

The influences of solvent properties on interfacial transfer kinetics in stirred two-phase systems of organic solvent–water *

F.H.N. de Haan and A.C.A. Jansen

Department of Pharmacochemistry, Subfaculty of Pharmacy, University of Leiden, 2300 RA Leiden (The Netherlands)

(Received June 25th, 1985)

(Modified version received November 13th, 1985)

(Accepted November 18th, 1985)

Key words: partition coefficient – interfacial transfer kinetics – convective diffusion – hydrodynamics – solvent properties – two-phase transfer cell

Summary

Interfacial transfer kinetics were determined for various solutes (mainly a homologous series of sulfonamides) in 16 two-phase systems of organic solvent–water. The transport experiments were performed in a two-phase transfer cell, an unbaffled vessel with an impeller rotating in the center. Starting from a model in which the interfacial transport is described as a convective diffusion process, the transport rate constants are corrected as far as possible for all physicochemical properties of the solvents which influence this process. It is concluded that additional influences of the type of organic solvent and of differences in the constitution of the aqueous layers on interfacial transfer kinetics are present. It is shown that these influences are qualitatively but not quantitatively the same for the diffusional resistances on the aqueous and organic side of the interface, respectively. Furthermore, it is found that the extent of these influences depends on the chemical class to which the organic solvent of the two-phase system of organic solvent–water belongs. It is proven that the origin of these influences is a hydrodynamic phenomenon. The results of the experiments suggest that viscous forces in the rotating interface cause a structuring of the interface (not accompanied by an energy barrier for transport across the interface) and in this way influence the diffusional resistances.

Introduction

For obtaining a better understanding on in vivo absorption processes (and so on Q.S.A.R.) research on transport processes across interfaces should be performed. This research principally has to be started in physicochemical model systems for determining which aspecific physicochemical processes govern this type of transport. In this

scope our group transport experiments were performed in two-phase systems of water and immiscible organic solvent in an unbaffled vessel with a double-bladed impeller rotating in the center.

In an earlier paper (De Haan et al., 1983) the validity of Eqns. 1 and 2 was shown for 9 systems of organic solvent–water investigated.

$$\log k_1^{\text{obs}} = \log P - \log \left(\frac{k_{\text{org}}}{k_{\text{aq}}} P + 1 \right) + \log k_{\text{org}} \quad (1)$$

$$\log k_2^{\text{obs}} = - \log \left(\frac{k_{\text{org}}}{k_{\text{aq}}} P + 1 \right) + \log k_{\text{org}} \quad (2)$$

* Transport in Q.S.A.R. X.

Correspondence: F.H.N. de Haan, Department of Pharmacochemistry, Subfaculty of Pharmacy, University of Leiden, P.O. Box 9502, 2300 RA Leiden, The Netherlands.

In Eqns. 1 and 2, k_1^{obs} and k_2^{obs} are overall (measured) transport rate constants for transport from the stirred aqueous bulk to the stirred organic bulk and vice versa. Furthermore, k_{aq} is the transport rate constant for transport from the stirred aqueous bulk to the interface and vice versa, while k_{org} is its analogue for the organic phase. In Eqns. 1 and 2 it is assumed also that k_{aq} and k_{org} are solute-independent parameters at least within a series of closely related compounds. The statistics obtained by application of Eqns. 1 and 2 to the transport data of these 9 systems showed the validity of the indicated assumptions (De Haan et al., 1983). Among other things it was shown in that paper that k_{aq} for *n*-octanol–water is almost three times higher than for *n*-hexane–water while the viscosities of both aqueous phases are equal. It was concluded that apparently some “unknown factors” influence the transport process to a large extent. In succeeding papers (De Haan and Jansen, 1983; De Haan and Jansen, 1984) it was shown that k_{aq} and k_{org} are diffusion rate constants of the laminar convective type and the validity of Eqns. 3 and 4 was shown experimentally.

$$k_{\text{aq}} = Y_{\text{aq}} \cdot \nu_{\text{aq}}^{-5/6} \cdot (\text{S.R.})^{1/2} \quad (3)$$

$$k_{\text{org}} = Y_{\text{org}} \cdot \nu_{\text{org}}^{-5/6} \cdot (\text{S.R.})^{1/2} \quad (4)$$

where ν_{aq} is the kinematic viscosity of the aqueous phase (water saturated with organic solvent at the experimental temperature), ν_{org} is its analogue for the organic phase, S.R. is the stirring rate and Y_{aq} and Y_{org} are constants for a given organic solvent–water system. Eqns. 3 and 4 were obtained from Eqn. 5 by substituting $D \sim \nu^{-1}$.

$$k_{\text{diff}} \sim D^{2/3} \cdot \nu^{-1/6} \quad (5)$$

where k_{diff} is the diffusion rate constant for convective diffusion under laminar flow conditions and D is the diffusion coefficient (De Haan and Jansen, 1983). In this present paper, experiments are described in various organic solvent–water systems with a large spread in physicochemical properties at a constant temperature and constant stirring rate. Eqns. 3 and 4 allow the influence of

viscosity on k_{aq} and k_{org} to be eliminated by using Eqns. 6 and 7.

$$k_{\text{aq}}^* = k_{\text{aq}} \cdot \nu_{\text{aq}}^{5/6} \quad (6)$$

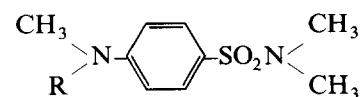
$$k_{\text{org}}^* = k_{\text{org}} \cdot \nu_{\text{org}}^{5/6} \quad (7)$$

These equations allow a more quantitative research on the influence of other physicochemical properties of the organic solvent–water system on transport rate.

Materials and Methods

Materials

The following solvents were used in the experiments: demineralized water, *n*-hexane (Baker grade), cyclohexane (Baker grade), Lytol (Witco), di-*n*-butyl ether (Baker grade), di-isopropyl ether (Baker Analyzed reagent), di-ethyl ether (Baker grade), *n*-decanol (Baker grade), *n*-octanol (Aldrich), *n*-hexanol (Fluka, Buchs S.G., pract.), *n*-butanol (Brockacef, chem. pure), cyclohexanol (U.C.B. tout pur), *n*-amyl acetate (Aldrich), *n*-butyl acetate (Baker grade) and propylene glycol (Brockacef Ph. Eur.). Before use cyclohexanol, *n*-octanol and *n*-decanol were washed with 1 N NaOH and 1 N HCl, respectively; di-ethyl ether, di-isopropyl ether and di-*n*-butyl ether were passed through a basic aluminium oxide column (removal of peroxides); *n*-hexanol was fractionally distilled (boiling range 155–156°C). Lytol is a hydrogenated petroleum fraction which was kindly supplied by Witco Chemicals. Before all experiments the aqueous and organic phases were mutually saturated at 20°C. Most solutes used in the transport experiments were derivatives of the following benzenesulfonamide:



Syntheses and physicochemical properties were described by Van de Waterbeemd et al. (1981). In some systems a few other compounds were used in order to obtain statistically sound values of k_{org} .

These compounds (sulfanilamide, nicotinamide, berberine hydrochloride, thiourea, cytidine and dimethylglyoxim) were all analytical grade. In Table 1 it is indicated which solute was used in each of the 16 solvent systems. The corresponding values of $\log P$ of the solutes are also given in Table 1.

Apparatus and methods

Transport rate constants and partition coefficients were determined in principal via the same method and using the same apparatus as described by Van de Waterbeemd et al. (1980) and which were also used in the experiments described in an earlier paper (De Haan et al., 1983). During experiments in the cyclohexanol–water system presented in the latter paper it appeared that a slight rise of temperature (due to the pump and the spectrophotometer) caused turbidity of the aqueous phase (phase separation). In order to overcome the practical problems of this phenomenon the mentioned methods were modified in the following ways.

(1) The tubing from the transport vessel to the pump was lengthened and partly cooled in ice (the temperature in both phases in the transport vessel remained $20.0 \pm 0.1^\circ\text{C}$). The contents of tubing plus flow-through cuvette amounted to $1.3 \times 10^{-5} \text{ m}^3$, while the total volume of the aqueous phase remained $11.0 \times 10^{-5} \text{ m}^3$; this did not influence the measured values of k_1^{obs} and k_2^{obs} .

(2) In transport experiments where the absorbances at equilibrium were needed for calculating k_1^{obs} and k_2^{obs} , in the present paper these absorbances were obtained from separate shake flask experiments. Furthermore, these absorbances and all absorbances needed for the determination of P were measured 5°C below the experimental equilibrium temperature.

Another modification is the use of an MPL E₁ range Metripump, which appeared to be more satisfactory for the described transport experiments. For standardization of the performed experiments these modified methods were used in all experiments presented in this paper.

It appeared that these modified methods produced better results. Linear regression analysis for

determining $(k_1^{\text{obs}} + k_2^{\text{obs}})$ produced correlation coefficients > 0.999 (often > 0.9999) in the transport experiments and the standard deviation of the mean of the simultaneous duplicate determination of $\log k_1^{\text{obs}}$ and $\log k_2^{\text{obs}}$ in two separate transport vessels decreased and was ≤ 0.015 for all experiments. Presented values of P were the mean of at least two determinations and the experimental deviation from the mean was $\leq 8\%$ for all presented values.

In this paper all transport experiments were performed in duplicate at 20.0°C and at $\text{S.R.} = 40 \text{ rpm}$ (0.67 s^{-1}). All P -values were determined at $20.0 \pm 0.1^\circ\text{C}$.

Kinematic viscosities were measured with a 2% precision using calibrated Ubbelohde viscosimeters and the presented data were the mean values of at least four determinations. Surface tensions of the aqueous phases (γ_{aq}), of the organic phases (γ_{org}) and interfacial tensions (γ_i) were determined using a Du Nouy tensiometer from Krüss (type K 8600-T). The presented values were the mean values of at least four determinations; the standard deviation of the presented mean values was $\leq 0.4 \times 10^{-3} \text{ N/m}$. The tension and viscosity determinations were performed at $20.0 \pm 0.1^\circ\text{C}$.

Results and Discussion

Transport experiments at 20.0°C and 40 rpm

Eqns. 1 and 2 were fitted to experimental data of $\log P$ and $\log k_1^{\text{obs}}$ and $\log k_2^{\text{obs}}$ as described by Van de Waterbeemd et al. (1981). The underlying computational method is a normal iterative procedure, starting with an estimate for β , with $(n - 2)$ degrees of freedom. The results are presented in Table 2. From Table 1 it can be seen which solutes were used in every individual two-phase system. It can be seen from Table 2 that the statistics of Eqns. 8–39 are very good, in this way confirming the validity of Eqns. 1 and 2 and the validity of the model on which these relationships are based. This implies that in none of the used two-phase systems a noticeable energy barrier is present at the interface for the actual transfer of solutes across this interface. Due to the fact that the two-phase systems under investigation are a very

TABLE 1

SOLUTES USED IN THE TRANSPORT EXPERIMENTS IN THE VARIOUS TWO-PHASE SYSTEMS AND THE MEASURED VALUES OF $\log P$

Solute ^a	Two-phase system and corresponding value of $\log P$							
	<i>n</i> -hexane–water	cyclohexane–water	Lytol–water	di-isopropyl ether–water	di-ethyl ether–water	<i>n</i> -decanol–water	<i>n</i> -octanol–water	<i>n</i> -hexanol–water
R = H	-0.980	-0.745	—	—	—	—	—	—
R = CHO	-1.821	-1.627	—	—	—	—	—	0.673
R = COCH ₃	-2.097	-1.943	-2.362	-0.936	-0.360	-0.009	0.230	0.567
R = COCH ₂ CH ₃	-1.380	-1.059	-1.496	-0.134	0.279	0.465	0.709	1.065
R = CO(CH ₂) ₂ CH ₃	-0.759	-0.511	-0.962	0.397	0.799	0.937	1.187	1.512
R = CO(CH ₂) ₃ CH ₃	-0.177	0.092	-0.425	0.942	1.326	1.459	1.631	1.991
R = CO(CH ₂) ₄ CH ₃	0.429	0.712	0.107	1.459	1.852	2.029	2.155	2.442
R = CO(CH ₂) ₅ CH ₃	0.963	1.374	0.646	—	—	—	—	2.896
R = CO(CH ₂) ₆ CH ₃	1.466	2.033	1.222	—	—	—	—	—
R = CO(CH ₂) ₂ CONH ₂	—	—	—	—	-2.030	-0.866	-0.560	-0.159
R = CO(CH ₂) ₂ SOCH ₃	—	—	—	—	—	—	—	-0.316
R = CO(CH ₂) ₂ OH	—	—	—	—	—	—	-0.261	—
R = CO(CH ₂) ₂ CN	—	—	—	—	—	—	-0.017	—
sulfanilamide	—	—	—	-1.682	-0.799	-0.898	—	—
nicotinamide	—	—	—	—	—	—	—	—
berberine HCl	—	—	—	—	—	—	—	—
dimethylglyoxim	—	—	—	—	—	—	—	—
thio urea	—	—	—	—	—	—	—	—
cytidine	—	—	—	—	—	—	—	—

^a R is chain in the benzenesulfonamide mentioned in "Materials". ^b Data are taken from Van de Waterbeemd et al. (1981).

— solute not used in transport experiments in indicated two-phase system.

heterogeneous group (large spread in physicochemical properties), it seems rational to generalize this finding and to conclude that this finding is generally valid for transport processes across interfaces both in vitro and in vivo.

Quantification of the "unknown factors"

From Eqns. 8–35 k_{org} and k_{aq} were calculated by using Eqns. 1 and 2; the values of k_{org}^* and k_{aq}^* were calculated by using Eqns. 6 and 7. These values are presented in Table 3. (Like k_1^{obs} and k_2^{obs} , k_{aq} and k_{org} are in s^{-1} .) The required values of ν_{aq} and ν_{org} were taken from Table 4 and are in cSt (1 cSt = $10^{-6} m^2 s^{-1}$). From the data in Table 3 it can be seen that the $\log k_{aq}^*$ -values for the various systems show a large spread.

So the differences in k_{aq} cannot be ascribed solely to differences in ν_{aq} -values. The system *n*-hexane–water has the lowest value of $\log k_{aq}^*$. This

system may serve as a reference system in order to obtain a parameter (Rel_{aq}) that allows a quick insight in the extent of the influence of the "unknown factors" on k_{aq}^* . The parameter Rel_{aq} is defined by Eqn. 40.

$$Rel_{aq} = \frac{(k_{aq}^*)_{\text{organic solvent-water}}}{(k_{aq}^*)_{n\text{-hexane-water}}} \quad (40)$$

Rel_{aq} -values are presented in Table 3.

From the data in Table 3 it can be seen that also the $\log k_{org}^*$ -values for the various systems show a large spread. However, for comparing these values the situation is more complicated. It has to be realized that Eqns. 6 and 7 are based on Eqn. 5. This might be an oversimplification when, as opposed to the comparison of k_{aq}^* -values resulting from almost identical aqueous phases, values of

<i>n</i> -butanol–water	cyclohexanol–water	<i>n</i> -amyl acetate–water	<i>n</i> -butyl acetate–water	<i>n</i> -hexane 50% v/v + <i>n</i> -octanol 50% v/v–water	cyclohexane–water 90% + propylene glycol 10% v/v	cyclohexane–water 80% v/v + propylene glycol 20% v/v
–	–	–	–	–	–0.863	–1.016
–	–	–	–	–	–1.640	–1.760
0.740	0.782	0.368	0.627	–0.354	–1.946	–2.041
1.059	1.226	0.942	1.232	0.172	–1.134	–1.243
1.427	–	1.429	1.727	0.766	–0.575	–0.690
1.842	–	1.825	2.236	1.334	0.021	–0.110
2.304	2.200	2.392	2.755	1.963	0.627	0.482
–	2.529	–	–	–	1.253	1.028
–	–	–	–	–	1.778	1.660
0.288	0.348	–1.282	–0.789	–	–	–
–	0.109	–	–	–	–	–
–	–	–	–	–	–	–
–	–	–	–	–	–	–
–	–	–0.360	–0.086	–1.773	–	–
0.143	–	–	–	–	–	–
–0.073	–0.332	–	–	–	–	–
1.014	–	–	–	–	–	–
–0.278	–	–	–	–	–	–
–0.979	–	–	–	–	–	–

k_{org}^* originating from different solvents are compared. Whereas the Stokes-Einstein relationship, predicting D , has been shown to break down for solutes with molecular weights significantly less than 1000, Wilke and Chang developed a semi-empirical relationship predicting D for smaller solutes in dilute solution (Byron et al., 1981). Experimental determinations of D for various low molecular weight solutes in various solvents fall within 10% of the values predicted by this relationship in which it is assumed that

$$D \sim (M \cdot \Psi)^{1/2} \cdot (\nu \cdot d)^{-1} \quad (41)$$

where d is the density of the solvent, M is its molecular weight and Ψ is an association parameter, taking into account the associating tendencies of the solvent molecules, which has the value 1.0 for unassociated liquids and 2.6, 1.9 and 1.5 for

water, methanol and ethanol, respectively (Chang and Wilke, 1955). The value of Ψ for the organic solvents in Table 3 is 1.0. For a reliable approach it is necessary to standardize the k_{org}^* -values according to Eqns. 5, 7 and 40 in order to eliminate as far as possible the influences of the organic solvent on D (and so on k_{org}^*). This can be achieved by multiplying k_{org}^* by $[(M \cdot \Psi)^{1/2} \cdot d^{-1}]^{-2/3}$. By again using *n*-hexane–water as a reference system the following expression is obtained:

$$\text{Rel}_{\text{org}} = \frac{[k_{\text{org}}^* \cdot (M \cdot \Psi)^{-1/3} \cdot d^{2/3}]}{[k_{\text{org}}^* \cdot (M \cdot \Psi)^{-1/3} \cdot d^{2/3}]}_{\text{n-hexane-water}} \quad (42)$$

where Rel_{org} indicates, as well as possible, how k_{org}^* of the corresponding system organic

TABLE 2

RELATIONSHIPS BETWEEN $\log k^{\text{obs}}$ AND $\log P$ IN VARIOUS TWO-PHASE SYSTEMS AT 20.0°C AND 40 rpm

Two-phase system	Relationship	n	r	F	s	Eqn.
<i>n</i> -hexane–water	$\log k_1^{\text{obs}} = \log P - \log(3.740 P + 1) - 3.509$	9	0.999	3869	0.026	(8)
	$\log k_2^{\text{obs}} = -\log(3.740 P + 1) - 3.509$	9	0.999	6578	0.026	(9)
<i>cyclohexane</i> –water	$\log k_1^{\text{obs}} = \log P - \log(1.185 P + 1) - 3.964$	9	0.999	2633	0.038	(10)
	$\log k_2^{\text{obs}} = -\log(1.185 P + 1) - 3.964$	9	0.999	3215	0.038	(11)
Lytol–water	$\log k_1^{\text{obs}} = \log P - \log(0.294 P + 1) - 4.587$	7	1.000	9385	0.026	(12)
	$\log k_2^{\text{obs}} = -\log(0.294 P + 1) - 4.587$	7	0.997	802	0.025	(13)
di- <i>n</i> -butyl ether–water ^a	$\log k_1^{\text{obs}} = \log P - \log(1.232 P + 1) - 3.894$	27	0.997	4309	0.051	(14)
	$\log k_2^{\text{obs}} = -\log(1.225 P + 1) - 3.896$	27	0.998	5608	0.050	(15)
di-isopropyl ether–water	$\log k_1^{\text{obs}} = \log P - \log(2.558 P + 1) - 3.486$	6	1.000	33973	0.006	(16)
	$\log k_2^{\text{obs}} = -\log(2.555 P + 1) - 3.486$	6	1.000	68887	0.006	(17)
di-ethyl ether–water	$\log k_1^{\text{obs}} = \log P - \log(3.778 P + 1) - 3.340$	7	0.999	1738	0.031	(18)
	$\log k_2^{\text{obs}} = -\log(3.775 P + 1) - 3.340$	7	0.999	5129	0.031	(19)
<i>n</i> -decanol–water	$\log k_1^{\text{obs}} = \log P - \log(0.277 P + 1) - 4.145$	7	0.996	578	0.066	(20)
	$\log k_2^{\text{obs}} = -\log(0.276 P + 1) - 4.146$	7	0.994	445	0.066	(21)
<i>n</i> -octanol–water	$\log k_1^{\text{obs}} = \log P - \log(0.340 P + 1) - 4.060$	8	0.998	1862	0.025	(22)
	$\log k_2^{\text{obs}} = -\log(0.340 P + 1) - 4.060$	8	0.999	4400	0.025	(23)
<i>n</i> -hexanol–water	$\log k_1^{\text{obs}} = \log P - \log(0.450 P + 1) - 3.887$	9	0.995	659	0.032	(24)
	$\log k_2^{\text{obs}} = -\log(0.450 P + 1) - 3.889$	9	0.999	5207	0.032	(25)
<i>n</i> -butanol–water	$\log k_1^{\text{obs}} = \log P - \log(0.801 P + 1) - 3.668$	11	0.992	558	0.046	(26)
	$\log k_2^{\text{obs}} = -\log(0.800 P + 1) - 3.669$	11	0.998	2393	0.046	(27)
cyclohexanol–water	$\log k_1^{\text{obs}} = \log P - \log(0.246 P + 1) - 4.328$	7	0.996	696	0.033	(28)
	$\log k_2^{\text{obs}} = -\log(0.247 P + 1) - 4.328$	7	0.999	2959	0.034	(29)
<i>n</i> -amyl acetate–water	$\log k_1^{\text{obs}} = \log P - \log(1.015 P + 1) - 4.009$	7	0.994	419	0.059	(30)
	$\log k_2^{\text{obs}} = -\log(1.017 P + 1) - 4.009$	7	0.998	1395	0.059	(31)
<i>n</i> -butyl acetate–water	$\log k_1^{\text{obs}} = \log P - \log(1.102 P + 1) - 3.920$	7	0.997	989	0.024	(32)
	$\log k_2^{\text{obs}} = -\log(1.105 P + 1) - 3.918$	7	1.000	11325	0.024	(33)
<i>n</i> -hexane 50% v/v	$\log k_1^{\text{obs}} = \log P - \log(1.149 P + 1) - 3.725$	6	0.999	1556	0.038	(34)
	$\log k_2^{\text{obs}} = -\log(1.146 P + 1) - 3.725$	6	0.999	2076	0.038	(35)
cyclohexane–water 90% v/v	$\log k_1^{\text{obs}} = \log P - \log(2.038 P + 1) - 3.904$	9	0.998	1587	0.044	(36)
	$\log k_2^{\text{obs}} = -\log(2.041 P + 1) - 3.904$	9	0.999	2551	0.044	(37)
propylene glycol 10% v/v	$\log k_1^{\text{obs}} = \log P - \log(3.405 P + 1) - 3.860$	9	0.998	2180	0.035	(38)
	$\log k_2^{\text{obs}} = -\log(3.494 P + 1) - 3.848$	9	0.999	2959	0.042	(39)

^a Taken from Van de Waterbeemd et al. (1981).

solvent–water is influenced by the “unknown factors” relative to k_{org}^* of the reference system *n*-hexane–water. Rel_{org} -values are presented in

Table 3. The required values of M and d were taken from Table 4. Because Lytol is a mixture, Rel_{org} for Lytol–water could not be calculated due

TABLE 3

VALUES OF $\log k_{aq}$, $\log k_{org}$, $\log k_{aq}^*$, $\log k_{org}^*$, Rel_{aq} , Rel_{org} AND Q_{rel} FOR VARIOUS TWO-PHASE SYSTEMS

	$\log k_{aq}$	$\log k_{org}$	$\log k_{aq}^*$	$\log k_{org}^*$	Rel_{aq}	Rel_{org}	Q_{rel}	chemical group of organic solvents
<i>n</i> -hexane–water	–4.082	–3.509	–4.070	–3.780	1.00	1.00	1.00	
cyclohexane–water	–4.037	–3.964	–4.029	–3.876	1.10	0.90	0.82	paraffins
Lytol–water	–4.055	–4.587	–4.043	–3.899	1.06			
di- <i>n</i> -butyl ether–water	–3.984	–3.895	–3.982	–3.932	1.21	0.68	0.56	
di-isopropyl ether–water	–3.893	–3.486	–3.873	–3.791	1.57	1.02	0.65	ethers
di-ethyl ether–water	–3.917	–3.340	–3.833	–3.711	1.73	1.30	0.75	
<i>n</i> -decanol–water	–3.586	–4.145	–3.582	–3.130	3.08	4.26	1.38	
<i>n</i> -octanol–water	–3.591	–4.060	–3.590	–3.201	3.02	3.85	1.27	
<i>n</i> -hexanol–water	–3.541	–3.888	–3.529	–3.222	3.48	3.95	1.14	alcohols
<i>n</i> -butanol–water	–3.573	–3.669	–3.441	–3.167	4.26	4.95	1.16	
cyclohexanol–water	–3.719	–4.328	–3.666	–3.162	2.54	5.08	2.00	
<i>n</i> -amyl acetate–water	–4.016	–4.009	–4.004	–3.987	1.16	0.65	0.56	
<i>n</i> -butyl acetate–water	–3.962	–3.919	–3.052	–3.986	1.31	0.68	0.52	esters

For the definitions of k_{aq}^* , k_{org}^* , Rel_{aq} , Rel_{org} and Q_{rel} , see Eqns. 6, 7, 40, 42 and 43, respectively.

to the absence of a reliable mean value for M . For the experiments presented in this paper, Rel_{aq} is a more exact parameter for quantifying the influences of the "unknown factors" on k_{aq}^* than

Rel_{org} is for quantifying these influences on k_{org}^* for a variety of reasons.

(1) The experimental values of k_{aq} are determined mainly by transport experiments with

TABLE 4

RELEVANT PHYSICOCHEMICAL PROPERTIES AT 20.0°C OF THE VARIOUS TWO-PHASE SYSTEMS USED IN THE EXPERIMENTS

Solvent system	$(\nu \text{ in } 10^{-6} \text{ m}^2 \cdot \text{s}^{-1})$			$(10^{-3} \text{ N} \cdot \text{m}^{-1})$		$M^{\text{a},\text{b}}$	$(10^{-3} \text{ kg} \cdot \text{m}^{-3})$	Mutual solubility in % weight	
	$\log \nu_{org}$	$\log \nu_{aq}$	γ_{org}	γ_{aq}	γ_i			water in solvent ^a	solvent in water ^a
<i>n</i> -hexane–water	–0.325	0.014	19.5	72.9	47.5	86.2	0.659	0.0111	0.00095 ^c
cyclohexane–water	0.106	0.010	26.3	73.0	45.8	84.2	0.779	0.010	0.0055 ^c
Lytol–water	0.826	0.014	24.3	73.0	47.3		0.805–0.825 ^e		
di- <i>n</i> -butyl ether–water	–0.044	0.002	24.2	70.6	26.4	130.2	0.768	0.19	0.03
di-isopropyl ether–water	–0.366	0.024	18.8	56.0	17.2	102.2	0.724	1.2	3.88
di-ethyl ether–water	–0.445	0.101	18.5	46.9	10.4	74.1	0.713	1.468 ^c	6.04 ^c
<i>n</i> -decanol–water	1.218	0.005	29.6	34.0	8.5	158.3 ^f	0.829 ^f	3 ^f	0.02 ^f
<i>n</i> -octanol–water	1.031	0.001	26.5	28.1	7.6	130.2	0.826	3.87 ^{c,g}	0.0538 ^{c,g}
<i>n</i> -hexanol–water	0.799	0.015	26.9	29.6	4.3	102.2	0.820	7.42	0.706
<i>n</i> -butanol–water	0.603	0.158	25.7	27.1	1.2	74.1	0.810	20.5 ^c	7.45 ^c
cyclohexanol–water	1.399	0.064	34.9	33.5	1.5	100.1	0.968 ^c	11.78	3.75 ^h
<i>n</i> -amyl acetate–water	0.027	0.014	25.6	46.0	15.0	130.2	0.875	1.15	0.17
<i>n</i> -butyl acetate–water	–0.081	0.012	25.1	41.9	13.1	116.2	0.876 ^c	1.86	0.43

^a Taken from Riddick and Bunger (1970). ^b Properties of the pure organic solvent. ^c At 25.0°C. ^e Taken from brochure from Witco Chemicals. ^f Taken from Marsden (1963). ^g Taken from Smith et al. (1975). ^h At 24.6°C.

For water $M = 18.0$ and $d = 0.998 \times 10^{-3} \text{ kg} \cdot \text{m}^{-3}$ (Riddick and Bunger, 1970).

solutes having high P-values, while the corresponding values of k_{org} are determined mainly by experiments with solutes having low P-values. From the data in Table 1 it is evident that generally more data points are available of solutes with relatively high P-values. Furthermore, it can be seen from Table 1 that the solutes with high P-values (determining k_{aq}) are all from a homologous series of sulfonamides, while the solutes with low P-values (determining k_{org}) are more heterogeneous.

(2) Eqn. 41 is based mainly on continuum mechanics (Stokes' law) in which the solvent is characterized by its viscosity and the solute by its radius. However, according to Evans et al. (1981) a second very different theoretical approach exists for understanding binary diffusion in the fluid state. This approach is based on statistical mechanics in which both solute and solvent are characterized in terms of molecular interactions. Because of the fact that no applicable relationships are presented, no correction of k_{org}^* based on this model could be performed but this approach stresses the fact that care has to be taken in comparing Rel_{org} -values of divergent solvents.

Relevant physicochemical properties of the two-phase systems and possible relationships with Rel_{aq} and Rel_{org}

In the paragraph "Transport experiments at 20.0°C and 40 rpm" it was shown that no noticeable energy barrier is present at the interface for the actual transfer of solutes across this interface. Hence the "unknown factors", indicated in the section "Introduction" and responsible for the spread in the values of Rel_{aq} and Rel_{org} in Table 3, must be ascribed to a possible influence of the mutual solubility of the aqueous and organic phases and/or to some hydrodynamic phenomenon. Both items will be discussed in this paragraph.

Mutual solubility data are presented in Table 4. These data indicate the constitution of the aqueous and organic phases of the various two-phase systems. It should be realized that water in the organic phase is in equilibrium with the aqueous phase and that water molecules transfer across the interface all the time. The same is valid for organic

solvent molecules in the aqueous phase. It is not unlikely that these phenomena influence mass transport across the interface. From Tables 3 and 4 it can be seen that for the two-phase systems of an alcohol and water Rel_{aq} and Rel_{org} and the mutual solubility data both have the highest values, suggesting some relationship. However, in general it is evident that no relationships exist between mutual solubility and Rel_{aq} or Rel_{org} . This can be seen, for instance, from the fact that mutual solubility data for cyclohexanol-water are in between those for *n*-butanol-water and *n*-hexanol-water, while Rel_{aq} and Rel_{org} for cyclohexanol-water are lower and higher, respectively, than those for *n*-butanol-water and *n*-hexanol-water. Furthermore it can be seen that Rel_{aq} and Rel_{org} for *n*-hexanol-water and *n*-decanol-water do not differ much while the mutual solubility data for *n*-hexanol-water are much higher than for *n*-decanol-water. From the lack of existence of relationships between mutual solubility and Rel_{aq} or Rel_{org} it must be concluded that the mutual solubility of organic and aqueous phases is not responsible for the spread in Rel_{aq} and Rel_{org} -values of the various two-phase systems. Hence some hydrodynamic phenomenon must cause the spread in Rel_{aq} - and Rel_{org} -values. In this scope it has to be realized that the aqueous and organic phases are stirred and the most likely explanation seems to be the formation of capillary waves or gravity waves caused by fluid flow along the interface. According to Lamb (1952), Davies and Rideal (1961) and Levich (1962), relevant parameters in the formation of capillary and gravity waves are surface tension and density. When these types of waves are responsible for the "unknown factors", the data in Tables 3 and 4 should reveal relationships between Rel_{aq} and Rel_{org} , respectively (Table 3), and γ_{aq} , γ_{org} , γ_i or d (Table 4).

From these data it can be recognized clearly that no relationships exist between Rel_{org} and γ_{aq} , γ_{org} , γ_i or d . Furthermore, it can be easily seen that no relationships exist between Rel_{aq} and γ_{org} or d . At the utmost it can be recognized that it qualitatively seems that Rel_{aq} increases with decreasing γ_{aq} and γ_i . For checking the possible existence of such relationships, experiments were

performed in more complex two-phase systems: *n*-hexane 50% v/v + *n*-octanol 50% v/v-water, cyclohexane-water 90% v/v + propylene glycol 10% v/v and cyclohexane-water 80% v/v + propylene glycol 20% v/v. The results of these experiments and relevant parameters are presented in Tables 2 and 5. For the system *n*-hexane 50% v/v + *n*-octanol 50% v/v-water it can be seen from the data in Tables 4 and 5 that γ_{aq} and γ_i for this complex system are very close to those for *n*-octanol-water and differ extremely from those for *n*-hexane-water. From the presented value of $\log k_{aq}^*$ in Table 5 it can be calculated that Rel_{aq} for the system *n*-hexane 50% v/v + *n*-octanol 50% v/v-water amounts to 1.96. This value is not close to that for *n*-octanol-water. So these data contradict the existence of a relationship between Rel_{aq} and γ_{aq} or γ_i . For this complex system it is noteworthy that the value of $\log k_{org}^*$ is exactly in between those for *n*-octanol-water and *n*-hexane-water also. For the systems with propylene glycol in the aqueous phase the most rational approach is to use cyclohexane-water as a reference system. The results of the experiments and relevant parameters are presented in Table 5. From Table 1 it can be seen that in both systems with propylene glycol in the aqueous phase k_{aq} and k_{org} were determined by experiments with the same solutes as was the case for cyclohexane-water. So in this case the indicated problems for comparing Rel_{org} -values (see paragraph "Quantifi-

cation of the unknown factors") are absent and so the k_{org}^* -values of the systems with cyclohexane as organic phase can be compared very well. In this case care has to be taken in comparing k_{aq}^* -values, since D in water and in water-propylene glycol mixtures may be influenced by other factors than just ν_{aq} (see Eqn. 41). From Table 5 it can be seen that k_{aq}^* decreases with increasing amounts of propylene glycol in the aqueous phase, while γ_i and γ_{aq} also decrease with increasing amounts of propylene glycol in the aqueous phase. So also these data contradict the existence of a relationship in which Rel_{aq} increases with decreasing γ_{aq} or γ_i . The decrease of k_{aq}^* with increasing amounts of propylene glycol in the aqueous phase probably has to be ascribed to a decrease of Ψ for the aqueous phase with increasing amounts of propylene glycol in this phase (see Eqn. 41). Furthermore, from Table 5 it can be seen that k_{org}^* increases slightly with increasing amounts of propylene glycol in the aqueous phase: k_{org}^* for cyclohexane-water 80% v/v + propylene glycol 20% v/v is 1.29 times that for cyclohexane-water. So this factor must be ascribed to the presence of propylene glycol, which is an alcohol. It can merely be recognized that the Rel_{aq} - and Rel_{org} -values in Table 3 are absolutely the highest for systems alcohol-water and it seems that in general the presence of alcohol causes Rel_{aq} - and Rel_{org} -values to increase.

From the experiments in the more complex

TABLE 5

VALUES OF $\log k_{aq}$, $\log k_{org}$, $\log k_{aq}^*$, $\log k_{org}^*$ AND RELEVANT PHYSICOCHEMICAL PROPERTIES AT 20.0°C OF THREE COMPLEX TWO-PHASE SYSTEMS

Two-phase system	$\log k_{aq}$ ^a	$\log k_{org}$ ^a	$\log \nu_{aq}$ ^b	$\log \nu_{org}$ ^b	$\log k_{aq}^*$	$\log k_{org}^*$	γ_{aq} ^c	γ_{org} ^c	γ_i ^c
<i>n</i> -hexane 50% v/v	-3.785	-3.725	0.006	0.255	-3.778	-3.512	37.4	21.7	11.5
<i>n</i> -octanol 50% v/v-water									
cyclohexane-water 90% v/v	-4.210	-3.904	0.169	0.107	-4.070	-3.816	61.8	26.1	34.1
propylene glycol 10% v/v									
cyclohexane-water 80% v/v	-4.392	-3.854	0.338	0.106	-4.110	-3.766	56.3	26.1	28.0
propylene glycol 20% v/v									

^a In s^{-1} . ^b ν in $10^{-6} \text{ m}^2 \cdot \text{s}^{-1}$. ^c In $10^{-3} \text{ N} \cdot \text{m}^{-1}$.

For propylene glycol $M = 76.1$ and $d = 1.036 \times 10^{-3} \text{ kg} \cdot \text{m}^{-3}$ (Riddick and Bunger, 1970).

two-phase systems it must be concluded that no relationships between Rel_{aq} and γ_{aq} or γ_i exist.

Transport experiments at moderate agitation conditions

At this stage it seemed rational to check whether the observed differences in Rel_{aq} and Rel_{org} originate from some hydrodynamic phenomenon or from some phenomenon overlooked so far. The already shown validity of Eqns. 3 and 4 at various stirring rates (De Haan and Jansen, 1984) indicates Rel_{aq} and Rel_{org} not to be influenced by stirring rate under the applied stirring conditions. However, as no energy barrier at the interface can be observed, it seems logical that k_{aq} -values for various two-phase organic solvent-water systems with identical ν_{aq} -values would be identical for the situation that no agitation is present (so no influence of hydrodynamics), since in that case k_{aq} is determined purely by molecular diffusion in the aqueous phase. So it was decided to perform transport experiments at moderate agitation conditions in two-phase systems with identical ν_{aq} -values and showing a large spread in k_{aq} -values.

In this context experiments were performed using solutes with high P-values in *n*-octanol-water and in cyclohexane-water at two different moderate agitation conditions. In these experiments the impeller was removed and the only agitation was caused by the influx in the transport vessel of the fluid that was circulated by the pump. The two pump rates used were $2.50 \times 10^{-7} \text{ m}^3 \cdot \text{s}^{-1}$ and $1.25 \times 10^{-7} \text{ m}^3 \cdot \text{s}^{-1}$, respectively. The results of these experiments are presented in Table 6.

Under the described circumstances (solute with

high P-values), k_1^{obs} approximates k_{aq} . It is evident from Table 6 that at a flow rate = $2.50 \times 10^{-7} \text{ m}^3 \cdot \text{s}^{-1}$ $\log k_{aq}$ -values for *n*-octanol-water and cyclohexane-water are about -4.44 and -4.15, respectively. So under these conditions k_{aq} for *n*-octanol-water is 1.9 times k_{aq} for cyclohexane-water, while from the data in Table 4 it can be calculated that at S.R. = 40 rpm this factor is 2.8. In the same way it can be calculated that at flow = $1.25 \times 10^{-7} \text{ m}^3 \cdot \text{s}^{-1}$ k_{aq} for *n*-octanol-water is only about 1.2 times that for cyclohexane-water. This is already close to 1.0 (k_{aq} being identical for both systems), which is expected in the case of no agitation at all.

From these findings it is clear that it is indeed some hydrodynamic phenomenon that is responsible for the "unknown factors". It is tempting to conclude that some agitation is needed to cause differences in the $\log k_{aq}$ -values for the various systems (no agitation results in no differences) and that already moderate agitation conditions suffice to cause differences in $\log k_{aq}$ which remain constant at least up to agitation conditions caused by S.R. = 40 rpm.

Are Rel_{aq} and Rel_{org} influenced quantitatively in the same way by the "unknown factors"?

A hydrodynamic phenomenon can manifest itself in two ways: enlargement of the interfacial area and/or the development of some turbulences. Both enlargement of the interfacial area and the development of turbulences cause an increase of interfacial transfer rate. When the hydrodynamic phenomenon would manifest itself solely by an increase of the interfacial area, Rel_{aq} and Rel_{org}

TABLE 6

RESULTS OF TRANSPORT EXPERIMENTS AT MODERATE AGITATION CONDITIONS IN *n*-OCTANOL-WATER AND CYCLOHEXANE-WATER

Solute ^a Two-phase system	$R \approx CO(CH_2)_4CH_3$		$R \approx CO(CH_2)_5CH_3$	
	cyclohexane- water	<i>n</i> -octanol- water	cyclohexane- water	<i>n</i> -octanol- water
P	5.15	143	23.7	409
$\log k_1^{obs}$ at flow = $2.50 \times 10^{-7} \text{ m}^3 \cdot \text{s}^{-1}$	-4.435	-4.149	-4.425	-4.155
$\log k_1^{obs}$ at flow = $1.25 \times 10^{-7} \text{ m}^3 \cdot \text{s}^{-1}$	-4.652	-4.580	-4.631	-4.550

^a R is chain in the benzenesulfonamide mentioned in the paragraph "Materials".

would be influenced quantitatively in the same way by the "unknown factors", since both k_{aq} and k_{org} are proportional to the magnitude of the interfacial area. The quotient of Rel_{org} and Rel_{aq} (defined in Eqn. 43 as Q_{rel}), should equal 1.00 when indeed k_{aq} and k_{org} are influenced quantitatively in the same way.

$$Q_{rel} = \frac{Rel_{org}}{Rel_{aq}} \quad (43)$$

Q_{rel} -values for the various systems are shown in Table 3. It can be seen that the Q_{rel} -values deviate significantly from 1.00. For the systems *n*-alcohol-water Q_{rel} has an average value of 1.24 while this factor for the systems ester-water is 0.54. So there is a difference of a factor 2.30 between these groups of two-phase systems.

From these findings it must be concluded that k_{aq} and k_{org} are not influenced quantitatively in the same way by the "unknown factors" and hence that these "unknown factors" are not solely due to an enlargement of the interfacial area. So, though a contribution of an enlargement of the interfacial area cannot be excluded, another hydrodynamic factor must be involved.

Closer examination of Rel_{aq} - and Rel_{org} -values

From a closer examination of the Rel_{aq} - and Rel_{org} -values presented in Table 3 two tendencies can be recognized.

(1) Both Rel_{aq} - and Rel_{org} -values can be arranged to the chemical groups of the organic solvents. For the Rel_{aq} -values the sequence is paraffins < esters < ethers < alcohols, while for the Rel_{org} -values the sequence is esters < paraffins ~ ethers < alcohols. These arrangements according to the chemical groups of the organic solvents of the two-phase systems suggest that the "unknown factors" are caused by some structuring of the interfaces and that the type of structuring depends on the chemical group to which the concerning organic solvent belongs. In the section "Transport experiments at 20.0°C and 40 rpm" it was concluded that no energy barrier was present, so this structuring is not accompanied by an energy barrier at the interface for transfer of solutes across this interface.

(2) For the parameter Rel_{aq} the tendency can be recognized that Rel_{aq} increases with decreasing chain length of the organic solvent: *n*-decanol ~ *n*-octanol < *n*-hexanol < *n*-butanol; di-*n*-butyl ether < di-isopropyl ether < di-ethyl ether and *n*-amyl acetate < *n*-butyl acetate. This tendency can be spotted most clearly for the systems ether-water. For the less exact parameter Rel_{org} this tendency is not noticeable in all cases; however, also for the Rel_{org} -values this tendency is very prominent for the systems ether-water. This tendency supports the above hypothesis that the "unknown factors" are caused by some kind of structuring of the interface.

In this context it is also understandable that Rel_{aq} for cyclohexanol-water differs from that expected from the Rel_{aq} -values of the *n*-alcohol-water systems. The structuring at the interface will be influenced by the bulkiness of the cyclohexanol molecule.

From the fact that Rel_{aq} - and Rel_{org} -values can be arranged according to the chemical groups of the organic solvents and from the tendencies within a distinct group of two-phase systems, predictions can be made for the Rel_{aq} - and Rel_{org} -values of two-phase systems that have not been used yet for experiments on interfacial transfer kinetics. Then by using Eqns. 6, 7, 40 and 42 also k_{aq} and k_{org} of these systems can be predicted. In this scope the following tendencies should be considered.

- (1) For the systems paraffin-water, Rel_{aq} and Rel_{org} are almost constant. The bulkiness of the cyclohexane and the longer chains of Lytol do not significantly influence the values of $\log k_{aq}^*$ and $\log k_{org}^*$ obtained for *n*-hexane-water.
- (2) For the systems ether-water it can be clearly recognized that both Rel_{aq} and Rel_{org} decrease with increasing chain length of the ether.
- (3) For the systems alcohol-water Rel_{aq} decreases slightly with increasing chain length of the alcohol. Furthermore, Rel_{aq} is decreased by the bulkiness of cyclohexanol. For Rel_{org} no clear tendencies can be recognized.
- (4) For the systems ester-water it seems that Rel_{aq} decreases slightly with increasing chain

length of the ester and that Rel_{org} is almost constant.

These findings are not solely useful for the prediction of interfacial transfer kinetics in our experimental set-up, but can be used also in a much broader field. Therefore, it has to be realized that in the section "Transport experiments at moderate agitation conditions" it is indicated that these findings are valid for a large range of agitation conditions. So these findings are important also with respect to e.g. rate of extraction on industrial scale in relation to energy consumption associated with stirring or shaking.

By combining the hypothesis presented here, namely that the "unknown factors" are caused by some kind of structuring of the interface, with the findings from the paragraph "Transport experiments at moderate agitation conditions", the following very likely explanation can be formulated: already slight shearing forces at the interface cause the structures of the interfaces to be changed in such a way that e.g. k_{aq} for an *n*-alcohol–water system increases relative to k_{aq} for a system paraffin–water. At larger shearing forces the modified structures of the interfaces do not change anymore with increasing agitation, since the differences in $\log k_{aq}$ remain constant with increasing S.R.

Striking data in literature

Byron et al. (1981) and Byron and Rathbone (1984) performed transport experiments in an experimental set-up that is more or less similar to ours, e.g. an impeller rotating in the center with upper and lower blade rotating in the same direction. In the described transport experiments (like in our experiments) in fact the term $(k_1^{obs} + k_2^{obs})$ is determined. Byron and Rathbone (1984) claim that the interfacial kinetics of a series of closely related compounds in a distinct two-phase system can be predicted from the results of transport experiments of only one compound from that series in the distinct two-phase system. In order to enable this prediction the P-values of the compounds and ν , Ψ , M and d of the organic solvent and water should be known. In the required calculations it is assumed implicitly that Eqn. 44 is valid.

$$\frac{k_{aq}}{k_{org}} = \left(\frac{\Psi_{aq} \cdot M_{aq}}{\Psi_{org} \cdot M_{org}} \right)^{1/3} \cdot \left(\frac{d_{aq}}{d_{org}} \right)^{-2/3} \cdot \left(\frac{\nu_{aq}}{\nu_{org}} \right)^{-5/6} \quad (44)$$

In fact Eqn. 44 is a combination of Eqns. 5 and 41. However, Eqn. 44 can only be valid when Rel_{aq} and Rel_{org} are identical. In the experiments presented in their paper for proving the validity of their theories, Byron and Rathbone (1984) used three different two-phase systems. However, for every individual two-phase system they used only solutes either with low P-values (cyclohexane–water) or high P-values (chloroform–water and *n*-octanol–water). In that case in fact only k_{aq} or k_{org} is measured and the other calculated, so differences between Rel_{aq} and Rel_{org} could not be observed. However, from our data (see Table 3) it is evident that Rel_{aq} and Rel_{org} are not identical ($Q_{rel} \neq 1.00$), so it has to be concluded that the theory of Byron and Rathbone is not valid.

According to our theories the interfacial kinetics of at least two compounds have to be determined in order to enable prediction of the interfacial kinetics of closely related solutes in the two-phase system under consideration. A reliable estimate of k_{org} can be obtained from transport experiments using a solute with a low P-value, while a reliable estimate of k_{aq} can be obtained from experiments using a solute with a high P-value. Then from knowing the P-values of closely related solutes their interfacial kinetics can be predicted by using Eqns. 1 and 2.

On a quantitative basis the data of Byron and Rathbone (1984) are very interesting. For a series of barbiturates ($n = 6$) in cyclohexane–water ($0.003 \leq P \leq 0.222$) they determined a so-called cell constant that amounted $1.79 \times 10^{-2} \text{ min}^{-1}$. From the definition this cell constant is identical to our k_{aq} . From the low P-values of the solutes it is evident that $(k_1^{obs} + k_2^{obs})$ is determined mainly by the step for which k_{org} is the diffusion rate constant (diffusional resistance in the organic phase is larger than in the aqueous phase). So the calculated cell constant is influenced by structuring of the interface with a factor that is proportional to Rel_{org} . For the same series of barbiturates the cell constant in *n*-octanol–water ($4.8 \leq P \leq 239$) was

found to be $6.10 \times 10^{-2} \text{ min}^{-1}$. From the high P-values of the solutes and from the above discussion it is evident that this value is proportional to Rel_{aq} . The quotient of these values for *n*-octanol–water and cyclohexane–water amounts to 3.41. Translating these described experimental conditions into the theories presented in the present paper gives: for cyclohexane–water the cell constant will be 0.90 ($= \text{Rel}_{\text{org}}$) times that for *n*-hexane–water, for *n*-octanol–water the cell constant will be 3.02 ($= \text{Rel}_{\text{aq}}$) times that for *n*-hexane–water. So according to our experimental data the quotient of the cell constants should equal the quotient of 3.02 and 0.90, which is 3.36. It is very striking that this is nearly identical to the quotient 3.41 obtained by Byron and Rathbone as it has to be mentioned that their experiments were performed at 37°C and at S.R. = 100 rpm in a vessel and with a stirrer that had dimensions that differ from ours. So under very different agitation conditions the same factors (3.41 and 3.36, respectively) are obtained. This strongly confirms our observation that Rel_{aq} and Rel_{org} are not influenced by the agitation conditions once both phases are stirred. Also the most likely explanation of this phenomenon that already slight shear forces induce a structuring of the interface, which does not change anymore with increasing shear forces at the interface, seems to be enforced by the similarity between the factors 3.41 and 3.36 under such different experimental conditions.

Conclusions

Conclusions that can be drawn from this paper are:

(1) The statistics of Eqns. 8–39 are good, confirming the validity of the interfacial transfer model used (De Haan et al., 1983). Since the same physicochemical processes occur both in vitro and in vivo, this theoretical model should be the starting point in the rational development of relationships describing in vivo absorption processes by passive diffusion (cf. forthcoming paper).

(2) Rel_{aq} and Rel_{org} (Eqns. 40 and 42, respectively) are the most suitable parameters for quanti-

fying the effect of the “unknown factors” on k_{aq} and k_{org} , respectively.

(3) From the lack of existence of relationships between mutual solubility data and Rel_{aq} or Rel_{org} it is concluded that the mutual solubility of organic and aqueous phases is not responsible for the “unknown factors”.

(4) The results of experiments at moderate agitation conditions clearly indicate that the “unknown factors” originate from some hydrodynamic phenomenon. Furthermore, these results strongly suggest that some agitation is needed to cause differences in the Rel_{aq} - and Rel_{org} -values of the various two-phase systems and that already moderate agitation conditions suffice to cause the differences between the Rel_{aq} - and Rel_{org} -values of the various systems which remain constant up to agitation conditions caused by S.R. = 40 rpm or even more.

(5) From the absence of existence of relationships between Rel_{aq} or Rel_{org} and the surface tensions of the various phases, the interfacial tensions of the various systems or the densities of the various solvents it is concluded that the hydrodynamic phenomenon indicated in conclusion (4) is not the formation of capillary or gravity waves.

(6) From the fact that Q_{rel} (quotient of Rel_{org} and Rel_{aq}) deviates significantly from 1.00 it is concluded that k_{aq} and k_{org} are not influenced quantitatively in the same way by the “unknown factors”. Hence the interfacial transfer kinetics of at least two compounds (with a low and a high P-value, respectively) have to be determined in order to enable prediction of the interfacial transfer kinetics of a series of closely related compounds. Furthermore, it can be concluded that the hydrodynamic phenomenon from conclusion (4) does not manifest itself solely by an increase of the magnitude of the interfacial area.

(7) From the fact that Rel_{aq} - and Rel_{org} -values can be arranged according to the chemical groups of the organic solvents of two-phase organic solvent–water systems and from the tendencies within a distinct group of two-phase systems predictions can be made for the interfacial transfer kinetics in our experimental set-up. Furthermore in conclusion (4) it is indicated that the above findings are valid for a large range of agitation

conditions, so these findings can also be applied in a much broader field (e.g. with respect to the rate of extraction on industrial scale).

From the discussions presented in this paper it can be summarized that the presented most likely explanation for the "unknown factors" is the following: slight shearing forces influence the structure of the interface. The modified structures do not change anymore with increasing agitation. So the onset of this structuring is the hydrodynamic phenomenon indicated in conclusion (4). This hydrodynamic phenomenon does not manifest itself solely by an increase of the magnitude of the interfacial area. The resulting structure of the interface is determined by the chemical structure of the organic solvent in the two-phase organic solvent-water system, i.e. the type of structuring depends on the chemical group to which the particular organic solvent belongs.

References

Byron, P.R., Guest, R.T. and Notari, R.E., Thermodynamic dependence of interfacial transfer kinetics of nonionized barbituric acid derivatives in two-phase transfer cell. *J. Pharm. Sci.*, 70 (1981) 1265-1269.

Byron, P.R. and Rathbone, M.J., Prediction of interfacial transfer kinetics. I. Relative importance of diffusional resistance in aqueous and organic boundary layers in two-phase transfer cell. *Int. J. Pharm.*, 21 (1984) 107-118.

Chang, P. and Wilke, C.R., Some measurements of diffusion in liquids. *J. Phys. Chem.*, 59 (1955) 592-596.

Davies, J.T. and Rideal, E.K., *Interfacial Phenomena*, Academic Press, New York, 1961, pp. 266-274.

De Haan, F.H.N., De Vringer, T., Van de Waterbeemd, J.T.M. and Jansen, A.C.A., Transport rate constants and transport rate parameters in various organic solvent-water systems. *Int. J. Pharm.*, 13 (1983) 75-87.

De Haan, F.H.N. and Jansen, A.C.A., Transport in Q.S.A.R. VIII. The influence of viscosity on transport rate constants in two-phase systems organic solvent-water. *Pharm. Weekbl. Sci. Edn.*, 5 (1983) 222-227.

De Haan, F.H.N. and Jansen, A.C.A., The hydrodynamics in a simple transport vessel in two-phase systems of organic solvent-water. *Int. J. Pharm.*, 18 (1984) 311-324.

Evans, D.F., Tominaga, T. and Davis, H.T., Tracer diffusion in polyatomic liquids. *J. Chem. Phys.*, 74 (1981) 1298-1305.

Lamb, H., *Hydrodynamics*, 6th edn., Cambridge University Press, New York, 1952, pp. 456-470.

Levich, V.G., *Physicochemical Hydrodynamics*, Prentice Hall, Englewood Cliffs, 1962, pp. 591-599.

Marsden, C. (Ed.), *Solvents Guide*, 2nd edn., Cleaver Hume Press, London, 1963, p. 163.

Riddick, J.A. and Bunger, W.B., *Organic Solvents. Physical properties and methods of purification*. In A Weissberger (Ed.), *Techniques of Chemistry*, Vol. II, 3rd edn., Wiley-Interscience, New York, 1970, pp. 66-289.

Smith, R.N., Hansch, C. and Ames, M.E., Selection of a reference partitioning system for drug design work. *J. Pharm. Sci.*, 64 (1975) 599-606.

Van de Waterbeemd, J.Th.M., Jansen, A.C.A. and Gerritsma, K.W., Transport in Q.S.A.R. III. The determination of transport rate constants. *Pharm. Weekbl. Sci. Edn.*, 2 (1980) 73-80.

Van de Waterbeemd, J.Th.M., Van Boeckel, C.C.A.A., De Sévaux, R.L.F.M., Jansen, A.C.A. and Gerritsma, K.W., Transport in Q.S.A.R. IV. The interfacial drug transfer model. Relationships between partition coefficients and rate constants of drug partitioning. *Pharm. Weekbl. Sci. Edn.*, 3 (1981) 12-25.