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Transport rate constants and transport rate parameters in various organic solvent–water systems *

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Summary

In various systems organic solvent–water transport rate constants and partition coefficients are determined. Nine organic solvents are used: *n*-hexane, cyclohexane, di-ethyl ether, di-isopropyl ether, di-*n*-butyl ether, *n*-hexanol, *n*-octanol, cyclohexanol and oleyl alcohol. Experimentally bilinear relationships between transport rate constants and partition coefficients are obtained with maximum transport rate constants (plateau values) for the transport from the aqueous to the organic bulk and for the reverse process. Both maximum transport rate constants are solute-independent and are used as system parameters. Viscosities of the 9 systems are measured and relationships between the mentioned parameters and viscosities are examined. It is concluded that transport is not solely dependent on viscosity, but is also influenced by other factors to a large extent. The maximum transport rate constants of a certain system are influenced by these factors at least qualitatively in the same way.

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* Transport in Quantitative Structure–Activity Relationships VII.

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Introduction

The biological activity of a drug after administration depends on the concentration of the drug in a receptor compartment and on the intrinsic activity of the drug. The concentration of a drug in the receptor compartment is influenced by a variety of processes, of which transport from the site of application to the site of action is generally assumed to be one of the most important factors. For a better understanding of the so-called Quantitative Structure Activity Relationships (QSAR) it is important to consider the relationships between the partition coefficient P and transport rate constants (Kubinyi, 1979). Often transport rate studies have been carried out using model systems of an organic solvent and water. If the transport of a solute takes place from an aqueous phase, with solute concentration C_{aq}, to an organic phase, with solute concentration C_{org}, (transport rate constant k_1^{obs}) and vice versa (transport rate constant k_2^{obs}), then the transport can be described as in Eqn. 1.

$$C_{aq} \underset{k_2^{obs}}{\overset{k_1^{obs}}{\rightleftarrows}} C_{org} \tag{1}$$

From simple kinetics it follows:

$$P = \frac{k_1^{obs}}{k_2^{obs}} \tag{2}$$

Using the data of Lippold and Schneider for the transfer of homologous quarternary alkylammonium bromides and *n*-alkyl sulfonates in a *n*-octanol–water system Kubinyi found an experimental bilinear relationship between log k_1^{obs} and log k_2^{obs}, respectively, and log P shown in Eqns. 3 and 4. (Lippold and Schneider, 1975a, 1975b, 1976; Kubinyi, 1977).

$$\log k_1^{obs} = \log P - \log(\beta P + 1) + c \tag{3}$$

$$\log k_2^{obs} = -\log(\beta P + 1) + c \tag{4}$$

The physicochemical meaning of the statistically obtained constants was unclear. A fundamental research on the relationship between k_1^{obs} and k_2^{obs}, respectively, and log P was performed by Van de Waterbeemd et al. using simple two-phase systems (Van de Waterbeemd et al., 1981a). For the transfer of a series of non-ionic sulfonamides in the systems *n*-octanol–water and di-*n*-butyl ether–water he obtained experimentally bilinear relationships between log k_1^{obs} and log$_2^{obs}$, respectively, and log P (Eqns. 5,6 and 7), which are shown in Fig. 1. For lipophilic compounds (high values for P) log k_1^{obs} approaches a plateau value, he called log k_{aq}; for hydrophilic compounds (low values for P) log k_2^{obs} approaches a plateau value, he called log k_{org}.

$$\log k_1^{obs} = \log P - \log(\beta P + 1) + \log k_{org} \tag{5}$$

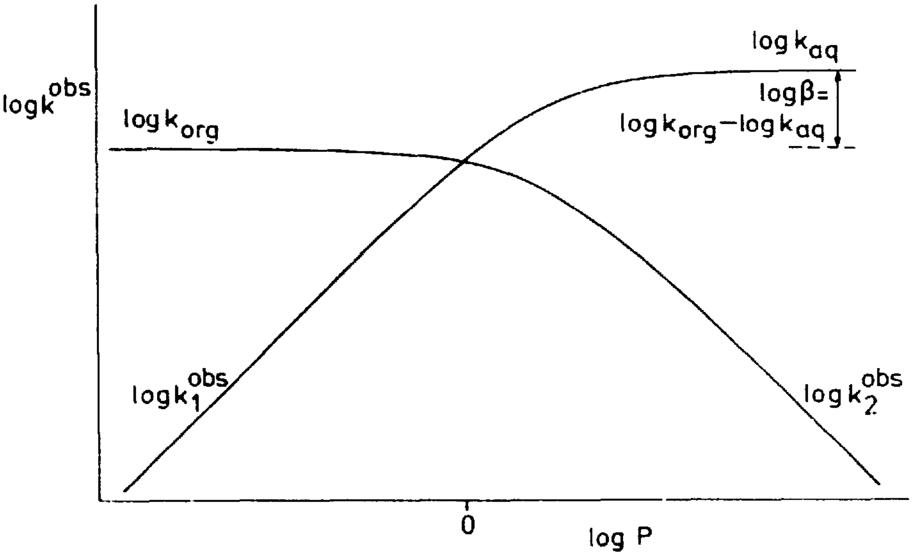


Fig. 1. Bilinear relationship between log k_1^{obs} and log k_2^{obs}, respectively, and log P.

$$\log k_2^{obs} = -\log(\beta P + 1) + \log k_{org} \tag{6}$$

$$\beta = \frac{k_{org}}{k_{aq}} \tag{7}$$

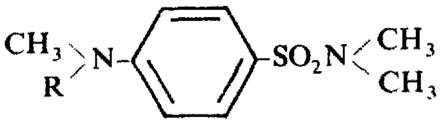
Eqn. 7 shows β to be equal to the quotient of the maximum values for k_2^{obs} and k_1^{obs}. These experimentally obtained relationships have very good statistics. It was also shown that k_{aq} and k_{org} (and so β) are system parameters independent of the solute (Van de Waterbeemd et al., 1981b). This means k_{aq} and k_{org} depend on, e.g. temperature, stirring rate and the solvents used, but not on the type of transferring solute. This implies a general validity for Eqns. 5, 6 and 7. According to these equations k^{obs} is determined by P, k_{aq} and k_{org}. For a good understanding of transport in QSAR a good understanding of transport in vivo is required. In vitro investigations on the factors influencing the transport parameters P, k_{org} and k_{aq}, can contribute significantly to this ultimate goal. In this paper experiments are presented using various organic solvent–water systems. The various systems show a large spread in physicochemical properties (e.g. viscosity, interfacial tension, polarity). In a search for experimental relationships between viscosities and transport parameters a first approach is made to study the effect of various physicochemical properties of the solvents on transport.

Materials and methods

Materials

Solvents used in the partition and transport experiments are: demineralized water; di-iso-propyl ether (Baker Analyzed reagent) and di-ethyl ether (Baker grade) passed through a basic aluminium oxide column to remove peroxides (Dasler and Bauer, 1946); cyclohexane (Baker grade) passed through a magnesium oxide column; *n*-hexane (Baker Analyzed reagent); *n*-hexanol (Baker grade) after fractional distillation (boiling range 158–159°C); cyclohexanol (U.C.B. tout pur) washed with 1 N NaOH and 1 N HCl, respectively, and oleyl alcohol (B.D.H. Technical) passed through a basic aluminium oxide column. In all experiments organic and aqueous phase are mutually saturated.

Solutes used in the partition and transport experiments are: derivatives of N,N-dimethyl-4-[(methyl)amino]benzenesulfonamide



For syntheses and physicochemical properties see: Van de Waterbeemd et al. (1981a).

In some cases (e.g. di-ethyl ether–water system) none of the members of this series possessed the needed hydrophilicity (low P-value) to obtain the plateau value for log k_{org}.

Then sulfadiazine, sulfanilamide, nicotinamide and berberine hydrochloride (all analytical grade) were used.

Apparatus and methods

Transport rate constants and partition coefficients are determined via the same method and using the same apparatus as described by Van de Waterbeemd et al. (1980). The circulation pump was changed to a MPL E_1 range Metripump in the transport experiments with the cyclohexanol–water and oleyl alcohol–water systems. In the transport experiments with the cyclohexanol–water system, the tubing from the transport vessel to the pump is cooled, since a slight rise of temperature (due to the pump) causes the aqueous phase to become cloudy. In all transport experiments the temperature is 20.0 ± 0.1°C and the stirring rate is 40 rpm. Kinematic viscosities are measured at 20.0 ± 0.1°C using Ubbelohde viscosimeters.

Calculations are performed on a Hewlett Packard 9815 A table calculator and (in A.P.L.) on an IBM 370/158 computer.

Theory

Basic in the theoretical background of Eqns. 5, 6 and 7, describing the relationships between k^{obs} and P, is the general acceptance that the equilibrium at the aqueous–organic interface is established instantaneously. The transfer of a drug from the stirred aqueous bulk to the interface and vice versa are kinetic processes with rate constant k_{aq}; k_{org} is the rate constant for the transfer of a drug from the stirred organic bulk to the interface and vice versa. This is illustrated in Fig. 2. k_1 and k_2 are the rate constants for the actual interfacial transfer and the values for k_1

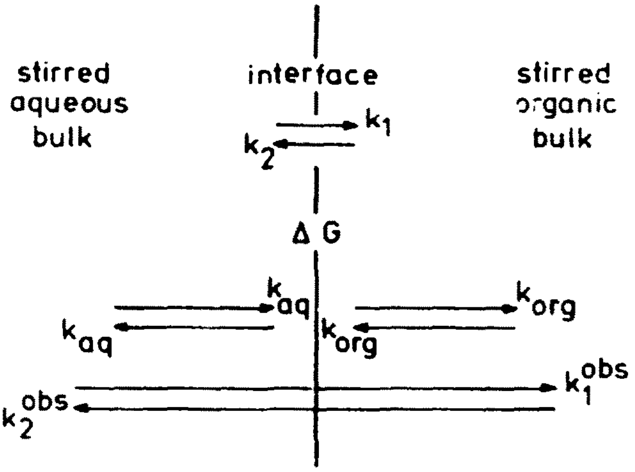


Fig. 2. Interfacial transfer as a 3-step process.

and k_2 are assumed to be much larger than those for k_{aq} and k_{org} as the equilibrium at the interface is established instantaneously. Describing drug transfer in this way leads to Eqns. 8, 9 and 10.

$$P = \frac{k_1^{obs}}{k_2^{obs}} \tag{8}$$

$$k_1^{obs} = \frac{k_{aq} \cdot k_{org} \cdot k_1}{k_{aq} \cdot k_2 + k_{aq} \cdot k_{org} + k_1 \cdot k_{org}} \tag{9}$$

$$k_2^{obs} = \frac{k_{aq} \cdot k_{org} \cdot k_2}{k_{aq} \cdot k_2 + k_{aq} \cdot k_{org} + k_1 \cdot k_{org}} \tag{10}$$

A clear analogy to the kinetics for proton transfer described by Eigen, also used by Murdoch, is noticeable (Eigen, 1963; Murdoch, 1972). Using k_1 and $k_2 \gg k_{aq}$ and k_{org} and substitution of Eqns. 7 and 8 in Eqns. 9 and 10 leads to Eqns. 5 and 6. This mechanism for drug transfer can also be compared to the process of diffusion through laminated structures (Flynn et al., 1974; Friedman and Donbrow, 1980). In both cases barriers (resistances) in series have to be passed. Using this approach leads to overall resistances given in Eqns. 11 and 12.

$$\frac{1}{k_1^{obs}} = \frac{1}{k_{aq}} + \frac{1}{P \cdot k_{org}} = \frac{k_{aq} + P \cdot k_{org}}{k_{aq} \cdot k_{org} \cdot P} \tag{11}$$

$$\frac{1}{k_2^{obs}} = \frac{1}{k_{org}} + \frac{P}{k_{aq}} = \frac{k_{aq} + P \cdot k_{org}}{k_{aq} \cdot k_{org}} \tag{12}$$

In this approach it is again implied that the equilibrium at the interface expressed by P is established instantaneously. Substitution of Eqn. 7 in Eqns. 11 and 12 again leads to Eqns. 5 and 6.

Many models allow for stagnant diffusion layers at the interface (e.g. Stehle and Higuchi, 1972; Flynn and Yalkowsky, 1972). This is also done by Van de Waterbeemd et al. (1981a). In his model, k_{aq} and k_{org} are diffusion rate constants in an aqueous and organic stagnant layer adjacent to the interface. However, the assumption of the existence of stagnant diffusion layers is only one (distinct) possibility to describe k_{aq} and k_{org}; in this paper we are more vague in the indication of the real physicochemical meaning of k_{aq} and k_{org} (see Fig. 2).

In all models diffusion is an essential feature. Diffusion and viscosity are highly intercorrelated. Using various organic solvents with a large range of physicochemical properties, including a large range of viscosities, it can be expected that relationships between transport parameters and viscosities will be found.

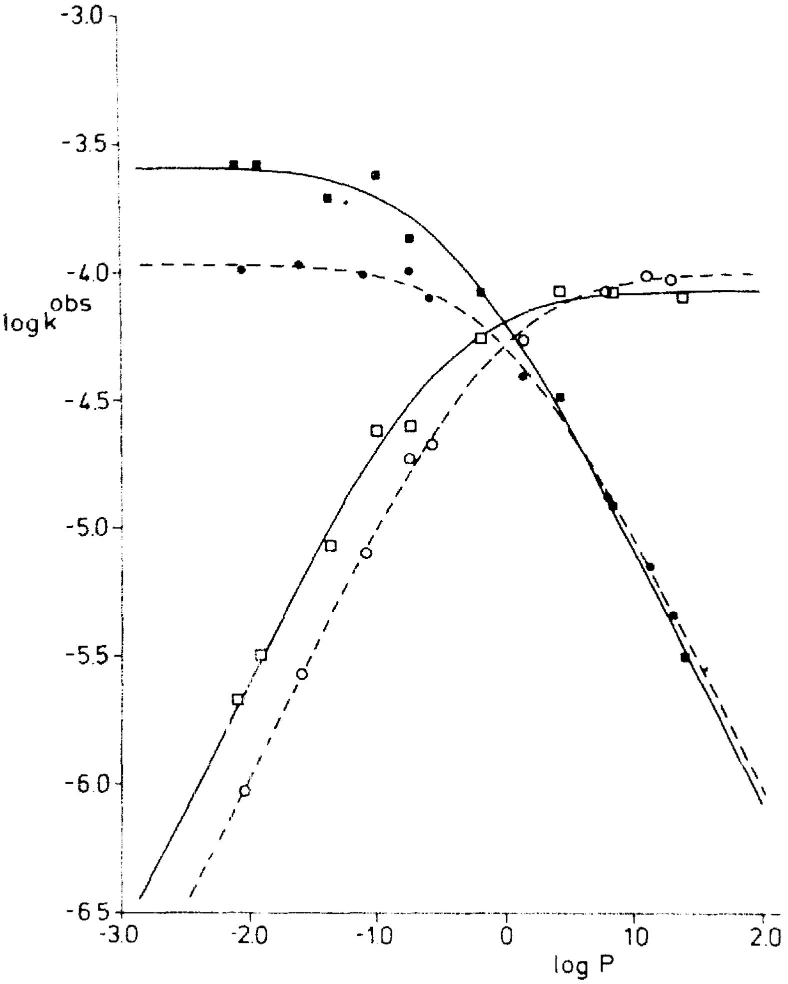


Fig. 3. Experimental plots of log k^{obs} vs log P. O- - -O, log k_1^{obs} vs log P for the cyclohexane-water system; □———□, log k_1^{obs} vs log P for the *n*-hexane-water system; ●- - -●, log k_2^{obs} vs log P for the cyclohexane-water system; ■———■, log k_2^{obs} vs log P for the *n*-hexane-water system.

TABLE I

RELATIONSHIPS BETWEEN log k_1^{obs} AND log k_2^{obs}, RESPECTIVELY, AND log P IN VARIOUS ORGANIC SOLVENT-WATER SYSTEMS

System	Relationship	*r*	n	*F*	s	Eqn. no.
cyclohexane-water	$\log k_1^{obs} = \log P - \log(1.122\ P + 1) - 3.968$	0.999	9	5799	0.027	Eqn. 13
	$\log k_2^{obs} = -\log(1.058\ P + 1) - 3.968$	0.998	9	1961	0.035	Eqn. 14
n-hexane-water	$\log k_1^{obs} = \log P - \log(3.032\ P + 1) - 3.590$	0.996	9	904	0.058	Eqn. 15
	$\log k_2^{obs} = -\log(3.005\ P + 1) - 3.590$	0.997	9	1043	0.060	Eqn. 16
di-ethyl ether-water	$\log k_1^{obs} = \log P - \log(3.759\ P + 1) - 3.358$	0.995	8	598	0.071	Eqn. 17
	$\log k_2^{obs} = -\log(3.649\ P + 1) - 3.368$	0.990	8	291	0.076	Eqn. 18
di-isopropyl ether-water	$\log k_1^{obs} = \log P - \log(2.408\ P + 1) - 3.465$	0.996	8	839	0.066	Eqn. 19
	$\log k_2^{obs} = -\log(2.406\ P + 1) - 3.466$	0.996	8	813	0.066	Eqn. 20
n-hexanol-water	$\log k_1^{obs} = \log P - \log(1.017\ P + 1) - 3.629$	0.917	8	32	0.082	Eqn. 21
	$\log k_2^{obs} = -\log(1.033\ P + 1) - 3.626$	0.997	8	1045	0.080	Eqn. 22
cyclohexanol-water	$\log k_1^{obs} = \log P - \log(0.246\ P + 1) - 4.328$	0.996	7	696	0.033	Eqn. 23
	$\log k_2^{obs} = -\log(0.247\ P + 1) - 4.328$	0.999	7	2959	0.034	Eqn. 24
oleyl alcohol-water	$\log k_1^{obs} = \log P - \log(0.283\ P + 1) - 4.376$	0.975	7	98	0.099	Eqn. 25
	$\log k_2^{obs} = -\log(0.283\ P + 1) - 4.376$	0.988	7	198	0.099	Eqn. 26

Results and discussion

Transport and partition experiments

The results of the transport and partition experiments are presented in Figs. 3–5. The data for log P, log k_1^{obs} and log k_2^{obs} are the mean values of two determinations. Eqns. 5 and 6 are fitted to these experimental data in the same way as described by Van de Waterbeemd et al. (1981a). These results are presented in Eqns. 13–26 in Table 1 and Figs. 3–5.

In general the statistics in Table 1 are good. Practical problems occur using the di-ethyl ether–water system: sometimes air bubbles, caused by the impact of the pump, interfere with the spectroscopic measurement. This is reflected by low values of the correlation coefficients for each separate measurement of k_1^{obs} and k_2^{ob} in the di-ethyl ether–water system compared to the correlation coefficients for the mea-

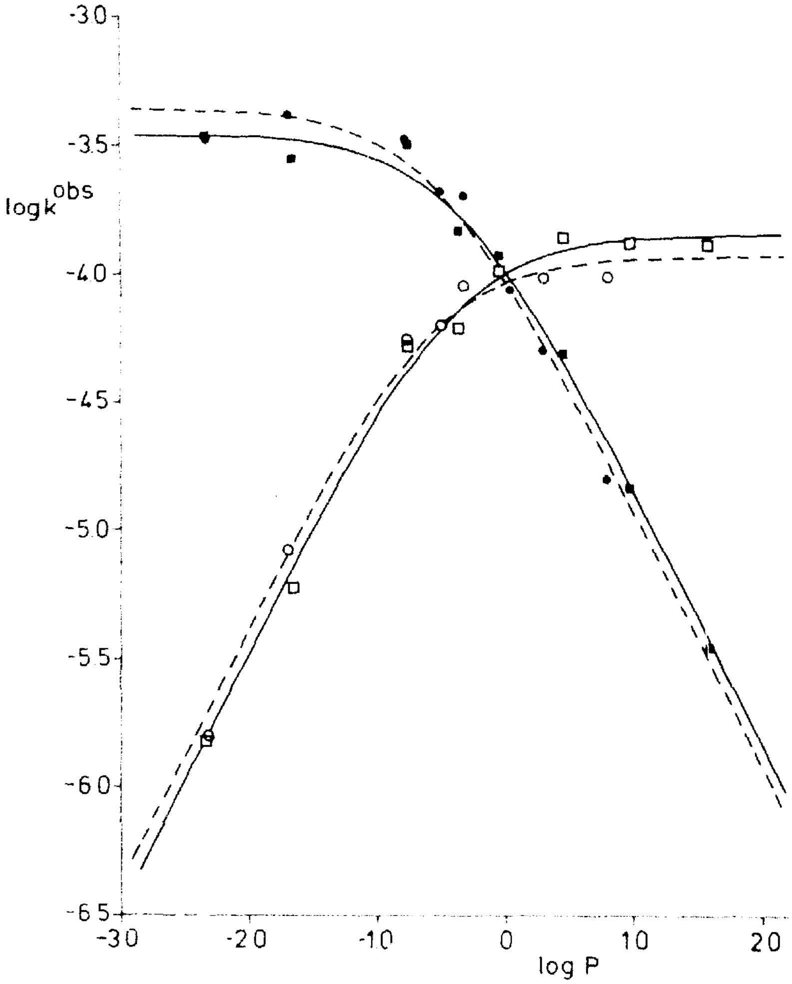


Fig. 4. Experimental plots of log k^{obs} vs log P. ○- - -○, log k_1^{obs} vs log P for the di-ethyl ether–water system; □——□, log k_1^{obs} vs log P for the di-isopropyl ether–water system; ●- - -●, log k_2^{obs} vs log P for the di-ethyl ether–water system; ■——■, log k_2^{obs} vs log P for the di-isopropyl ether–water system.

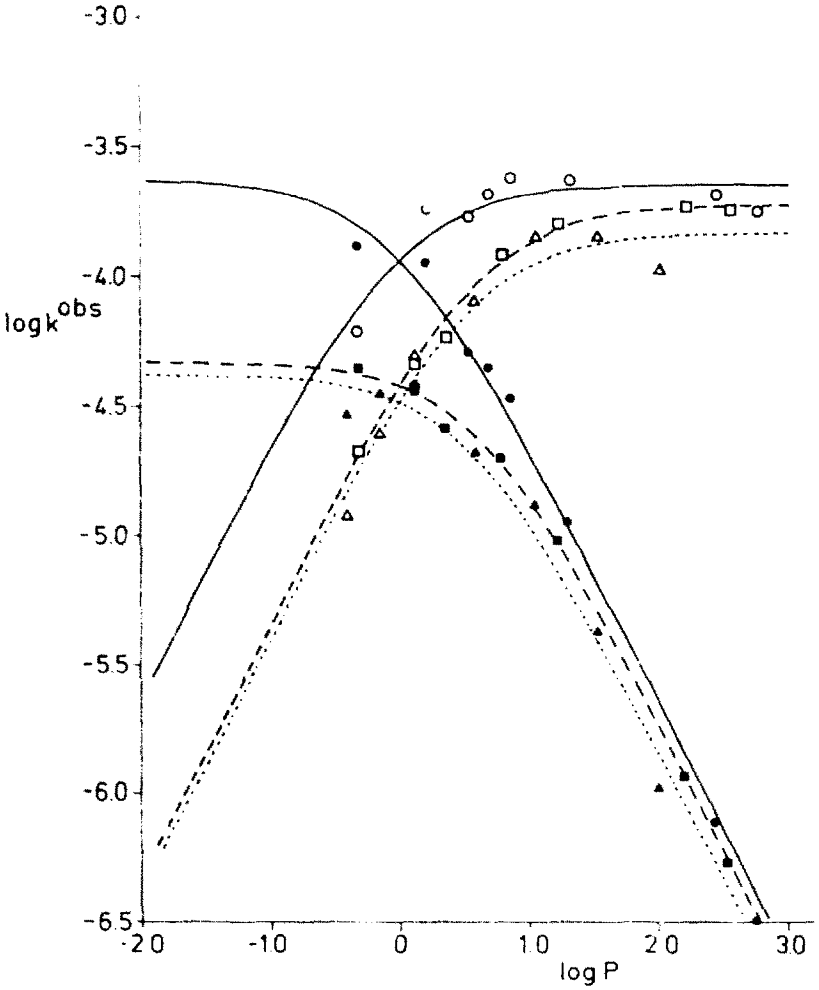


Fig. 5. Experimental plots of log k^{obs} vs log P. ○———○, log k_1^{obs} vs log P for the *n*-hexanol–water system; □– – –□, log k_1^{obs} vs log P for the cyclohexanol–water system; △- - - - - -△, log k_1^{obs} vs log P for the oleyl alcohol–water system; ●———●, log k_2^{obs} vs log P for the *n*-hexanol–water system; ■– – –■, log k_2^{obs} vs log P for the cyclohexanol–water system; ▲- - - - - -▲, log k_2^{obs} vs log P for the oleyl alcohol–water system.

surements in the other systems. Nevertheless the statistics of the resulting Eqns. 17 and 18 in Table 1 are better than those of Eqn. 21 for the *n*-hexanol–water system and Eqns. 25 and 26 for the oleyl alcohol–water system. The relatively bad statistics of Eqn. 21 in Table 1 are caused by the transport experiments with the solutes $R = CO(CH_2)_4CH_3$ and $R = CO(CH_2)_5CH_3$. Their resulting values for k_1^{obs} and k_2^{obs} are lower than predicted by Eqns. 21 and 22 (see Fig. 5, the experiments with the solutes having the largest values for P used in this system) and the values for the correlation coefficients for the transport experiments are low. The relatively bad statistics of Eqns. 25 and 26 for the oleyl alcohol–water system are the result of the relatively low values for the correlation coefficients of all individual transport experiments in the oleyl alcohol–water system. The origin of these deviating correlation coefficients is not clear yet. Nevertheless, for our first goal, the search for relationships between transport parameters and physicochemical parameters, the statistics are acceptable.

For the *n*-octanol–water system (Eqns. 27 and 28) and the di-*n*-butyl ether–water system (Eqns. 29 and 30) Van de Waterbeemd et al. found (Van de Waterbeemd et al., 1981a):

$$\log k_1^{obs} = \log P - \log(0.406\ P + 1) - 3.996 \quad (n = 27;\ r = 0.993;\ F = 1694;\ s = 0.040) \qquad (27)$$

$$\log k_2^{obs} = -\log(0.405\ P + 1) - 3.996 \quad (n = 27;\ r = 0.998;\ F = 7390;\ s = 0.041) \qquad (28)$$

$$\log k_1^{obs} = \log P - \log(1.232\ P + 1) - 3.894 \quad (n = 27;\ r = 0.997;\ F = 4309;\ s = 0.051) \qquad (29)$$

$$\log k_2^{obs} = -\log(1.225\ P + 1) - 3.896 \quad (n = 27;\ r = 0.998;\ F = 5608;\ s = 0.050) \qquad (30)$$

These experimental results are obtained in the same way as Eqns. 13–26 in Table 1, and the statistics of Eqns. 27–30 are good compared to those in Table 1. So Eqns. 27–30 can be used also for our goal. It is important to realize that the values in Eqns. 13–30 and the resulting values for k_{org}, k_{aq} and β depend on the stirring rate and the dimensions of the transport vessel used. The hydrodynamics of the apparatus used are good (Van de Waterbeemd et al., 1980) but do not enable us to calculate the thickness of stagnant layers as is the case with the nowadays often used rotating diffusion cell (Albery et al., 1976).

TABLE 2

TRANSPORT PARAMETERS AND KINEMATIC VISCOSITIES OF EXAMINED SYSTEMS ORGANIC SOLVENT–WATER AND DENSITIES OF PURE ORGANIC SOLVENTS AT 20.0°C

Solvent	$\log k_{aq}$	$\log k_{org}$	β	ν_{aq}(cSt)	ν_{org}(cSt)	d_{org}(g/cm^3)[a]
cyclohexane	−4.005	−3.968	1.090	1.024	1.275	0.779
n-hexane	−4.070	−3.590	3.018	1.033	0.473	0.659
di-ethyl ether	−3.932	−3.363	3.704	1.262	0.351	0.713
di-isopropyl ether	−3.847	−3.466	2.407	1.058	0.461	0.724
di-*n*-butyl ether	−3.984	−3.895	1.229	1.004	0.903	0.768
n-hexanol	−3.639	−3.628	1.025	1.034	6.293	0.820
n-octanol	−3.605	−3.996	0.406	1.003	10.74	0.826
cyclohexanol	−3.719	−4.328	0.246	1.159	25.06	0.968[b]
oleyl alcohol	−3.828	−4.376	0.283	1.071	39.09	0.85[c]

[a] $d_{aq} = 0.998$ g/cm^3.

[b] Value at 25°C.

[c] Value from the B.D.H. container of oleyl alcohol.

However, the apparatus and obtained data are very suitable for our goal, the search for relationships between transport parameters and physicochemical parameters, because only the relative values are needed for comparison.

Viscosities and relationships with transport parameters

Kinematic viscosities of the organic solvent saturated with water (ν_{org}) and of water saturated with the organic solvent (ν_{aq}) are measured with a 2% precision. The data for ν_{org} and ν_{aq} in Table 2 are the mean values of at least 4 determinations. The data for log k_{aq}, log k_{org} and β are taken from Eqns. 13–30 in combination with Eqns. 5–7; the data for the densities of the pure organic solvents at 20°C (d_{org}) are taken from Riddick and Bunger (1970); see Table 2. From the definition of β (Eqn. 7) and the assumption that diffusion will influence the values for k_{aq} and k_{org} to a large extent, a relationship between β and the quotient of ν_{org} and ν_{aq} can be expected. The experimentally obtained relationship is given in Eqn. 31.

$$\log\beta = -0.527\log\left(\frac{\nu_{org}}{\nu_{aq}}\right) + 0.207 \quad (n = 9;\ r = 0.962;\ s = 0.129) \tag{31}$$

As a first approximation for the dynamic viscosities of the organic phases (η_{org}) and the aqueous phase (η_{aq}), the kinematic viscosities in Table 2 are multiplied by the corresponding densities of the pure solvents. In this way Eqn. 32 is obtained.

$$\log\beta = -0.502\log\left(\frac{\nu_{org}\cdot d_{org}}{\nu_{aq}\cdot d_{aq}}\right) + 0.145 \quad (n = 9;\ r = 0.965;\ s = 0.122) \tag{32}$$

The statistics of Eqns. 31 and 32 are very much the same. Despite the acceptable statistics of the experimental relationships between $\log(\frac{\nu_{org}}{\nu_{aq}})$ and $\log(\frac{\nu_{org}\cdot d_{org}}{\nu_{aq}\cdot d_{aq}})$, respectively, and log β (Eqns. 31 and 32), the statistics for the experimental relationships between log ν_{org} and log ($\nu_{org}\cdot d_{org}$), respectively, and log k_{org} (Eqns. 33 and 34) are bad.

$$\log k_{org} = -0.384\log\nu_{org} - 3.685 \quad (n = 9;\ r = 0.845;\ s = 0.206) \tag{33}$$

$$\log k_{org} = -0.373\log(\nu_{org}\cdot d_{org}) - 3.731 \quad (n = 9;\ r = 0.848;\ s = 0.205) \tag{34}$$

Furthermore attention must be paid to the fact that log k_{aq} varies between −3.605 (*n*-octanol–water) and −4.070 (*n*-hexane–water) at almost a constant value for ν_{aq} (see Table 2). This implies a spread in k_{aq} of almost a factor 3, from $8.511\cdot10^{-5}\ s^{-1}$ to $2.483\cdot10^{-4}\ s^{-1}$ without any obvious reason.

In the stagnant diffusion layer theory of Van de Waterbeemd et al. it can be assumed that a structuring of the aqueous diffusion layer originates from the physicochemical properties of the adjacent organic layer, and conversely the aqueous layer influences the structuring of the organic diffusion layer. Using this theory, it

should be concluded from the data in Table 2 that polar solvents induce a different kind of structuring in the aqueous diffusion layer, with a higher value for k_{aq}, than apolar solvents do. Different kinds of structuring in the organic diffusion layers caused by the aqueous phase would account for the bad statistics of Eqns. 33 and 34. Considering viscosities, the aqueous phase induces a structuring in the organic diffusion layer with a relatively high value for k_{org} in polar solvents and a relatively low value for k_{org} in apolar solvents; see Table 2. Generalization gives: (i) water–polar solvent—the mutual structure-induction of both organic and aqueous diffusion layers causes relatively high values for both diffusion rate constants k_{aq} and k_{org} (considering viscosities). The mutual structure-induction results in a low resistance; and (ii) water–apolar solvent—the mutual structure-induction causes relatively low values for both k_{aq} and k_{org} and so results in relatively high resistances.
In (i) and (ii), k_{aq} and k_{org} are influenced in the same direction. This could account for the fact that the experimental relationships between $\log(\nu_{org}/\nu_{aq})$ and $\log(\nu_{org} \cdot d_{org}/\nu_{aq} \cdot d_{aq})$, respectively and $\log \beta$ (Eqns. 31 and 32) have acceptable statistics.

Conclusion

Under the experimental conditions used, the statistics of Eqns. 13–30 are good, so it can be concluded that the relationships between $\log k^{obs}$ and $\log P$ are bilinear, as was found experimentally before by Kubinyi and Van de Waterbeemd (Eqns. 3–6). Further investigation regarding the experiments producing relatively bad statistics (e.g. Eqns. 21, 25 and 26; transport experiments of the solutes $R = CO(CH_2)_4CH_3$ and $R = CO(CH_2)_5CH_3$ in *n*-hexanol–water) may reveal more of the fundamentals of the transport process.

In respect to the influence of the viscosities of the solvent phases on the transport parameters k_{aq}, k_{org} and β it can be concluded: (1) k_{aq} and k_{org} are not solely dependent on the viscosities of the bulk liquids, but apparently other factors play an important role also, because k_{aq} varies with a factor 3 at almost a constant value for ν_{aq} and because the statistics of Eqns. 33 and 34 are bad; (2) these unknown factors influence k_{aq} and k_{org} at least qualitatively in the same way. When considering viscosities, values for k_{aq} and k_{org} both are relatively high for systems polar organic solvent–water (see Table 2); and (3) the acceptable statistics for Eqns. 31 and 32 (relationship between viscosities and β, the quotient of k_{org} and k_{aq}) can be explained by (2), and still indicate diffusion to be an essential feature in the transport process.

More experimental results are needed to obtain a better understanding of the actual transport processes. It is important to realize that the aqueous phase is not pure water and the organic phase is not pure either. So the physicochemical properties of a certain phase can be quite different from those of the pure solvents (e.g. compare surface tension of pure water to surface tension of water saturated with *n*-octanol). These properties of the organic solvent–water systems have to be studied to explain the above mentioned findings.

Furthermore, it is valid that studies on the thermodynamics of distribution (Kinkel et al., 1981), on which we also are working in this moment, will also contribute significantly to a better understanding of the mechanism of transport.

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