Transport in Quantitative Structure–Activity Relationships VI: Relationship between Transport Rate Constants and Partition Coefficients

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Abstract □ The transport rate constant of a drug partitioned in a two-phase system from an aqueous to an organic phase (k_1^{obs}) and vice versa (k_2^{obs}) is a function of the partition coefficient P and of a solvent system-dependent parameter β. Drug transport is shown to be independent of molecular structure for a number of arbitrary compounds.

Keyphrases □ Drug transport—relationship between drug transport rate constants and partition coefficients □ Partition coefficients—relationship between drug transport rate constants and partition coefficients □ Structure–activity relationships—relationship between drug transport rate constants and partition coefficients

Partition coefficients (P) often are used as parameters in quantitative structure–activity relationships. A quadratic log P term also is necessary in many relationships to obtain good statistics. The appearance of quadratic terms has been attributed to the influence of drug transport from the site of application to the site of action (1). However, partition coefficients are equilibrium constants, and transport is kinetic in nature. Thus, the relationship between the kinetic and equilibrium parameters of partitioning is important.

BACKGROUND

Recently, it was shown that relationships exist between transport rates and partition coefficients (2, 3). A new transport model was developed to explain these relationships (2, 3).

A kinetic approach of this interfacial drug transport model reveals the following bilinear relationships between transport rate constants (k^{obs}) and P:

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

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

where k_1^{obs} is the observed rate constant for the drug transport from water to an organic solvent, k_2^{obs} is the observed rate constant for the reverse process, and k_{org} and k_{aq} are the diffusion rate constants of the drug through the two adjacent stagnant layers, which are assumed to be at an interface. The β value, known from Kubinyi's bilinear model (4, 5), appears to be identical to the quotient of k_{org} and k_{aq} (2, 3).

Moreover, it can be understood from this theory how drug transport in a biological system can be described with partition coefficients and why bilinear and parabolic relationships are found experimentally (6). This new interfacial drug transfer model is related closely to other literature models (6).

The theoretical equations were tested with a series of 30 sulfonamide derivatives, and it was demonstrated that β under fixed conditions is a constant for a certain two-phase solvent system (3). In the n-octanol–water system, and in the chosen vessel and at a certain fixed temperature and stirring rate, the experimental regression equations are:

$$\log k_1^{obs} = \log P - \log(0.412P + 1) - 3.985$$
$$n = 30 \quad r = 0.990 \quad F = 1397 \quad s = 0.045 \qquad \text{(Eq. 3)}$$

$$\log k_2^{obs} = -\log(0.411P + 1) - 3.985$$
$$n = 30 \quad r = 0.998 \quad F = 6218 \quad s = 0.046 \qquad \text{(Eq. 4)}$$

From these experimental equations, it is concluded that the transport model and the theoretically found relationships between transport rate constants and P have a physicochemical reality at least for a series of congeneric compounds. It was concluded previously that the effective volumes of the compounds of this sulfonamide series are all very similar. Differences in intrinsic molecular volume and polarity of the compounds are obviously compensated by a change in solvent association of the solute (3). It is tempting to assume that a compensation mechanism of intrinsic radius, polarity, and charge distribution holds for other compounds with variations even in the molecular skeleton. The present paper describes the results of transport rate measurements of compounds with variations in structure, size, and lipophilicity, including ion-pairs and partly ionized compounds.

EXPERIMENTAL

Transport rate constants were determined with the apparatus and method previously described (7).

Partition coefficients were taken from the literature (8) or were determined by UV detection[1] after shaking appropriate amounts of mutually saturated solvents and allowing overnight separation.

All chemicals were available commercially and were analytical grade.

RESULTS AND DISCUSSION

The observed (k^{obs}) and calculated (k^{cal}) transport data are given in Table I. Apparent partition coefficients (P_{app}) were used to calculate the rate constants with Eqs. 3 and 4. The observed rate constants and apparent partition coefficients of ion-pairs and ionic compounds are dependent on the initial concentration (9). The data are plotted in Fig. 1. All points are situated very near to the curves calculated for the sulfon-

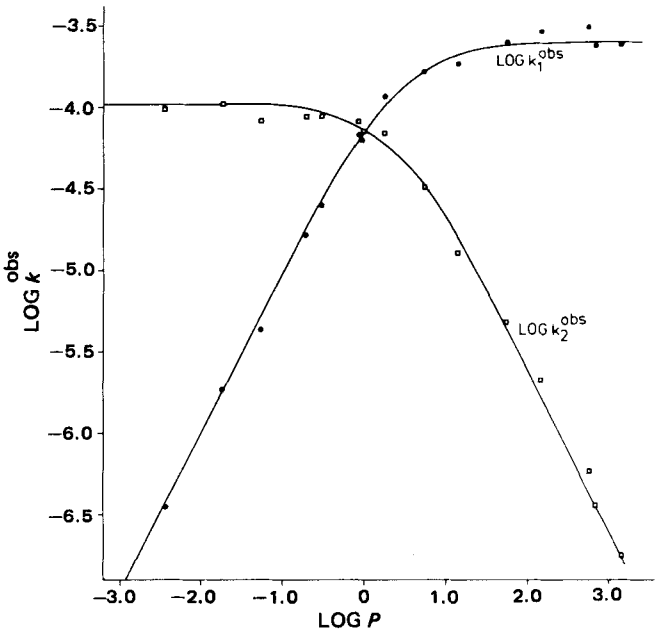

Figure 1—*Log* k^{obs} versus *log* P *curves for the compounds of Table I. The plotted data are the log* k^{obs} *values, and the drawn curves were calculated with Eqs. 3 and 4.*

[1] Gilford spectrophotometer 250.

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Table I—Transport Data of Various Compounds in *n*-Octanol–Water [a,b]

Compound	Molecular Weight	log P_{oct}^{app}	log k_1^{obs}	log k_1^{calc}	$\Delta_1^{obs-calc}$	log k_2^{obs}	log k_2^{calc}	$\Delta_2^{obs-calc}$	C_0[c], moles per liter
Ephedrine hydrochloride	202	−2.45	−6.444	−6.436	−0.008	−4.020	−3.986	−0.034	5.0×10^{-5}
Adrenaline bitartrate	333	−1.75	−5.725	−5.738	0.013	−3.978	−3.988	0.010	3.0×10^{-5}
Berberine chloride	372	−1.28	−5.369	−5.274	−0.095	−4.089	−3.994	−0.095	6.2×10^{-2}
Sulfanilamide	172	−0.72[d]	−4.781	−4.738	−0.043	−4.061	−4.018	−0.043	1.1×10^{-4}
Benzilonium *n*-hexanesulfonate	518	−0.55	−4.593	−4.578	−0.015	−4.048	−4.033	−0.015	2.5×10^{-3}
Benzilonium *n*-heptanesulfonate	532	−0.03	−4.199	−4.156	−0.043	−4.170	−4.126	−0.044	2.5×10^{-3}
Caffeine	194	−0.07[d]	−4.156	−4.186	0.030	−4.086	−4.115	0.029	2.0×10^{-4}
Antipyrine	188	0.23[d]	−3.925	−3.985	0.060	−4.155	−4.215	0.060	5.8×10^{-5}
Aminopyrine	231	0.71	−3.783	−3.768	−0.015	−4.495	−4.479	−0.016	1.4×10^{-4}
Triamcinolone	394	1.16[d]	−3.732	−3.667	−0.065	−4.892	−4.826	−0.066	6.7×10^{-5}
Benzocaine	165	1.73	−3.590	−3.619	0.029	−5.320	−5.348	0.028	9.0×10^{-5}
Benzene	78	2.15[d]	−3.518	−3.607	0.089	−5.668	−5.756	0.088	9.4×10^{-3}
Toluene	92	2.73[d]	−3.499	−3.602	0.103	−6.229	−6.331	0.102	3.0×10^{-3}
Diazepam	285	2.82[d]	−3.613	−3.601	−0.012	−6.432	−6.420	−0.012	2.3×10^{-5}
p-Xylene	106	3.15[d]	−3.605	−3.601	−0.004	−6.755	−6.750	−0.005	1.7×10^{-3}

[a] The log k^{calc} calculated from Eqs. 3 and 4. [b] Stirring rate was 0.667 sec^{-1}, and temperature was 20 ± 0.1° (7). [c] Initial concentration in aqueous or organic phase (7). [d] Taken from Ref. 8.

amide derivatives (3) (Eqs. 3 and 4). The regression equations for the compounds of Table I are:

$$\log k_1^{obs} = \log P - \log (0.364P + 1) - 4.010 \quad (\text{Eq. 5})$$
$$n = 15 \quad r = 0.999 \quad F = 4401 \quad s = 0.051$$

$$\log k_2^{obs} = -\log (0.358P + 1) - 4.016 \quad (\text{Eq. 6})$$
$$n = 15 \quad r = 0.999 \quad F = 5375 \quad s = 0.051$$

When the data of the compounds of Table I are combined with the data of the sulfonamide derivatives, the regression equations are:

$$\log k_1^{obs} = \log P - \log (0.386P + 1) - 3.999 \quad (\text{Eq. 7})$$
$$n = 45 \quad r = 0.997 \quad F = 7332 \quad s = 0.047$$

$$\log k_2^{obs} = -\log (0.385P + 1) - 4.002 \quad (\text{Eq. 8})$$
$$n = 45 \quad r = 0.998 \quad F = 12{,}055 \quad s = 0.047$$

Because β can only be determined with a relative standard deviation of ~10% (3, 10), it can be concluded that Eqs. 5–8 do not differ significantly and that all compounds behave as belonging to one series with regard to partitioning.

Since diffusion rate constants through the stagnant layers largely determine the overall transport rates, dependency on the radius of the molecules is expected (Stokes–Einstein relation). However, because this effect was not observed, it was concluded that the effective molecular radii of the sulfonamide derivatives all are very similar (3). This fact also holds for other compounds. These observations show that the absolute magnitude of transport rate constants in a two-phase system is not dependent on the intrinsic molecular size of a compound.

In conclusion, transport rate constants of drug partitioning in a chosen two-phase system are determined by the partition coefficient (P) and the solvent system parameter (β). This β value, which equals k_{org}/k_{aq}, is a new parameter that can be calculated from the plateau values of a log k^{obs}/log P curve (3).

Drug transport in biological systems includes a series of interphase aqueous environment to membrane transfers and vice versa. For each transfer process, a certain β value can be defined; thus, it is interesting to know the factors that determine this parameter. It is assumed that the stagnant layers at an interface are more or less structured (3) and that this structuring originates from a mutual influencing of the two adjacent phases (water–organic solvent or water–membrane). Polarity and polarizability of the solvents seem to be important properties. Investigations on this subject are in progress. Studies on the partitioning kinetics of drugs will produce more knowledge of the transport properties of drugs, which then can result in improved pharmacokinetic parameters of drugs (11, 12) and the successful application of quantitative structure–activity relationships.

REFERENCES

(1) R. F. Rekker, "The Hydrophobic Fragmental Constant," Elsevier, Amsterdam, The Netherlands, 1977, p. 4.

(2) J. T. M. van de Waterbeemd, C. A. A. van Boeckel, A. C. A. Jansen, and K. W. Gerritsma, *Eur. J. Med. Chem.*, **15**, 279 (1980).

(3) J. T. M. van de Waterbeemd, C. A. A. van Boeckel, R. L. F. M. de Seraux, A. C. A. Jansen, and K. W. Gerritsma, *Pharm. Weekbl. Sci. Ed.*, in press.

(4) H. Kubinyi, *Arzneim.-Forsch.*, **26**, 1991 (1976).

(5) H. Kubinyi, *J. Pharm. Sci.*, **67**, 262 (1978).

(6) J. T. M. van de Waterbeemd and A. C. A. Jansen, *Pharm. Weekbl. Sci. Ed.*, in press.

(7) J. T. M. van de Waterbeemd, A. C. A. Jansen, and K. W. Gerritsma, *ibid.*, **2**, 73 (1980).

(8) C. Hansch and A. Leo, "Substituent Constants for Correlation Analysis in Chemistry and Biology," Wiley–Interscience, New York, N.Y., 1979.

(9) B. C. Lippold and G. F. Schneider, *Arzneim.-Forsch.*, **25**, 843 (1975).

(10) H. Kubinyi and O.-H. Kehrhahn, *ibid.*, **28**, 598 (1978).

(11) J. K. Seydel, D. Trettin, H. P. Cordes, O. Wassermann, and M. Malyusz, *J. Med. Chem.*, **23**, 607 (1980).

(12) B. Testa and B. Salvesen, *J. Pharm. Sci.*, **69**, 497 (1980).