n*-propanol, 1.15, △; ethanol, 1.26, ×; methanol, 1.70, ○; and tritiated water, 2.41, ●. The diffusion constants in *n*-octanol are likely to be similar for all the solutes considered (Lusis and Ratcliff 1971) and to be somewhat greater than that for ethylene glycol (Karthikeyan and Laddha 1976). A value of 3×10^{-6} cm^2/s has been assumed. The alternative analysis in terms of access permeabilities (see text) does not require values for the diffusion constants. The straight lines are drawn to minimize $S = [(\text{experimental value} - \text{prediction})/(\text{experimental value})]^2$, which corresponds to the assumption that the fractional errors in the data points are equal. The ratio of the standard deviations to the values for the water drop data are near 10%. For the octanol drop data they increase from 2% for *n*-butanol to 9% for tritiated water. The root mean square percentage deviations between the points and the line are 10.5% for the water drops and 4.6% for the octanol drops

The apparent unstirred layer thicknesses calculated from Fig. 1 are much less than those encountered in lipid bilayer experiments. They are also much less than the size of the drops employed in the moving drop technique, which requires, as noted by Miller, that the inside of the drops is stirred by convection. This stirring occurs because the movement of the drop through the surrounding medium drags the interface from the front to the rear end of the drop. Detailed description of this process and its consequences for transport in the bulk phases is possible (Lewis 1954; Linton and Sutherland 1957; Johnson and Hamielec 1960; Horton et al. 1965; Davies 1972; McManamey et al. 1975), but it is not warranted here because the present data do not distinguish between constant d_w, $D_w/d_w \propto D_w^{0.5}$, or even constant D_w/d_w. Thus the data do not specify whether diffusion or convection is the dominant transfer process close to the interface. Somewhat smaller unstirred layer thicknesses, but still in the range 1 – 10 μm, have been obtained experimentally with red blood cells in suspension but only under turbulent conditions (Sha'afi et al. 1967; Brahm 1983).

The rate of the interfacial step in the transfer of a solute from water to octanol is limited either by the rate of dehydration of the solute or by the rate of permeation of some sort of special surface layer of *n*-octanol. Evaporation of a water molecule from a free water surface also requires removal of the surrounding molecules, but this process has a large rate constant, $\alpha \times 0.35$ cm/s (Rideal 1925), where $\alpha \simeq 1$ (Hickman 1954; Barnes 1986) is the fraction of water molecules which stick when they strike the liquid surface from the vapour. Thus the rate at which water molecules can be removed from water is about 1,500 times faster than the rate of transfer of water between water and octanol observed in the moving drop experiments. Furthermore at the octanol-water interface as water of hydration is removed it can be replaced by octanol which should substantially reduce the free energy needed for transfer. (The equilibrium constant for the transfer of water is 2,000 times greater for transfer into octanol than for transfer into air.) Hence the presence of the octanol should increase rather than decrease the rate of dehydration and the rate of the interfacial step can be slow only if there is a special interfacial barrier. Condensed monolayers at air-water interfaces such as that formed by *n*-hexadecanol can reduce the rate of evaporation of water as much as 15,000 fold (Rideal 1925; Barnes 1986). However, short-, branched-, or unsaturated-chain compounds including *n*-octanol do not form condensed monolayers at the air-water interface and are not effective at reducing the rate of evaporation. *n*-octanol should be even less able to form a cohesive barrier when the air is replaced by a solvent, i.e. *n*-octanol, as the medium adjacent to the hydrophobic chains of the surface molecules (Davies and Rideal 1963). Thus it is also unlikely that a surface layer of *n*-octanol could account for the slow rate of phase-transfer observed with the moving drops.

The variation in the rates of transfer observed for water and the short-chain alcohols in the octanol-water moving drop experiments can be explained quantitatively on the basis of rate limiting convection or diffusion. As there is no plausible basis for a sufficiently slow interfacial step, it must be presumed that for these simple phase transfers the observed rates are limited by the movements of the solutes up to and away from the interface.

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