

INTERPHASE DISTRIBUTION OF 2-FURYLETHYLENES

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The distribution kinetics of 35 2-furylethylene derivatives in two-phase system 1-octanol–water was investigated. The transport rate parameters in direction water–1-octanol (l_1) and backwards (l_2) are partition coefficient $P = l_1/l_2$ dependent according to equations $l_1 = \log P - \log . (\beta P + 1) + \text{const.}$, $l_2 = -\log (\beta P + 1) + \text{const.}$, $\text{const.} = -5.600$, $\beta = 0.261$. Importance of this finding for assesment of distribution of compounds under investigation in biosystems and also the suitability of the presented method for determination of partition coefficients are discussed.

The invasion of the majority of xenobiotics into a cell proceeds *via* transport through the lipidic component of membranes. This process is studied on model systems *in vitro*^{1–3} and *in vivo*^{4–7}. Fundamental aspects of the key step characterized by transition from aqueous to unpolar phase can advantageously be studied in more detail employing the system water–immiscible organic solvent. The interface of model system resembles a real one represented by membrane–water; both have an immiscible diffusion layer from aqueous and organic sides.

Our study was directed towards distribution kinetics of 2-furylethylene derivatives in a two-phase system 1-octanol–water aiming to verify the published relationships between the transport rate parameters l_1 and l_2 and the partition coefficient P (ref.^{8–11}).

$$\log l_1 = \log P - \log (\beta P + 1) + \text{const.} , \quad (1)$$

$$\log l_2 = -\log (\beta P + 1) + \text{const.} , \quad (2)$$

where the β and const. constants are dependent on the model system. At the same time it was decided to test the presented method for determination of partition coefficients.

MATERIAL AND METHODS

Compounds for experiments were synthesized according to^{12–17}.

Arrangement of the Experiment

The two-phase system 1-octanol–water in a glass vessel covered with an aluminium foil and tempered to 25°C was stirred with a glass stirrer (Fig. 1). The stirring frequency (1.3 rps) was adjusted so as no concentration gradients could appear in either phase and the motion of the phase interface was minimal. The interface was not planar during stirring, but slightly conical; at constant stirring rate the size of phase interface was virtually constant as well.

The measuring vessel was filled with redistilled deionized 1-octanol-saturated water (175 ml), tempered to 25°C and surfaced with the solution of the respective compound in freshly distilled 1-octanol saturated with water (20 ml). Samples (2 ml) for spectrophotometric determination of the compound concentration were withdrawn with a syringe at certain time intervals. The UV and VIS spectra were recorded in the complete spectral range; this measurement also served for monitoring the stability of compounds in the given medium. The samples were replaced to the vessel immediately after each measurement.

Data Processing

Transport of a compound in the two-phase system 1-octanol–water can be expressed by a system of two linear differential equations:

$$-dc_1/dt = (Sl_1/V_1)c_1 - (Sl_2/V_1)c_2, \quad (3)$$

$$-dc_2/dt = -(Sl_1/V_2)c_1 + (Sl_2/V_2)c_2, \quad (4)$$

where c stands for concentration of the compound, V for volume (the subscripts in Eqs (3) and (4) refer to aqueous and 1-octanol phases, respectively), S for interface surface, l for transport rate parameters in direction water–1-octanol (subscript 1) and backwards (subscript 2), and t for time. Provided the compound is present in 1-octanol only at the beginning of partition and its concentration is c_0 , the time course of concentration in aqueous phase (c_1) can be expressed by equation (5):

$$c_1 = c_0 l_2 V_2 [1 - \exp(-S(l_1/V_1 + l_2/V_2)t)] / (l_1 V_2 + l_2 V_1). \quad (5)$$

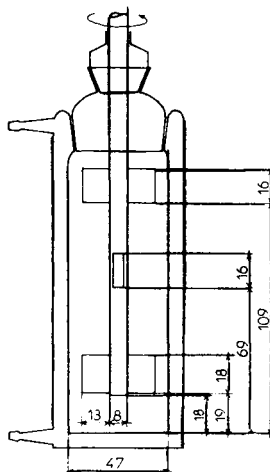


FIG. 1

A sketch of tempered cell for transport monitoring (dimensions in mm)

The time course of absorbance in the aqueous phase is expressed by equation (5) multiplied by $\epsilon \cdot d$ (ϵ is the molar absorption coefficient, d is the length of light path).

Adaptation of equation (5) expressed by absorbance afforded equations (6) for $t \rightarrow 0$ and (7)

$$A = \epsilon d c_0 l_2 S t / V_1 \quad (t \rightarrow 0), \quad (6)$$

$$\ln(A_e - A) = \text{const.} - S(l_1/V_1 + l_2/V_2) t, \quad (7)$$

where A_e is the value for absorbance at the end of distribution. The values of transport rate parameters l_1 and l_2 were determined by a nonlinear regression analysis¹⁸ according to equation (5) expressed through absorbance; equations (6) and (7) served for initial assessments of l_2 and l_1 , respectively.

RESULTS AND DISCUSSION

The time dependence of concentration in the aqueous phase and its linearization according to equation (7) is plotted in Fig. 2. Structures, transport rate parameters l_1 and l_2 , and partition coefficients P are presented in Table I. Good statistical parameters of the mathematical description of the distribution kinetics according to equa-

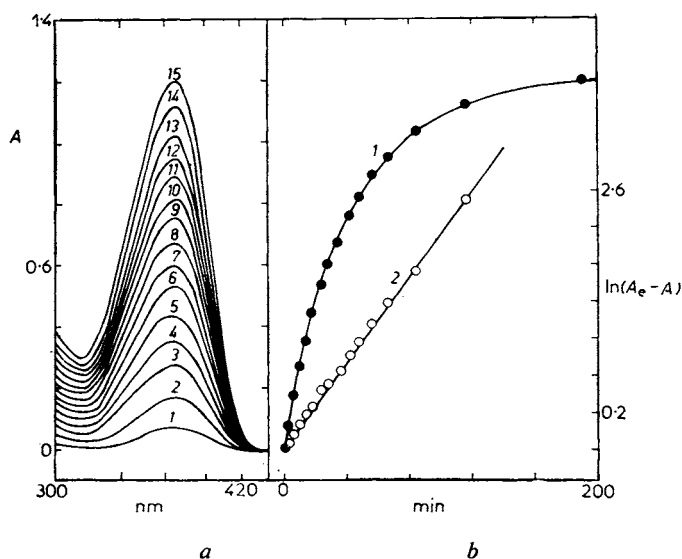


FIG. 2

Distribution of 3-(5-nitro-2-furyl)acrylic acid ethylamide. *a* UV and VIS spectra of water phase in time (min): 3(1), 6(2), 10(3), 14(4), 18(5), 24(6), 28(7), 34(8), 42(9), 48(10), 56(11), 66(12), 84(13), 116(14), 190, 220 and 300(15). *b* Absorbance at 370 nm in time (full circles), the line 1 corresponds to equation (5) expressed through absorbance ($c_0 = 2.250 \cdot 10^{-3} \text{ mol dm}^{-3}$, $\epsilon \cdot d = 1.765 \cdot 10^4 \text{ dm}^3 \text{ mol}^{-1}$) and 2 its linearization according to Eq. (7)

TABLE I

Structures of the investigated 1-(5-R₁-2-furyl)-2-R₂,R₃-ethylenes, values of transport rate parameters in direction water-1-octanol (I_1) and backwards (I_2) in m s^{-1} , values of partition coefficients $P = I_1/I_2$. The I_1 and I_2 values were determined by a nonlinear regression analysis¹⁸ of kinetics according to equation (5). The lowest values of experimental points, correlation coefficient and F -test were: $n = 14$, $r = 0.991$ and $F = 188.3$, the maximum value of standard deviation $s = 0.057$

R ¹	R ²	R ³	$-\log I_1$	$-\log I_2$	$\log P$
NO ₂	H	COOH	4.703	5.383	0.680
NO ₂	H	CONH ₂	4.702	5.351	0.649
NO ₂	H	CONHCH ₃	4.602	5.587	0.984
NO ₂	H	CONHCH ₂ CH ₃	4.527	5.913	1.386
NO ₂	H	CON(CH ₃) ₂	4.650	5.469	0.819
NO ₂	H	CONH(CH ₂) ₂ CH ₃	4.534	6.395	1.860
NO ₂	H	CONHCH(CH ₃) ₂	4.503	6.307	1.803
NO ₂	H	CONH(CH ₂) ₃ CH ₃	4.709	7.065	2.356
NO ₂	H	CONHCH ₂ CH(CH ₃) ₂	4.506	6.730	2.225
NO ₂	H	CONHCH(CH ₃)CH ₂ CH ₃	4.544	6.827	2.284
NO ₂	H	CONHC(CH ₃) ₃	4.509	6.842	2.333
NO ₂	H	CONHCH ₂ C(CH ₃) ₃	4.661	7.266	2.605
NO ₂	H	CONHCH(CH ₃)(CH ₂) ₁₀ CH ₃	4.432	8.129	3.697
NO ₂	H	COOCH ₃	4.471	6.122	1.652
NO ₂	H	COOCH ₂ CH ₃	4.421	6.518	2.098
NO ₂	H	COO(CH ₂) ₂ CH ₃	4.352	7.025	2.673
NO ₂	H	COOCH(CH ₃) ₂	4.454	7.095	2.641
NO ₂	H	COO(CH ₂) ₃ CH ₃	4.389	7.215	2.827
NO ₂	H	COOCH ₂ CH(CH ₃) ₂	4.323	7.457	3.135
NO ₂	H	COOCH(CH ₃)CH ₂ CH ₃	4.382	7.472	3.091
NO ₂	H	COOC(CH ₃) ₃	4.535	7.596	3.060
NO ₂	H	COO(CH ₂) ₄ CH ₃	4.521	7.925	3.404
H	CN	COOCH ₃	4.424	6.073	1.648
CH ₃	CN	COOCH ₃	4.475	6.561	2.086
SCH ₃	CN	COOCH ₃	4.363	6.972	2.609
Cl	CN	COOCH ₃	4.413	6.702	2.290
Br	CN	COOCH ₃	4.367	6.776	2.409
I	CN	COOCH ₃	4.401	7.148	2.747
H	CN	CN	4.411	5.811	1.400
SCH ₃	CN	CN	4.396	6.841	2.445
Br	CN	CN	4.338	6.500	2.161
I	CN	CN	4.407	6.828	2.422
NO ₂	H	Br	4.260	6.707	2.447
NO ₂	H	NO ₂	4.400	5.703	1.303
NO ₂	COOCH ₂ CH ₃	COOCH ₂ CH ₃	4.385	6.889	2.504

tion (5) indicate that the presumptions needed (homogeneous stirring of phases, constant surface of interface, negligible effect of hydrolysis and sample withdrawal) have been met.

Dependence of rate transport parameters l_1 and l_2 upon the partition coefficient P (Fig. 3) can be expressed by equations (1) and (2). The values of $\text{const.} = -5.600$ and $\beta = 0.261$ were determined by a nonlinear regression analysis¹⁸ with following statistical parameters: number of points $n = 70$, correlation coefficient $r = 0.997$, standard deviation $s = 0.091$, the F -test value $F = 3\,600$. The difference between ours and the reported⁹ values of const. and β is likely due to a different hydrodynamics of the systems involved and, consequently, to a various quality of diffusion layers of the interface.

Our results are in a qualitative agreement with those of Waterbeemd⁹⁻¹¹; he also showed that the constant const. is a decadic logarithm of the rate constant characterizing the transport through organic layer and β is the ratio of rate constants for transport through organic and aqueous diffusion layers. Constants const. and β depend on kinematic viscosity of organic phase and water¹⁹, in other words on character of the model system. For the kinetics of distribution in several-phase systems (inclusive biological) the only important factor of physicochemical properties of transported compounds is the partition coefficient. Its influence on concentration of compounds in the individual compartments can be monitored by means of experimental values l_1 and l_2 dependent on partition coefficient P according to equations (1) and (2), ref.^{20,21}.

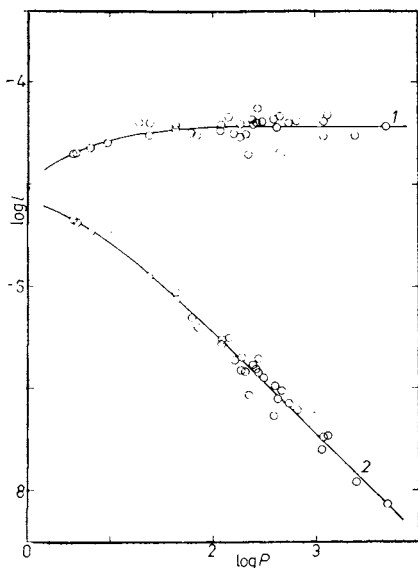


FIG. 3
Dependence of transport rate parameters on partition coefficient P in m s^{-1} ; direction water-1-octanol (l_1 , curve 1) and backwards (l_2 , curve 2)

Investigation of distribution kinetics in a two-phase system is a suitable method for determination of the partition coefficient especially of compounds undergoing decomposition. Supposing that decomposition of compounds is far slower than the distribution, it is sufficient to determine the time within which the lipophilic-hydrophilic equilibrium is virtually achieved and the effect of chemical reaction is negligible (our case); if velocity of the mentioned process is comparable, it is necessary the chemical reaction to be involved in description of the kinetic process (equation (5)).

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