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A general description of water–oil partitioning rates using the rotating diffusion cell

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Summary

Water–oil partitioning rates are reported for a chemically diverse set of solutes with 4 solvents: $CHCl_3$, 2,2,4-trimethylpentane, octanol and propylene glycol dipelargonate acting as oil phase, in a rotating diffusion cell. A predictive model for partitioning rates in terms of fundamental physicochemical properties of the solutes and solvents has been developed. Anomalous aqueous diffusivity effects found previously in simple stirred two-phase cells are shown to be absent in the hydrodynamically well-defined rotating diffusion cell system. A small but necessary dependence of partitioning on solute molecular volume is demonstrated. No evidence is found for the existence of a measurable water–oil interfacial resistance to solute transfer.

Introduction

The biological activity of a drug depends on its concentration at the site of action which is generally a function of the rate at which the drug passes through the various membrane barriers on its route from the site of administration. Since movement of a drug through a membrane barrier involves partitioning into a lipid phase, the absorption and subsequent distribution of a drug is normally related to its lipophilicity, as measured by its oil–water partition coefficient, K_D.

Much is known about the way in which a drug's structure affects its partition coefficient (Leo, 1975; Kamlet et al., 1984; Rekker, 1977), particularly for octanol as a model solvent, but the relationships between structure, partition coefficient and the rate of transport across membranes is much less clear. This is particularly true for in vivo membrane transport processes such as intestinal permeability (Martin, 1981).

In vitro models of membrane transport processes previously reported have commonly been two-phase water–oil, or three-phase water–oil–water arrangements with organic solvents or soft polymers acting as models of the lipid membrane. Kubinyi (1977) showed empirically that there were

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bilinear relationships between water–oil partitioning rates, (aqueous–organic and organic–aqueous) and alkyl chain length (and hence log K_D) for a homologous series of diphenyl glycolic acid esters of dimethyl-(2-hydroxyethyl)alkyl ammonium bromides.

A systematic study of the relationships between partition rate and equilibrium for a series of substituted *N,N*-dimethyl-4-(methylamino)-benzenesulphonamides has been reported by Van de Waterbeemd and Jansen (1980). The bilinear relationship between log (partitioning rate constant) and log K_D was confirmed and ascribed to the contributions of partition coefficient to the concentration gradient across the water–oil interface as well as the limiting diffusion control in the unstirred layers on either side of the membrane. Similar relationships were found for solvents other than octanol (De Haan and Jansen, 1983a and b, 1984, 1986; De Haan et al., 1983; Byron et al., 1981; Byron and Rathbone, 1984, 1986).

Such studies in simple in vitro models have provided an experimental basis for the attempts to model in vivo absorption processes (Eposito, 1983; Higuchi et al., 1981; Ho and Higuchi, 1974; Suzuki et al., 1970; Winne, 1978) where the importance of partition coefficient and diffusivity within unstirred layers is well established.

Our present understanding can be summarised as follows; the diffusive flux of a solute through a membrane barrier is determined by the concentration gradient across the membrane and the transport resistances arising from the barrier. Increasing partition coefficient increases the concentration gradient within the organic phase leading to a reduction in the organic phase resistance and greater flux. At higher partition coefficient, flux is limited by diffusion through the unstirred aqueous diffusion layer and becomes independent of partition coefficient, thus leading to the bilinear relationship observed.

A few important questions remain however. Firstly, it has been shown that the aqueous diffusion layer resistance is apparently highly dependent on the organic receptor phase (De Haan and Jansen 1983a, and b; de Haan et al., 1983). The origins of this effect remain unclear, although it was suggested that the organic solvent produced water-structuring effects at the water–oil interface which were dependent on the nature of the organic phase. The significance of the interfacial resistance is also unclear. It has been claimed (Fleming et al., 1983), that water-oil interfaces are significant barriers to solute transport, although this suggestion has been challenged (Leahy and Wait, 1986). Unfortunately, in the simple two-phase stirred cell system used by Van de Waterbeemd, de Haan et al., since the hydrodynamics of flow at the water–oil interface are ill-defined, and the thickness of the unstirred layers is not known, it is not possible to separate the relevant resistances. An assessment of the relative significance of the various barriers to solute transport was therefore not possible. The third important unresolved question concerns whether the models are completely general for all solutes and all solvents, a question which needs to be considered if these results are to be extrapolated to drug transport processes across biological membranes.

The work reported in this paper can be regarded as an extension of that of Van de Waterbeemd, de Haan et al. which differs in several important ways. Firstly, we have chosen a different range of solutes which encompass a wide diversity of chemical functionality, bearing in mind the important chemical characteristics which largely influence solvation properties, e.g. hydrogen bonding, polarity and solute molecular volume (Leahy, 1986). Secondly, 4 organic solvents have been chosen for the study to represent important solvation characteristics, viz. a hydrogen bond donor ($CHCl_3$), a hydrogen bond acceptor (propylene glycol dipelargonate, PGDP), an amphihydrogen bonding solvent (*n*-octanol) and an alkane (2,2,4-trimethylpentane, TMP). We feel that the diversity of solute and solvent structure used in this study should allow some confidence in the extrapolation of our results to other systems.

The third and most important difference is that we have used a rotating diffusion cell (RDC) to study the water–oil partitioning process. The RDC is a well characterised system which, in operation, produces a convective flow across a water–oil interface which is dependent on the speed at which the planar interface rotates and which has been used previously, with some success, as a model of

solute transport processes (Albery et al., 1976; Fleming et al., 1983). Its most important feature is that because the hydrodynamics of the flow at the interface are well characterised, it is possible to assess the relative contributions of the component diffusive and interfacial resistance to the overall transport process.

Our results considerably extend those given in a preliminary report (De Meere and Tomlinson, 1984) and lead to a reasonably accurate predictive model of the water–oil partitioning process which we believe to be general.

Theory

Development of the model

Our analysis closely follows that of previous workers (Albery et al., 1976) and has been fully reported elsewhere (De Meere and Tomlinson, 1983, 1984; De Meere, 1985; Leahy and Wait, 1986). In the water–oil–oil arrangement, Fig. 1, the outer receptor compartment contains the oil which also saturates the membrane. The rate constant k_f (s^{-1}) for transport of solute from inner donor phase phase to outer receptor phase is given by:

$$k_f = k_{obs}/(1 + V_D/V_R K_D) \quad (1)$$

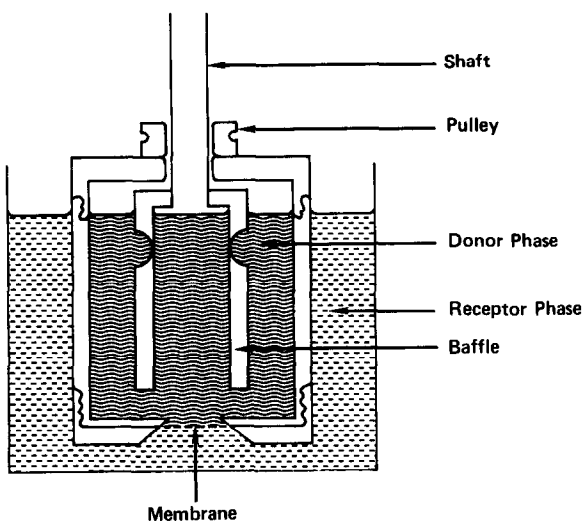


Fig. 1. The rotating diffusion cell. The cell is rotated by a belt looped around the pulley system and a drive motor.

where k_{obs} is the observed rate constant and V_D and V_R are the volumes (cm^3) of donor and receptor phases respectively. The aqueous–organic permeability P (cm/s) is related to k_f by:

$$P = k_f V_D/A \quad (2)$$

where A is the contact surface area (cm^2). Reciprocal permeability is given by the sum of resistance to transport which, in the system studied here is as follows:

$$P^{-1} = R_{TOTAL} = R_a + R_o/K_D + R_I + R_M/K_D \quad (3)$$

where R indicates resistance (reciprocal permeability) and the subscripts a, o, M and I refer to the aqueous, organic and membrane diffusional and the interfacial barriers respectively. Eqn. 3 can be recast to give Eqn. 4, the familiar bilinear relationship:

$$\log P = \log K_D - \log(\beta K_D + 1) + C \quad (4)$$

In the water–oil–oil case $\beta = (R_a + R_I)/(R_o + R_M)$ and $C = -\log(R_o + R_M)$.

Since in the RDC the thickness of the diffusional layers are defined by the hydrodynamics of the system, then R_a and R_o can be expressed in terms of more fundamental parameters. From the Levich equation (Levich, 1962), it follows that:

$$R_i = 0.643 \nu_i^{1/6} D_i^{-2/3} \omega^{-1/2} \quad (5)$$

where ν_i is the kinematic viscosity of phase i, D_i is the solute diffusivity (cm^2 s) within that phase and ω is the rotation speed. The membrane resistance is given by,

$$R_M = L/(\alpha \cdot D_{o,i}) \quad (6)$$

where L is the membrane thickness (cm), α is the membrane porosity and $D_{o,i}$ is the solute diffusivity (cm^2/s) within the organic phase that saturates the membrane.

To develop the general model to relate water–oil partitioning rates to physicochemical descriptors of solute and solvent pairs, Eqn. 3, the relation-

ship between inverse permeability and resistance is combined with Eqns. 5 and 6, the expressions for the relevant resistances in the RDC, to give Eqn. 7 for the water–oil–oil system:

$$P^{-1} = 0.643\left(\nu_a^{1/6} D_a^{-2/3} + \nu_o^{1/6} D_{o,i}^{-2/3} / K_D\right)\omega^{-1/2} + L/(\alpha K_D D_{o,i}) + 1/(\alpha k_I) \quad (7)$$

where k_I is the interfacial rate constant. The kinematic viscosities of water, TMP, octanol, PGDP, and chloroform are known and the organic diffusivities can be related to those in water by the Wilke–Chang relationship (Wilke and Chang, 1955; Hayduk and Laudie, 1974);

$$D = 7.4 \times 10^{-8}(\phi \cdot \mathrm{MW})^{1/2} T/\eta V^{0.6} \quad (8)$$

In this equation ϕ is an empirical association factor included to correct for the diffusivity in highly self-associated solvents such as water ($\phi = 2.26$) and $\phi = 1$ for non-associated solvents. MW is the molecular weight of the solvent, T is the temperature (°K) and V is the molar volume of the solute measured at the boiling point.

Diffusivity of a solute in the organic solvent relative to that in water is given by the following:

$$D_{rel} = D_a/D_{o,i} \quad (9)$$

$$D_{rel} = (\phi_a \mathrm{MW}_a)^{1/2}/(\phi_o \cdot \mathrm{MW}_o)^{1/2} \eta_o/\eta_a \quad (10)$$

In this way, the term D_{rel} for a given solvent can be estimated from the solvent viscosity and molecular weight. Aqueous diffusivity can be estimated from the same parameters if the solute molecular volume, V, is known. In the original Wilke–Chang equation, solute molecular volume was estimated by a group additivity method using Le Bas increments (Le Bas, 1915). The molecular volume calculated in this way is an estimate of the volume at the boiling point. For complex molecules, such group additivity schemes are difficult, inaccurate and time-consuming. In this study we have used an estimate of the intrinsic or van der Waals molecular volume, V_I, which was calculated using a computer-based molecular modelling system and which has proved useful as a measure of the cavity term in correlations of important solubility properties such as log K_D (octanol/water) and aqueous solubility, log S_w, with solute physicochemical properties (Leahy, 1986). Correlation of published aqueous diffusivities with V_I gives the following result:

$$D_a = 9.28 \times 10^{-5} \cdot V_I^{-0.58} \quad (11)$$

The expression for the water–oil partitioning permeability, Eqn. 7, can therefore be expressed in terms of more fundamental parameters by the substitution of the expressions for $D_{o,i}$, Eqn. 10, and D_a, Eqn. 11, as well as the known parameter values for ν_a, L (60 μm) and α (0.85), to give:

$$P^{-1} = 358 \cdot V_I^{0.39} \cdot \omega^{-1/2} \cdot \left(0.456 + \nu_o^{1/6} \cdot D_{rel}^{2/3}/K_D\right) + 92.9 D_{rel} V_I^{0.58}/K_D + 1.18/k_I \quad (12)$$

The term k_I is the water–oil interfacial rate constant (cm/s) for a particular solute and organic solvent. Measurement of interfacial water–oil, k_I and oil to water, k_{-I}, rate constants by the drop technique (Brodin and Agren 1971; Brodin and Nilsson, 1973; Brodin, 1974; Brodin et al., 1976) for a range of solutes and organic solvents, showed log k_I to be linearly dependent on log K_D with constants of proportionality ($\rho_{I,i}$) of the order 0.8 to 0.9 and intercept log $m_{I,i}$. Similar relationships were found for log k_{-I} where the slopes are, *of necessity*, from -0.1 to -0.2. That the value of the slope tends towards unity for the aqueous → organic interfacial rate constant can be understood by analogy with a more familiar example of a rate/equilibrium relationship, the Brönsted catalysis equation (Kresge, 1973), so that for $\rho_{I,i} \gg 0.5$ a late transition state is indicated, i.e., near complete dehydration is required to reach the transition state. Accepting then that the water–oil interfacial rate constant is approximately inversely proportional to the partition coefficient we put $k_I = 1/(m_{I,i} \cdot K_D)$ where $m_{I,i}$ is the unknown slope of this relationship for solvent i. For water–oil permeabilities for the wide range of solutes shown in Scheme 1, at a range of rotation speed ω, with

$CHCl_3$, TMP, PGDP and octanol as solvents, see Figs. 2–5.

Statistical methodology

The predictive model of the water–oil partitioning process, Eqn. 12, is deceptively simple, being linear with a single unknown parameter, $m_{I,i}$ to be estimated for each solvent. However, the intermediate steps in deriving Eqn. 12 from Eqn. 3 introduce a complicated error structure. In addition, the estimation of the parameters of Eqn. 12 is made more difficult by the presence of measurement errors in several of the independent variables. For this reason Eqn. 12 is not a classical regression model but belongs instead to the class of models described as functional relationships in the statistical literature (Kendall and Stuart, 1979). Furthermore some of the 'known' parameters are not exact since they are based on measurements which are subject to error, e.g. membrane thickness. If the measurement error in K_D is ignored, it is possible to regard Eqn. 12 as a classical regression model giving a predicted permeability, P, corresponding to the values of K_D, V_I, ν and D_{rel} of a solvent-solute combination at a particular rotation speed, ω. However, the use of the Wilke–Chang relationship to replace D_a and $D_{o,i}$ by functions of V_I induces a complex correlation structure for the residual error in Eqn. 12 with additional complications caused by the non-linearity of the model. Statistically, it is convenient to make use of the inverse Wilke–Chang relationship and regard V_I as consisting of a function of $D_{o,i}$ and an error term. A further simplification is achieved by working with the logarithm of P and V_I. This is because the standard deviations of the error in Eqn. 12 and the inverse Wilke–Chang relationship are approximately proportional to the magnitudes of P and V_I respectively.

The full functional relationship model is specified as follows:

$$-\log P = \log\left[\left(0.293 + 0.643\nu_o^{1/6}D_{rel}^{2/3}K_D^{-1}\right)\omega^{-1/2}D_a^{-2/3} + 7.06\times10^{-3}D_{rel}D_a^{-1}K_D^{-1} + 1.18m_{I,i}^{-1}K_D^{-1}\right] + e_1 \quad (13)$$

$$\log V_I = -11.125 - 1.297\log D_a + e_2 \quad (14)$$

$$\log K_D^{obs} = \log K_D + e_3 \quad (15)$$

where K_D^{obs} is the observed value of K_D and e_1, e_2 and e_3 are normally distributed errors with mean zero. Eqn. 13 is derived from Eqns. 7 and 9 and Eqn. 14 is the inverse Wilke–Chang relationship which is obtained by regression of $\log V_I$ on $\log D_a$. The S.D. of e_1 is unknown but is at least as large as the measurement error in $\log P$ which was estimated to be log(1.05), i.e. half the estimated $\pm5\%$ error in K_D. The S.D. of the error about the regression obtained when fitting the Wilke–Change relationship, 0.112, provides an estimate of the standard deviation of e_2. The S.D. of the measurement error in $\log K_D$ was estimated to be log(1.025). The model specified by Eqn. 13 was further generalised as follows:

$$-\log P = \log\left[\left(a_i + b_i\nu_o^{1/6}D_{rel}^{2/3}K_D^{-1}\right)\omega^{-1/2}D_a^{-2/3} + c_iD_{rel}D_a^{-1}K_D^{-1} + 1.18m_{I,i}^{-1}K_D^{-1}\right] + e_1 \quad (16)$$

where a_i, b_i, c_i, and $m_{I,i}$ for $i = 1,\ldots4$ represent parameters for each solvent. The parameters a_i, b_i, and c_i were introduced to examine the validity of Eqn. 13. The theoretical model, for instance, predicts that $a_i = 0.293$, for $i = 1,\ldots4$, but by fitting Eqn. 16 it is possible to assess the magnitude of departures from the theoretical equation. In the case of parameter c_i, there is also the possibility of error in the measurements of the thickness and porosity of the membrane and it cannot be assumed that the parameter is known exactly.

Eqn. 9 assumes that the diffusivities of all solutes in a particular solvent are simply proportional to the aqueous diffusivities. To allow for possible solute–solvent interaction effects, Eqn. 14 was generalised to allow a separate error for each solvent. For each solvent the relationship was specified as

$$\log V_I = -11.125 - 1.297\log D_{o,i} + 1.297\log D_{rel} + e_4 \quad (17)$$

where e_4 is a normally distributed error with mean zero. It was then necessary to use Eqn. 7 to include $D_{o,i}$ explicitly in Eqns. 16 and 13 following Eqn. 8.

A partially regularised Marquardt-like algorithm has recently been developed for least-squares estimation of functional relationships (Schwetlick and Tiller, 1985) which is only four times as expensive in computer time as most algorithms performing classical non-linear regression analysis. However, this algorithm was not available when most of the analyses reported here were being done. The functional relationships were fitted using a modification of a standard non-linear regression algorithm (SAS, 1985). Consequently the fitting of the functional relationship model was extremely expensive in computer time and several approximations had to be made.

The model fit was achieved by simultaneously fitting models (14) and (15) to the logarithms of V_I and K_D^{obs} as well as fitting Eqn. 16 to the permeability data. The model parameters consisted of the structural parameters a_i, b_i, c_i and $m_{I,i}$ for each solvent, a pair of parameters K_D and D_a for each solute, and a parameter $D_{o,i}$ for each solute–solvent combination.

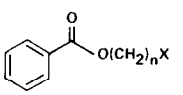
The major drawback of using the non-linear regression package to perform the fit was the inability to estimate the standard deviation of e_1. Instead, the ratios of the S.D.s of e_1, e_2 and e_3 were specified using the weighting facility of the SAS program. The S.D. of e_1 was of course not known, but a crude estimate was obtained by using the residuals from the fit of Eqn. 13 (with $1/m_{I,i}$ assumed zero) and D_a, $D_{o,i}$ replaced by their estimates from the Wilke–Chang relationship. A first-order Taylor series expansion is given in the appendix to demonstrate that the residuals from the above fit approximately satisfy a multiple linear regression whose coefficients are the error terms in Eqns. 14 and 17. Correction for the first order terms described in the appendix reduced the residual sum of squares from 32.5 to 2.95. The part of the residual sum of squares of log P attributable to the estimated measurement error was estimated to be 1.41 and hence the true residual sum of squares was assumed to lie between 1.41 and 2.95. The S.D. of e_1 was arbitrarily estimated to be 0.025 which corresponds to a residual sum of squares of 2.

Materials and Methods

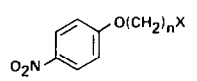
The results reported in this paper were obtained by groups at the University of Amsterdam and ICI Pharmaceuticals Division working in parallel. The RDC assemblies used were identical in all important respects and a common list of compounds was examined. The procedures used by the two groups are fully reported for the work in TMP and $CHCl_3$ (De Meere and Tomlinson, 1983, 1984) as well as for octanol and PGDP (Leahy and Wait, 1986). There are minor differences in procedure and ancilliary equipment which can be discerned by an examination of these earlier reports but reproducibility of results between the two groups was excellent.

Materials

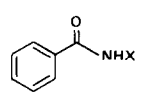
The compounds used in this study are shown in Schemes 1 and 2. The sources of materials used by the Amsterdam group have been detailed in the



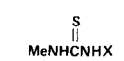
	n	X
1	2	H
8	4	H
9	0	^{i}Pr
10	0	7–norbornadienyl
14	4	CN
15	2	OMe
16	2	OCOMe
25	4	$CONH_2$
26	3	4–imidazolyl
35	2	$NHCOCF_3$
38	2	OH
39	2	$O(CH_2)_2OH$
40	2	$(OCH_2CH_2)_2OH$



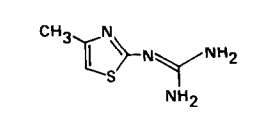
	n	X
2	1	H
12	3	SMe
17	3	SOMe
18	3	SO_2Me
19	2	1–pyrrolidinone
20	2	4–morpholinyl
21	2	1–imidazolyl
22	2	1–triazolyl
24	3	SO_2NH_2



	X
3	Me
4	Et
36	CH_2(2–hydroxybenzene)
37	CH_2(4–hydroxybenzene)



	X
5	*n*–hexyl
6	*n*–$C_3F_7CH_2$
7	1–adamantyl
11	benzyl



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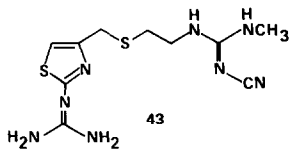

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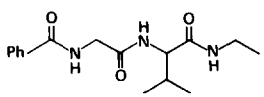

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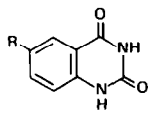
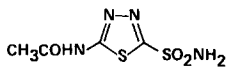


R
47 H
48 Me



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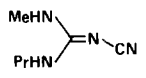

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13	Aniline	41	*para*–cresol
23	Quinoline–*N*–oxide	42	*para*–toluamine
27	4–chloroaniline	44	phenylsulphonamide
30	4–nitrophenol	45	caffeine
31	4–chlorophenol	46	4–quinolone
32	*N*–methylaniline	51	$PhCH(CF_3)_2OH$
33	4–hydroxyacetophenone	53	$PhCONHCH_2CONHEt$
34	2–nitrophenol		

earlier report. Compounds noted to have been provided by ICI were prepared in-house by standard synthetic techniques and satisfied the usual spectroscopic and analytical criteria for structural integrity and purity. All these compounds were used as received except for aniline which was distilled under vacuum before use. Chloroform (analytical grade, Merck, Amsterdam) was washed 3 times with distilled water and then distilled (B.P. 61–62°C) before use. Octanol (Spectroscopic grade, Fisons, U.K.) was used as received. PGDP (Emery Industries, Chicago, U.S.A.) was washed twice with 0.1 M NaOH and twice with distilled water. Water for the preparation of buffer solutions was either deionised or glass-distilled before use. Both aqueous and organic phases were presaturated with each other. Phosphate buffer (pH 7.2, 0.01 M, NaH_2PO_4) was used for non-ionizing solutes. For ionizing solutes, either borate (pH 9.2, 9.8, 0.01 M), acetate (pH 4.9, 0.01 M) or disodium hydrogen phosphate solution (pH 12, 0.01 M) was chosen such that the test solute was almost completely unionized (i.e., final pH at least two pH units away from the pK_a value). In the studies using PGDP as the organic phase, the ionic strength of the solutions used was 0.05 M. Depending on the molar extinction coefficient of a solute the concentration of the solution was normally of the order of 10^{-4} M. The temperature of the measurements was 25 ± 0.3°C.

Methods

The RDC methodology used by both groups has been described but, briefly, the steady-state rate of transfer of the test solute from an aqueous inner compartment across an organic solvent-saturated Millipore membrane into an outer receptor phase was measured by following the change in UV absorbance of the inner donor solution. The water–oil interface, which is formed on the surface of the Millipore filter, is rotated such that there is laminar flow of solvent across the surface of the filter. In these circumstances the thickness of the diffusion layers becomes dependent on the rotation speed. The experiment is repeated at a range of rotation speeds for each solute.

Partition coefficients of the solutes used in this study were determined by standard methods, i.e. Shake flask, Filter probe (Tomlinson, 1982), and HPLC (Mirrlees et al., 1976).

pK_a values were measured by titration or spectrophotometrically where literature values were not available.

The kinematic viscosity of PGDP was measured by standard methods using a Technico 0.01 CS/S viscometer.

Kinematic viscosities ($\times 10^2$ cm^2/s) for water, octanol, chloroform, iso-octane and PGDP were taken as 0.899, 8.76, 0.364 (Smith et al., 1975), 0.650 (De Meere, 1985) and 10.04 (this work), respectively, while viscosities (cP) were 0.887, 7.26, 0.539 (Smith et al., 1975), 0.503 (Landolt-Bornstein, 1974) and 11.17 (this work), respectively.

Results and Discussion

Relationship between permeability and partition coefficient

Partition coefficients and, where appropriate, pK_a values are reported in Table 1. Figs. 2–5 *

* Measured permeability data used in the construction of Figs. 2–5 can be supplied by the authors on request.

TABLE 1

Partition coefficients, pK_a values and intrinsic volumes, V_I

Cmpd	p*K*a	Log K_D				V_I (ml/mol)
		TMP	$CHCl_3$	Oct.	PGDP	
1		2.34	2.89	2.64	2.81	84
2		1.32	3.18	2.03	2.40	78
3		−1.76	1.00	0.86	−0.05	124
4		−1.10	1.54			84
5		−0.94	2.36	2.31	1.41	105
6		−1.17	1.25	1.99	1.91	102
7		−1.12	2.23	2.67		123
8		2.34	2.54			103
9		2.57	2.59	3.18	3.30	95
10		1.25	2.23	3.03		106
11		−2.13	1.45		0.75	99
12		1.85	2.96	3.24	3.70	108
13	4.60	−0.11	1.32	0.90		56
14		1.03	3.10	2.04	2.44	127
15		1.34	3.20	1.78	2.03	110
16		1.27	2.75	1.85	2.26	110
17		−2.53	2.00	0.93	−0.15	120
18		−1.86	2.49	1.10	1.07	126
19		−1.27	2.25	1.33	0.69	125
20	6.30	−0.02	2.94	1.54	1.38	129
21	6.65	−2.00	2.28	1.69	0.68	126
22		−1.84	2.32	1.19	0.92	78
23		−2.38	0.78	0.36	−0.86	78
24		−3.11	0.68	0.97	0.66	123
25		−2.13	1.68	1.39	0.41	123
26	7.35	−1.92	1.99		0.86	122
27	3.98	0.48		1.83		65
28			−0.03	0.42	−1.01	100
29	7.05	−2.00	−0.32	1.24	0.02	100
30	7.16	−2.13	0.18	1.91	1.42	66
31	9.40	−0.45	1.11	2.39	2.13	63
32	4.68	1.03	1.30	1.68	1.87	64
33	4.73		0.08	1.35		74
34	7.23	1.29	2.57	1.79	2.17	65
35		0.06	2.61	2.25	2.18	120
36		−0.63	2.32	2.55	2.10	123
37		−2.61	0.68	1.87	0.91	125
38		−0.98	1.28	1.12	0.68	89
39		−0.99	1.85	1.16	0.42	111
40		−1.29	1.98	1.09	0.14	136
41	10.3	0.4	1.06	1.94		64
42	5.08	0.34	1.99	1.39		66
43	6.80	−3.34	−1.50	0.63	−1.62	182
44	10.6		−0.24	0.31	0.03	80.3
45		−2.38	1.30	−0.07	−0.72	90
46		−3.34	−1.13		−1.53	76
47			−0.88	0.55	−0.43	80
48		−2.69	−0.28			80
50			−2.15			
51				3.41	3.35	97.1
52				1.05	−1.21	168
53				0.58	−0.10	112
54				−0.26	−1.40	91

show our results for permeability as a function of log K_D. The first step was to examine the theoretical model with parameters set at their postulated values, i.e. $a = 0.293$, $b = 0.643$, $c = 7.06 \times 10^{-3}$ and $1/m_{I,i} = 0$. Fig. 6 shows the residuals for a typical solvent plotted by solute. There are clear solute effects present in the data although Fig. 7 shows reasonable agreement between predicted and observed permeabilities.

The full functional relationship as specified by Eqns. 14–16 was fitted next. However, to allow for the solute-related error observed in Fig. 6 an interaction term $D_{o,i}$ was introduced for each solvent. It was also apparent at this stage that the measurement error in K_D was too small to substantially affect parameter estimation and hence it was decided to treat K_D as a variable measured without error. Seven models were fitted to the data including the theoretical model for which $a_i = 0.293$, $b_i = 0.643$, $c_i = 7.06 \times 10^{-3}$, $m_{I,i} = 0$, $i = 1, \ldots 4$. In fitting the 7 models, parameters were either estimated from the data or set at the theoretical value. The 7 models fitted to the data are specified as in Table 2.

The goodness of fit of an 'errors in variables' model is more difficult to assess than those of more simple regression models. One useful approach is to examine the residuals of the different variables measured with error. Three groups of

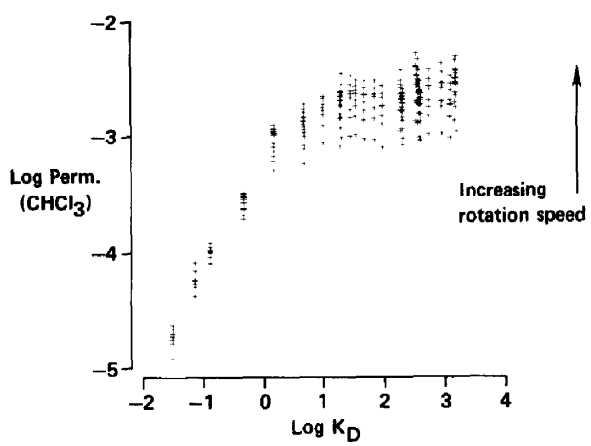

Fig. 2. Observed solute permeabilities against partition coefficient in water/$CHCl_3$/$CHCl_3$ system. Increasing permeabilities for a given solute result from repeat determinations at increasing rotation speed.

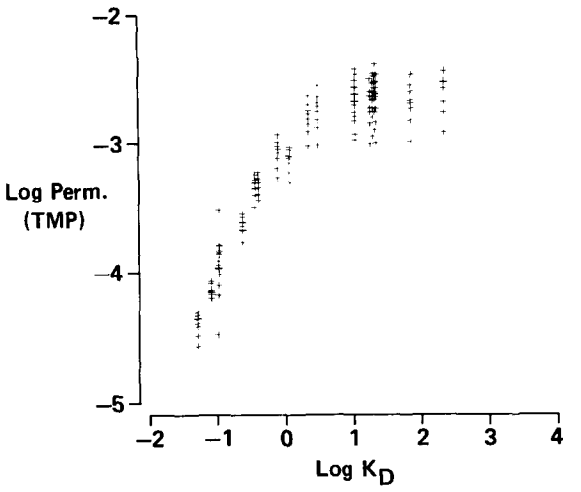

Fig. 3. Observed solute permeabilities against partition coefficient in water/TMP/TMP system. Increasing permeabilities for a given solute result from repeat determinations at increasing rotation speed.

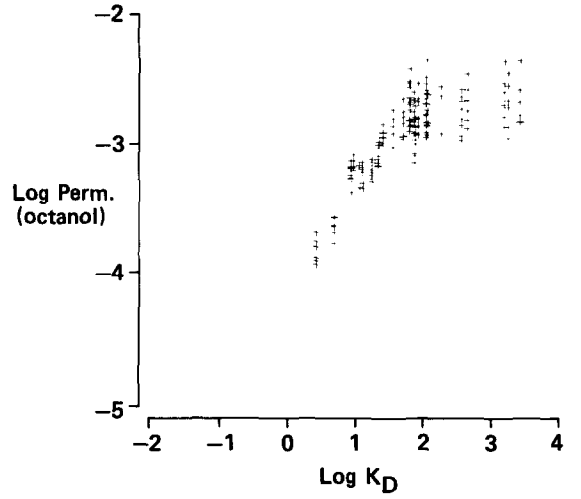

Fig. 5. Observed solute permeabilities against partition coefficient in water/octanol/octanol system. Increasing permeabilities for a given solute result from repeat determinations at increasing rotation speed.

residuals were examined, the log permeabilities, the diffusivities in water and the diffusivities in the organic solvent.

Fig. 8 presents the mean ± S.D. of each class of residual for each of the 7 models. Theoretical limits for the S.D.s of the diffusivities in water and solvent are also shown. It is clear that the theoretical model, model A, and models B and C, are not supported by the data. The best fitting model was model F, but the improved fit was achieved at the expense of negative estimates of the interfacial resistances, R_I, which is physically impossible. Model G was only marginally better than model E at the cost of an extra estimated parameter. This along with the smaller residuals

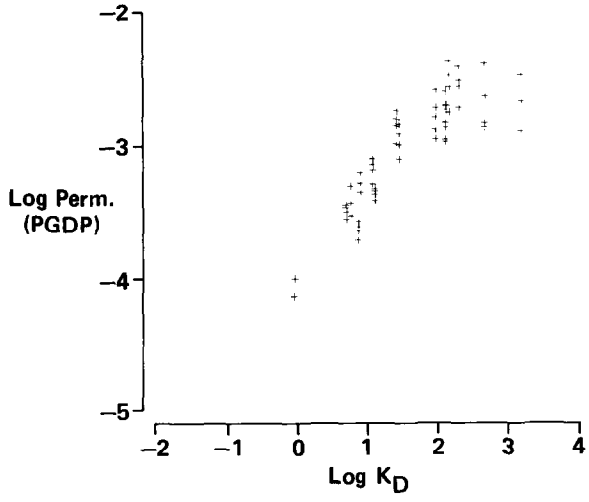

Fig. 4. Observed solute permeabilities against partition coefficient in water/PGDP/PGDP system. Increasing permeabilities for a given solute result from repeat determinations at increasing rotation speed.

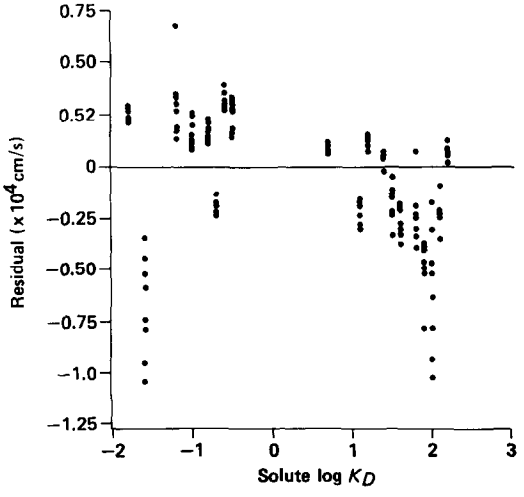

Fig. 6. Examples of residuals of fitting theoretical model A to data, plotted by solute and showing clear dependence on solute. Results for TMP.

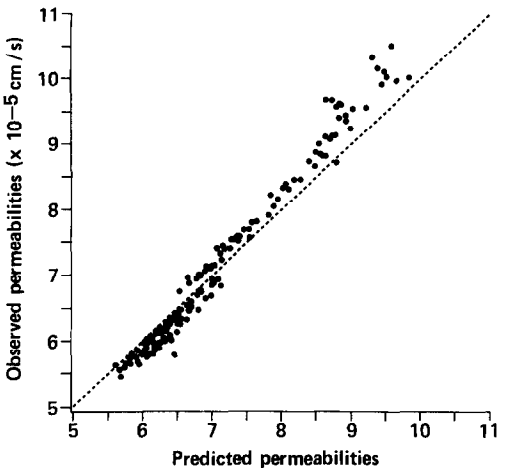

Fig. 7. Plot of observed permeabilities against those predicted by the theoretical model A.

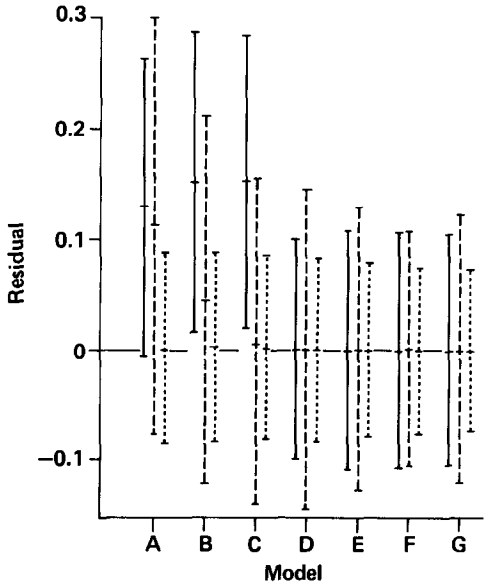

Fig. 8. Mean and S.D. of each class of residuals for the 7 models A–G. Residuals (log units) are, for each model, aqueous diffusivity (———), organic diffusivity (— — —) and overall permeability (- - - - -).

for model E compared to model D suggested that model E was the minimum model necessary to describe the data. The estimated parameters from Model E are shown in Table 3 where it can be seen that the estimated plateau term for octanol lies outside the 95% confidence intervals for the plateau terms of the other 3 solvents and none of the confidence intervals contain the theoretical estimate.

The parameter estimates given in Table 3 are dependent upon the Wilke–Chang relationship. The solutes in this study, however, had a different range of values to those in the training set of published aqueous diffusivities used to derive Eqn. 12 as shown in Fig. 9. The relationship between the logarithm of diffusivity and V_I shows signs of curvature in the region where the V_I of compounds in the training set and the current study overlap. In order to assess the effect of possible curvature in the Wilke–Chang relationship, Eqns. 14 and 17 were replaced by the piecewise linear relationship as shown in Fig. 10. The lower section of the curve follows the Wilke–Chang relationship while the upper section is arbitrarily chosen to represent the possible curvature. Use of the piecewise relationship, linear over the range of volumes

TABLE 2

Description of models tested against the data

Model	Parameters			
	a_i	b_i	c_i	$m_{I,i}$
A	f	f	f	f
B	f	f	f	e_i
C	f	f	e	f
D	e	f	e	f
E	e_i	f	e	f
F	e_i	f	e_i	e_i
G	e_i	e	e_i	f

f, Parameter fixed as theoretical value. e, Parameter estimated but same for all four solvents. e_i, Parameter estimated but allowed to take different values for each of solvents.

TABLE 3

Parameter estimates and 95% confidence intervals derived using inverse Wilke–Chang relationship (model E)

Parameter	Solvent	Estimate	95% Interval		Theoretical
a	Chloroform	0.243	0.225–	0.262	0.293
a	TMP	0.235	0.218–	0.251	0.293
a	Octanol	0.203	0.187–	0.218	0.293
a	PGDP	0.227	0.207–	0.247	0.293
c	–	13.3×10^{-3}	12.0	-14.7×10^{-3}	7.1×10^{-3}

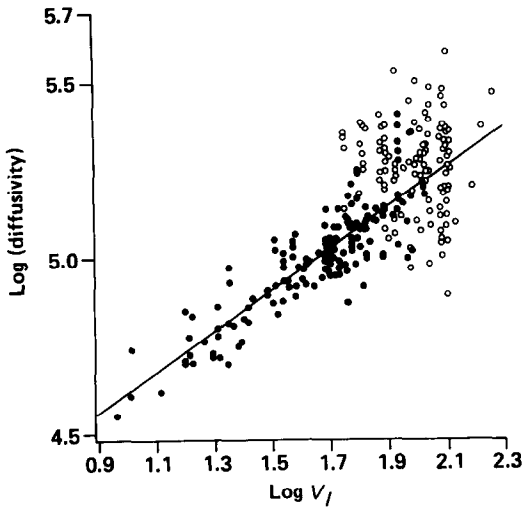

Fig. 9. Published aqueous diffusivities (●) and those estimated in this study (○) using the linear Wilke–Chang equation.

of solutes in this study, gave estimated plateau terms more consistent with the theoretical model and estimated diffusivities consistent with the pattern displayed by the training set, as shown in Fig. 10. Table 4 shows the estimated parameters corresponding to this relationship. It should be noted that the plateau term for octanol is still marginally lower than those of the other solvents.

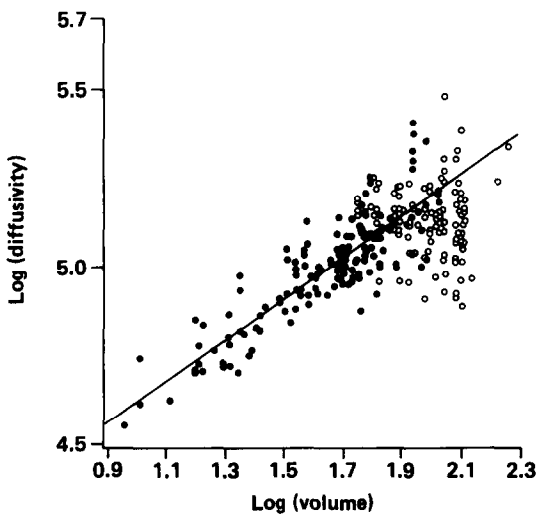

Fig. 10. As Fig. 9, but solute diffusivities (○) estimated using piecewise Wilke–Chang relationship.

TABLE 4

Parameter estimates and 95% confidence intervals derived from postulated piecewise Wilke-Chang relationship

Parameter	Solvent	Estimate	95% Interval		Theoretical
a	Chloroform	0.285	0.270–	0.300	0.293
a	TMP	0.285	0.274–	0.297	0.293
a	Octanol	0.248	0.235–	0.261	0.293
a	PGDP	0.280	0.262–	0.298	0.293
c	–	20×10^{-3}	18.7	-21.1×10^{-3}	7.1×10^{-3}

The point to be noted here is that the large and surprising difference in permeability plateau levels for different solvents observed in the simple stirred two-phase system with different organic solvents by Van de Waterbeemd, De Haan and coworkers are absent in this work which uses the hydrodynamically well-characterised RDC. There is a small difference for the octanol results but this is perhaps understandable given the much greater water content of octanol. The Wilke–Chang relationship is established for the pure solvent and it is not surprising that it fails to hold exactly for the hydrated solvent. Nevertheless, the differences are small as can be seen by a simple visual comparison of the results shown in Figs. 2–6. We can only assume that the striking differences observed in the simpler stirred two-phase system of Van de Waterbeemed and De Haan are artefactual, arising perhaps from changes in interfacial surface area between solvents in the vortex formed on rapid stirring.

A second point is that our results demonstrate, for the first time, the expected dependence of water–oil permeability on solute molecular volume. One surprising feature of the Van de Waterbeemd and De Haan results was that for solutes of higher partition coefficient, K_D, where permeability was determined solely by diffusivity within the aqueous phase, then permeability appeared to be independent of molecular size and hence aqueous diffusivity. It is fair to say, however, as the authors themselves concluded, that given the relatively small spread of molecular volume of the solutes used and the nature of the function relating permeability to molecular volume

($P\alpha V_I^{-0.39}$) that such solute volume-dependent variation in permeability is not readily observed. In our work, we believe that our success in detecting a significant effect is simply due to the much larger number of observations as well as the wider spread in molecular volume of the solutes chosen.

A further point we would wish to make is that, as can be seen in Fig. 9, aqueous diffusivities estimated from our results show poor agreement with an extrapolation of the Wilke–Chang relationship. There is a great deal of variability in estimates of diffusivity for solutes of comparable molecular volume and the mean lies somewhat below the Wilke–Chang line. We have noted before (Leahy and Wait, 1986) that in both our own and previous work by other groups there is poor agreement between the diffusivity estimated by the RDC and those determined independently by more accurate techniques. This is partly a result of the large errors associated with diffusivity estimated in the RDC, errors which are amplified by the double reciprocal relationship between permeability and rotation speed from which the estimates of diffusivity arise. Unfortunately, the RDC cannot be used as a means of estimating solute diffusivity with any accuracy as Figs. 9 and 10 clearly demonstrate. We also find that improved model fits to the theoretical estimates of the aqueous diffusional plateau levels are achieved by use of a piecewise linear relationship in place of the Wilke-Chang relationship which was established for solutes of smaller volume.

Estimates of the membrane diffusional resistance (c) are larger than theoretical values based on the gross properties of the membranes, suggestive of perhaps the need for consideration of the effects of tortuosity in the membrane matrix, although no tortuosity factor was found in earlier work with similar membranes (Albery and Fisk, 1981). Doubtless, inaccuracies in the estimation of the Wilke–Change constant, D_{rel}, also contribute to this discrepancy.

It is also of interest that examination of residuals of the model fit by solute (Fig. 6) show some solute-dependent error. We have used the Wilke–Chang relationship which establishes diffusivity as a function of solute volume alone. An alternative view is that diffusivity is a function both of molecular volume as well as the extent of the interaction between solute and solvent. Correlations (Flynn et al., 1974) of aqueous diffusivity with partial molar volume in water show a strong dependence on the chemical functionality of the solute and the correlations show family lines, with solutes which interact strongly with water, e.g. alcohols, having lower diffusivity than the alkane of comparable volume. However, the family dependence observed here more likely arises from the relationship between partial molar volume in water and chemical functionality (Edward, 1970); strongly interacting solutes have lower partial molar volumes than alkanes of the same Van der Waals or intrinsic volume. Our own correlation of published aqueous diffusivities (Eqn. 11 and Fig. 9) with a measure of the Van der Waals or intrinsic molecular volume, V_I, shows no such functional group dependence. Nevertheless, inclusion of a term to allow for a solute dependent effect in our model (Eqn. 13) does lead to significantly reduced residual error and begs the question of whether this indicates some remaining partial dependence of diffusivity on functionality or whether this arises from some other error, perhaps in our estimation of the partition coefficient. In future work, we hope to examine this further by a consideration of the values of the "residual interaction term" alongside potential physicochemical solute–solvent interactions such as hydrogen bonding effects.

Interfacial resistance

In most earlier investigations of water–oil partitioning rates (e.g. Van de Waterbeemd and Jansen 1980) the assumption has been that the resistance of the interface is negligible in relation to the total resistance for the flux of a drug through the membrane. However, other authors, working with a similar RDC to our own have stated that the interfacial transfer step can be an important barrier to solute transport (Albery et al., 1976; Fleming et al., 1983; Guy et al, 1982a and b; Guy and Honda 1984; Kinkel, 1982). For certain organic solutes, such as methyl nicotinate, *p*-methylbenzyl chloride and salicylic acid, the k_I was found to be ca. 10^{-5} ms^{-1} and independent of log K_D. Recently, two of us have shown (Leahy

and Wait, 1986), by comparison of the rotation speed-independent resistances for methyl nicotinate in water/oil/oil, water/oil/water and all-oil systems, which should differ by an interfacial resistance term, that there is no detectable interfacial resistance in these systems. Furthermore, a recent report (Byron and Rathbone, 1986) showed, in an RDC identical to that used by Hadgraft and Guy with an unclamped, albeit different membrane that interfacial resistance was negligible for a dialkyl barbiturate in the water/octanol/octanol system.

A recent report (Hanna et al., 1987) showed lower interfacial resistance than previously observed for transfer of 3 carboxylic acids from decane to water and pointed out the difficulty of estimating interfacial resistances when the membrane resistance is greater than 10% of the total rotation speed independent resistance. A series of papers by Brodin et al. (1971, 1973, 1974, 1976), using the drop technique to measure interfacial resistance showed that the logarithm of the aqueous to organic rate constant, log k_1, was linearly dependent on log K_D for a range of solutes and organic solvents with constants of proportionality ρ_I of the order 0.8–0.9. These results were extended for a series of alcohol solutes by Miller (1986).

A small but significant effect of solute molecular volume, hence diffusivity, on water–oil partitioning rates, has been demonstrated for the first time. Our results show no evidence for the existence of a measurable aqueous–organic interfacial resistance as we have suggested earlier (Leahy and Wait, 1986) and raises doubts as to the validity of estimates of R_I made by use of the RDC methodology (e.g. Fleming et al., 1983).

Although our results do not allow the estimation of any interfacial resistance, as in our earlier work (Leahy and Wait, 1986), we accept that this conclusion remains controversial and deserves further consideration. We are currently preparing a fuller discussion of this issue but it is worth noting that the principal disagreement lies not in the observed permeability data, which are roughly comparable given the differences in membrane used, but in the interpretation of that data. We have found that estimation of R_I by extrapolation of P^{-1} vs $\omega^{-1/2}$ plots to be inherently unreliable given the errors involved and do not find the intercept values to allow estimation of any significant R_I. There are, however, some differences in technique. Our experiments are generally carried out with lower concentrations (ca. 10^{-4} M) of solute and we have used an RDC with a bevelled clamp arrangement to hold the membrane. However, we constructed our RDC in this way following the advice of Albery et al. (1976) who compared clamped and unclamped membrane systems and concluded that there was no significant difference in the results obtained with the two different techniques. Moreover, the RDC used by Byron and Rathbone (1986) where no significant R_I was found is also 'unclamped'. There is therefore no evidence that the clamped membrane RDC does not establish proper rotating disk hydrodynamics.

Conclusions

It has been recognised for some time that the diffusion rate of non-electrolytes from water into some organic phase is a complex process that depends not only on the partition coefficient but also on a number of factors that may include diffusional resistances, interfacial resistances, and the possibility of specific solute–solvent interactions. However, the relative weighting of these factors has never been assessed in detail, and in particular it has not been clear whether the standard hydrodynamic equations will adequately handle the observed permeation rates without recourse to special solute-specific factors or other terms not previously identified. The present study, concerning as it has done a variety of organic phases and a very much wider range of molecular sizes and functionalities than has hitherto been examined, was addressed specifically to that question. We find, in fact, that a simple model of the water–oil partitioning process in the RDC which is based on these standard equations, combined with a modification of the Wilke–Chang equation made necessary by the different molecular weight range involved, is predictive of observed partitioning rates with almost no residual error. In particular, our results show no evidence of measurable

effects due to chemical functionality or interfacial resistance; the latter is consistent with our earlier study (Leahy and Wait, 1986) and raises doubt as to the validity of previous estimates made by use of the RDC methodology (e.g. Fleming et al., 1983). However, we have demonstrated, for the first time, a small but significant effect of solute molecular volume, hence diffusivity, on water–oil partitioning rates; we owe this demonstration both to the large number of observations and the large spread in molecular size.

We believe, therefore, that almost all the factors that govern water–oil partitioning rates in these simple model systems are now not only understood but quantitatively predictive. Nevertheless, there remain some discrepancies such as the presence of some residual solute-dependent error and the continuing controversy over the magnitude of the interfacial resistance and we expect to present further results on this interesting question at a later data.

Appendix

Derivation of an approximate linear regression relationship for log P. Manipulation of Eqns. 15 and 18 gives

$$D_a = e^{e_2}\hat{D}_a, \tag{A1}$$

$$D_{o,i} = e^{e_4} D_{rel}\hat{D}_a, \tag{A2}$$

where $D_a = 1.88 \times 10^{-4}\ V_I^{-0.77}$, the estimated diffusivity from the functional relationship. Eqn. 14 with $D_{o,i}$ included explicitly as in Eqn. 8 may be rewritten using Eqns. A1 and A2 as

$$\begin{aligned} -\log P &= \log\left[\left(0.293\ e^{-2/3e_2} + 0.643\nu_o^{1/6}\ e^{-2/3e_4}K_D^{-1}\right)\right. \\ &\quad \times\omega^{-1/2}\hat{D}_a^{-2/3} + 7.06\times10^{-3}\ e^{-e_4}\hat{D}_a^{-1}K_D^{-1} \\ &\quad \left.+1.18m_{I,i}^{-1}K_D^{-1}\right] + e_1 \end{aligned} \tag{A3}$$

A Taylor series expansion of Eqn. A3 in e_4 and e_2 gives

$$\begin{aligned} -\log P &\approx -\log\hat{P} - \left[\tfrac{2}{3}\left(e_2\ 0.293 + e_4\ 0.643\nu_o^{1/4}K_D^{-1}\right)\right. \\ &\quad \times\omega^{-1/2}\hat{D}_a^{-2/3} + e_4\ 7.06\times10^{-3}\hat{D}_a^{-1}K_D^{-1}\left.\right]\hat{P} \\ &\quad + e_1 \end{aligned} \tag{A4}$$

where

$$\begin{aligned} \hat{P}^{-1} &= \left(0.293 + 0.643\nu_o^{1/6}K_D^{-1}\right)\omega^{-1/2}\hat{D}_a^{-2/3} + 7.06 \\ &\quad \times10^{-3}\hat{D}_a^{-1}K_D^{-1} + 1.18m_{I,i}^{-1}K_D^{-1} \end{aligned}$$

If $1/m_{I,i}$ is assumed to be zero then Eqn. A4 is approximately a multiple linear regression with parameters e_2 and e_4.

Acknowledgements

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