Drug Partitioning: Relationships between Forward and Reverse Rate Constants and Partition Coefficient

HUGO KUBINYI

Received February 28, 1977, from the *Research Institute of KNOLL AG, D-6700 Ludwigshafen/Rhein, Germany.* Accepted for publication April 18, 1977.

Abstract □ The rate constant, k_1, of drug transport from an aqueous phase to an organic phase and the rate constant, k_2, of the reverse process can be described as functions of the partition coefficient, P: $\log k_1 = \log P - \log(\beta P + 1) + c'$ and $\log k_2 = -\log(\beta P + 1) + c'$. In a homologous series, where $\log P$ is a simple function of the number of CH_2 groups, $\log k_1$ and $\log k_2$ also can be described as functions of the number of CH_2 groups. The relationships between these equations and current physicochemical models of drug absorption are discussed.

Keyphrases □ Partition coefficients—relationship to forward and reverse rate constants and number of CH_2 groups in a homologous series □ Drug partitioning—relationship of partition coefficients to forward and reverse rate constants and number of CH_2 groups in a homologous series

The partition coefficient, P, of a drug is an equilibrium constant defined in terms of the ratio of k_1, the rate constant of drug transport from the aqueous phase to the organic phase, and k_2, the rate constant of the reverse process, according to:

$$P = \frac{k_1}{k_2} \qquad \text{(Eq. 1)}$$

It is possible to assess the individual rate constants, as shown by Lippold and Schneider (1–3), who determined k_1 and k_2 in homologous series using a three-compartment model (Table I).

THEORETICAL

From the data of Table I, it is evident that there must be additional relationships between k_1 and k_2 beside that expressed in Eq. 1. Examination of the data indicates that k_2 is linearly related to k_1 for the homologs previously studied (1–3); *i.e.*:

$$k_2 = -\beta k_1 + c \qquad \text{(Eq. 2)}$$

Equations 3 and 4 can be derived for the dependence of either k_1 or k_2 on the partition coefficient, P, by substitution of Eq. 2 into Eq. 1, solving first for k_1 (Eq. 3) and then for k_2 (Eq. 4):

$$k_1 = \frac{cP}{\beta P + 1} \qquad \text{(Eq. 3)}$$

$$k_2 = \frac{c}{\beta P + 1} \qquad \text{(Eq. 4)}$$

If Eqs. 3 and 4 are written in the logarithmic form, then Eqs. 5 and 6 result:

$$\log k_1 = \log P - \log(\beta P + 1) + c' \qquad \text{(Eq. 5)}$$

$$\log k_2 = -\log(\beta P + 1) + c' \qquad \text{(Eq. 6)}$$

where the term c' has been substituted for the constant, $\log c$.

Since, in homologous series, $\log P$ is a function of the number of CH_2 groups, N (4):

$$\log P = aN + b \qquad \text{(Eq. 7)}$$

Eqs. 5 and 6 can be rewritten in terms of the relationship expressed in Eq. 7:

$$\log k_1 = aN - \log(\beta' 10^{aN} + 1) + b' \qquad \text{(Eq. 8)}$$

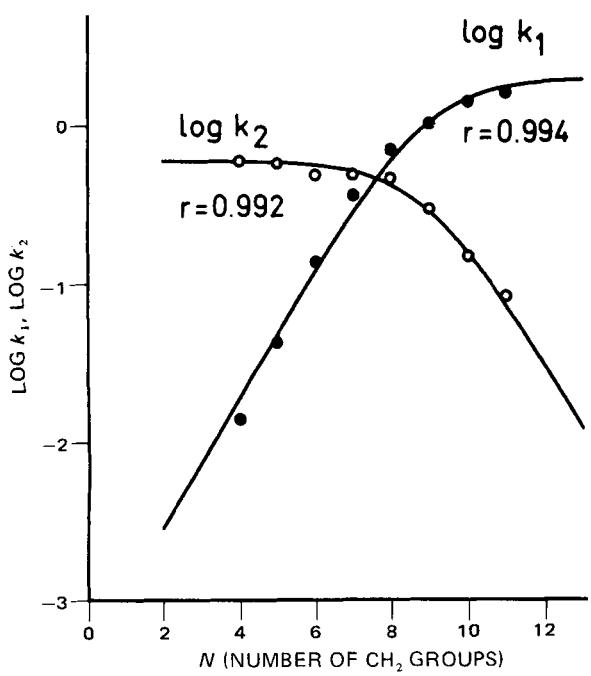

Figure 1—*Rate constants* k_1 *and* k_2 *of the partitioning of homologous quaternary alkylammonium bromides; comparison of experimental values from a three-compartment system (no salt added) (1) and values calculated from Eqs. 8 and 9* (a, b, β, *and* c *values from Table II).*

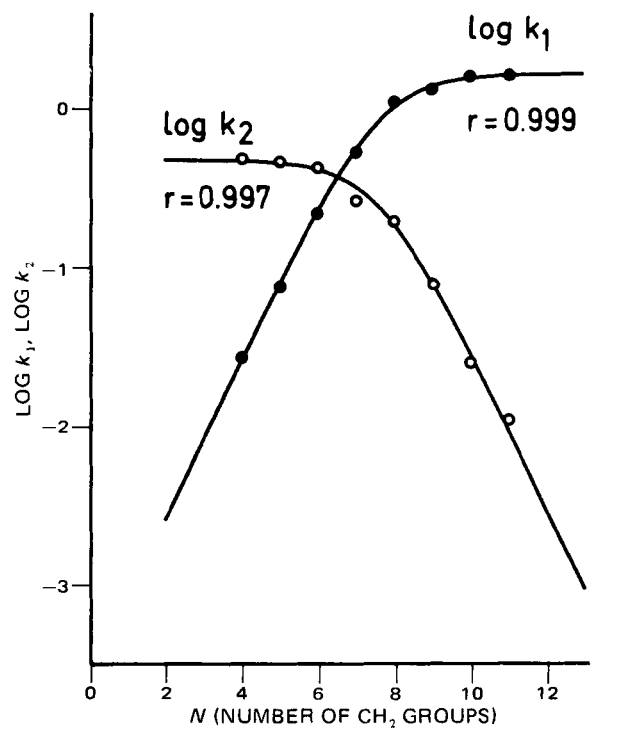

Figure 2—*Rate constants* k_1 *and* k_2 *of the partitioning of homologous quaternary alkylammonium bromides; comparison of experimental values from a three-compartment system (sodium bromide added) (2) and values calculated from Eqs. 8 and 9* (a, b, β, *and* c *values from Table II).*

Table I—Experimental k_1 and k_2 Values from Lippold and Schneider (1–3) for Quarternary Alkylammonium Bromides and *n*-Alkylsulfonates Using Three-Phase Model (Water–1-Octanol–Water)

	Quaternary Alkylammonium Bromides									
	No Salt Added		Plus Sodium Bromide		Plus Sodium Butanesulfonate		Plus Sodium Trichloroacetate		Benzilonium *n*-Alkylsulfonates	
N^a	k_1	k_2	k_1	k_2	k_1	k_2	k_1	k_2	k_1	k_2
2	—	—	—	—	—	—	0.057	1.130	—	—
3	—	—	—	—	—	—	0.115	0.940	—	—
4	0.014	0.600	0.027	0.490	0.055	0.920	0.224	0.824	—	—
5	0.043	0.578	0.076	0.470	0.143	0.640	0.435	0.585	—	—
6	0.140	0.490	0.217	0.425	0.345	0.360	0.930	0.396	0.095	0.635
7	0.370	0.500	0.534	0.264	0.808	0.276	1.200	0.198	—	—
8	0.715	0.471	1.112	0.196	1.140	0.128	1.244	0.076	0.63	0.425
9	1.064	0.300	1.340	0.078	—	—	1.560	0.042	—	—
10	1.440	0.149	1.620	0.025	—	—	—	—	1.33	0.15
11	1.648	0.084	1.650	0.011	—	—	—	—	—	—
12	—	—	—	—	—	—	—	—	1.46	0.02

[a] Number of CH_2 groups.

Table II—*a*, *b*, β, and *c* Values[a], Calculated from k_1 and k_2 Values of Table I, Using Eqs. 2 and 7

	Quaternary Alkylammonium Bromides				
Parameter	No Salt Added	Plus Sodium Bromide	Plus Sodium Butanesulfonate	Plus Sodium Trichloroacetate	Benzilonium *n*-Alkylsulfonates
$k_2 = -\beta k_1 + c$ (Eq. 2)					
β	0.296 (±0.07)	0.286 (±0.04)	0.612 (±0.56)	0.688 (±0.16)	0.430 (±0.15)
c	0.598 (±0.06)	0.480 (±0.04)	0.770 (±0.36)	1.020 (±0.14)	0.686 (±0.16)
n	8	8	5	8	4
r	0.975	0.989	0.896	0.975	0.994
s	0.047	0.032	0.161	0.100	0.038
F	115	267	12.3	114	153
$\log \frac{k_1}{k_2} = aN + b$ (Eq. 7)					
a	0.412 (±0.04)	0.501 (±0.02)	0.546 (±0.06)	0.420 (±0.02)	0.442 (±0.06)
b	−3.146 (±0.31)	−3.265 (±0.15)	−3.373 (±0.35)	−2.179 (±0.10)	−3.440 (±0.57)
n	8	8	5	8	4
r	0.996	0.999	0.998	0.999	0.999
s	0.103	0.051	0.057	0.045	0.063
F	672	4036	918	3674	974

[a] The 95% confidence limits are given in parentheses.

$$\log k_2 = -\log(\beta' 10^{aN} + 1) + c' \qquad \text{(Eq. 9)}$$

where b' has been substituted for the constant $b + c'$ and β' has been substituted for $\beta \times 10^b$.

RESULTS AND DISCUSSION

If Eqs. 2 and 7 are applied to k_1 and k_2 values of Table I, the *a*, *b*, β, and *c* values given in Table II result. Log k_1 and log k_2 values can be calculated from these values using Eqs. 8 and 9; a comparison of observed and calculated log k_1 and log k_2 values is given in Table III and Figs. 1 and 2.

Either Eqs. 3 and 4 or Eqs. 8 and 9 are generally applicable for the quantitative description of k_1 and k_2 values. Equation 3 corresponds to previous drug absorption models (5–14). However, all β values differ significantly from one, giving strong evidence for the validity of the diffusion models (6–12); other models (5, 13, 14) predict $\beta = 1$ for the *in vitro* system used by Lippold and Schneider (1–3). In all cases, the influence of molecular size effects on diffusion coefficients is negligible.

Equations 5 and 6 are special forms of the bilinear model (15, 16) derived recently for the quantitative description of the dependence of biological activity of drugs on their hydrophobic character.

Table III—Comparison of Observed and Calculated log k_1 and log k_2 Values (*a*, *b*, β, and *c* Values of Table II Were Used to Calculate log k_1 and log k_2 from Eqs. 8 and 9, Respectively)

	Quaternary Alkylammonium Bromides				
	No Salt Added	Plus Sodium Bromide	Plus Sodium Butanesulfonate	Plus Sodium Trichloroacetate	Benzilonium *n*-Alkylsulfonates
log k_1 values: r	0.994	0.999	0.995	0.993	0.997
log k_2 values: r	0.992	0.997	0.955	0.996	0.999
log k_1 and log k_2 values[a]					
n	16	16	10	16	8
r	0.994	0.999	0.984	0.995	0.998
s[b]	0.068	0.040	0.092	0.060	0.047
F[b]	335	1414	63	377	429

[a] Log k_1 and log k_2 values were combined because both values are predicted by Eqs. 8 and 9 using the same *a*, *b*, β, and *c* values. [b] The $(n - 4)$ degrees of freedom; F values are only rough estimates because Eqs. 8 and 9 are nonlinear.

REFERENCES

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

(2) *Ibid.*, **25**, 1683 (1975).

(3) B. C. Lippold and G. F. Schneider, *Pharmazie*, **31**, 237 (1976).

(4) A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).

(5) T. Koizumi, T. Arita, and K. Kakemi, *Chem. Pharm. Bull.*, **12**, 413 (1964).

(6) R. G. Stehle and W. I. Higuchi, *J. Pharm. Sci.*, **56**, 1367 (1967).

(7) A. Suzuki, W. I. Higuchi, and N. F. H. Ho, *ibid.*, **59**, 644 (1970).

(8) *Ibid.*, **59**, 651 (1970).

(9) R. G. Stehle and W. I. Higuchi, *J. Pharm. Sci.*, **61**, 1922 (1972).

(10) *Ibid.*, **61**, 1931 (1972).

(11) G. L. Flynn and S. H. Yalkowsky, *J. Pharm. Sci.*, **61**, 838 (1972).

(12) S. H. Yalkowsky and G. L. Flynn, *ibid.*, **62**, 210 (1973).

(13) J. G. Wagner and A. J. Sedman, *J. Pharmacokinet. Biopharm.*, **1**, 23 (1973).

(14) J. G. Wagner, "Fundamentals of Clinical Pharmacokinetics," Drug Intelligence Publications, Hamilton, Ill., 1975, p. 203 ff.

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

(16) H. Kubinyi, *J. Med. Chem.*, **20**, 625 (1977).