# The Determination of Interfacial Transfer Constants Using Side-by-Side Diffusion Cells

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*Received January 11, 1994; accepted April 28, 1994*

A side-by-side diffusion cell setup has been used to determine the pH 7.4 buffer-octanol interfacial transfer constants for twelve compounds. The compounds are a diverse selection of pharmaceuticals, amino acids, and small organics which covers a log distribution coefficient (K) range of −3 to 2. A model based on the resistance summation approach, which deals explicitly with the various barriers involves in the transport process, was used to derive transfer constants from the transport data for each compound. The model gave constants that were well behaved in a published model describing the correlation of the forward and reverse transfer constants to equilibrium K values ($r^2$ = 0.999). These studies demonstrate the utility of side-by-side diffusion cells for the determination of interfacial transfer constants. This type of setup offers the advantages of controlled interfacial area, measurable hydrodynamic effects, and a commercially available apparatus.

KEY WORDS: interfacial transfer; partition coefficients; side-by-side diffusion cells; kinetics; modeling.

## INTRODUCTION

One of the most important factors governing the passive transport of a compound across both biological and synthetic membranes is the compound's lipophilicity. As a result, the literature is filled with values for partition coefficients in numerous solvent systems; one of the most popular being octanol/water. In the mathematical description of membrane transport, the resistance to transport offered by the solvent-membrane interface is often ignored (1,2). Instead, an equilibrium partition coefficient or Henry's Law constant is included to describe the effective thermodynamic activity in the various phases. This is valid when the interfacial kinetics are rapid relative to the overall transport process. In order to determine the role of interfacial transfer kinetics in membrane transport, numerous investigators have pursued the measurement of the individual forward and reverse interfacial rate constants (3,4,5). To accomplish this, several types of experimental approaches have been used, each with advantages and disadvantages.

Interfacial transport rate constants are usually determined from one of three basic experimental systems: jets, falling drops and layers. The first system involves the movement of one phase through the other in the form of a jet. Although the effect of unstirred layers is negligible, and the surface areas are well defined, the transport rates must be very fast for use of this system. The movement of drops of one phase through another constitutes the second system (4). A broad range of transport rates can be measured by this technique and surface areas are again well defined. However, the determination of the effect of unstirred layers is difficult to assess (6). The third experimental system began as a layering of solvents based on their specific gravity (two-phase transfer cell). The entire system is mechanically mixed and transport from one phase to the other is measured. Attempts to reduce the thicknesses of the unstirred layers by increasing mixing, results in turbulence and a poorly defined interfacial area (7). This is overcome in the rotating diffusion cell where transport is measured at different rotational speeds (7,8). By extrapolating the transport rates to a theoretical infinite rotation speed, the effect of unstirred layers is eliminated.

The present study utilizes horizontal side-by-side diffusion cells where the solvent phases are separated with a microporous membrane. By controlling the interfacial area in this manner, and being able to quantitate the hydrodynamics of the cells, some of the disadvantages of earlier (9) experimental approaches have been eliminated.

## EXPERIMENTAL

### Materials

Radiolabeled $^{14}$C-n-butanol, $^{14}$C-caffeine, $^{3}$H-dexamethasone, $^{3}$H-l-dopa, $^{3}$H-l-phenylalanine, and $^{3}$H-l-propranolol were obtained from Du Pont NEN® (Boston, MA). $^{3}$H-estrone and $^{14}$C-mannitol were from Amersham (Arlington Heights, IL) and $^{14}$C-enalapril maleate came from Merck Research Laboratories (Rahway, NJ). $^{14}$C-l-tyrosine, Krebs-Henseleit buffer and other non-radiolabeled compounds were purchased from Sigma (St. Louis, MO). In all studies, the buffer phases (pH 7.4 Krebs-Henseleit) and n-octanol phases were saturated with each other before use. The membrane filters were 47 mm diameter PVP-free polycarbonate with 1.0 μm pores from Poretics® Corp. (Livermore, CA). The pore fraction was 0.157 and the thickness averaged 0.0011 cm. The diffusion cells (Precision Instrument Design, Tahoe City, CA) were of a side-by-side design with gas-lift mixing and external blocks for temperature control. Computer modeling of the data utilized the PC based program *Scientist* version 2.0 (MicroMath® Scientific Software, Salt Lake City, UT).

### Methods

#### *Diffusion Coefficient Determinations*

Diffusion coefficients of the compounds in the liquid phases were determined by the method of Taylor-Aris (10,11) using conditions that minimized error (12). A Perkin-Elmer 1020 LC Plus HPLC system was used for these studies with 10 m of 0.0762 cm i.d. stainless steel tubing connecting the ISS-200 autosampler to the LC-135 diode-array detector. Temperature was 25 ± 1°C. Solvent flow from the 250-LC pump was 0.1 ml/min for the buffer phase determinations and 0.05 ml/min for the octanol phase determinations. Injections of 10 μl were made from solutions of the nonradiolabeled compounds in the phase being evaluated. The concentra-

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0724-8741/94/0900-1325$07.00/0 

tions of the injected solutions were approximately 0.7 mM, or at saturation solubility, whichever was less. Detection was at 210 nm for buffer and 220 nm for octanol. The peak retention times were determined by the 1020 integrator and peak widths were measured manually from the chromatogram printouts using 8 and 16 s/mm scales for the buffer and octanol respectively. The diffusion coefficients were then determined from Equation 1, where D is the diffusion coefficient, r is the radius of the capillary tube

$$D = \frac{0.231\ r^2\ t_R}{(W_{1/2})^2} \quad (1)$$

(determined from calibration runs), $t_R$ is the residence time of the solute in the tube, and $W_{1/2}$ is the eluted peak width at half height (13). Calibration runs for the buffer phase used water as the flowing stream and two compounds of known diffusivity in water; benzyl alcohol ($9.46 \times 10^{-6}$ cm$^2$/s)[6] and p-amino benzoic acid (paba) ($8.43 \times 10^{-6}$ cm$^2$/s)[14]. The octanol phase calibration was accomplished with benzyl alcohol ($1.96 \times 10^{-6}$ cm$^2$/s)[15]. Replicate determinations/calibrations were made on different days (n = 2 for buffer, n = 3 for octanol). A molecular volume was calculated for each compound from it's structure using a van der Waals radius based volume program and the Merck High Performance Computing service.

*Unstirred Layer Thickness Determinations*

Polycarbonate membrane filters were cut into 15 × 30 mm rectangular sections and soaked for 1 hour in the solvent under study; either octanol or buffer. The membranes were measured for thickness and assembled between acrylic diffusion half cells (pins located in the cells for securing tissue were removed to allow the membrane and half-cells to seal tightly). The use of an exterior clamp was also required to maintain the seal. After assembly, three cell setups were placed in the supplied temperature block at 25 ± 1°C and the lines from the gas manifold attached. A perfusion of 95:5, $O_2/CO_2$ (routinely used for tissue studies in these cells) was started and the cells were filled with the solvent of interest. For the determination of the octanol unstirred layer thickness, 6.5 ml of octanol were added to each half-cell and the membrane was presoaked with octanol. The rate of gas flow into each half cell was increased to the point to where the individual bubbles could just barely be observed. The study was started with the addition of 2 μCi of $^{14}$C-butanol to one half-cell in each pair. At times of 2, 5, 10, 15, 20 and 25 minutes, 10 μl samples were taken from each donor and receptor half-cell and added to 12.5 ml scintillation cocktail for counting. The buffer unstirred layer studies used a slower gas flow (approximately 140 bubbles/min), membranes presoaked in buffer and $^{14}$C-mannitol as the permeant. Since published values existed for the diffusion coefficient of mannitol in water and not buffer, studies in water were also undertaken.

*Interfacial Transport Studies*

The diffusion cells were assembled as above with membranes soaked in buffer in all cases. After the gas flow was initiated, octanol was added to one half-cell and buffer to the other. Simultaneous filling of the half-cells was required in order to maintain separation of phases across the membrane. The potential for convection due to solvent density differences was minimized by using an equal mass of solvent on each side of the membrane (7.55 ml of the octanol phase and 6.0 ml of the buffer phase). Likewise, the sample volumes withdrawn for analysis were adjusted for density differences (10 μl from the octanol side and 8 μl from the buffer side) and not replaced. The gas flow rates were adjusted to match the rates above for each half-cell, i.e. ~140 bubbles/min for the buffer and the faster rate for the octanol. Each study was initiated with the addition of 2 μCi of the permeant compound to the half-cell selected as the donor. Sample times were as above, and both donor and receiver samples were assayed. Only the larger of the two interfacial constants (octanol-to-buffer or buffer-to-octanol) was measured for each compound. Thus octanol was the donor solvent for all compounds having equilibrium distribution coefficients <1 and buffer was the donor solvent for the rest. For the non-radiolabeled peptides (Phe-Phe and Phe-Phe-Phe), the donor phase was octanol containing 0.05 mg/ml of the peptide prepared before filling the half-cells; sample sizes for HPLC analysis were 30 μl for the buffer side and 37 μl for the octanol side. Only the buffer samples were assayed for these two compounds.

*Equilibrium Distribution Coefficients*

For each of the compounds, approximately 0.2 μCi of the radiolabeled material were added to a glass HPLC vial containing equal volumes (500 μl) of buffer and octanol. The vials were capped, vortexed and mixed by inversion for 24 hours at 25 ± 1°C. Thirty microliters of each phase were then sampled and counted. For the non-radiolabeled peptides, Phe-Phe and Phe-Phe-Phe, 100 μl aliquots of the initial and equilibrium buffer phases were taken and assayed by HPLC. Mean octanol/buffer distribution coefficients were calculated from six replicates.

*HPLC Assay of Peptides*

The assay of the peptides Phe-Phe and Phe-Phe-Phe used the Perkin Elmer system described above with a C-8 Brownlee 100 × 4.6 mm, 5-μm, column, a 3-cm guard column and detection at 210 nm. The mobile phase was acetonitrile:buffer (50 mM $NaH_2PO_4$ with 0.1% $H_3PO_4$) delivered at 1 ml/min. The percentages of buffer in the mobile phase and retention times for Phe-Phe and Phe-Phe-Phe were 80%, 5.5 min, and 60%, 3.1 min, respectively. The injection volume was 20 μl.

## RESULTS AND DISCUSSION

### Diffusion Coefficient Determinations

In the Taylor-Aris method, a small sample (10 μl) of a solution is injected into a stream of solvent (either buffer or n-octanol in the present case) as it flows through a tube. When the flow through the tube is laminar, the combination of flow and diffusion results in a Gaussian distribution of solute concentration along the tube. The retention time and peak width of this distribution is related to the diffusion coefficient of the species in the solvent by Equation 1. The

apparatus is calibrated by measuring retention times and peak widths for compounds of known diffusivity and using Equation 1 to solve for an effective tube radius. For the water studies, radius values of 0.0408 cm and 0.0407 cm were calculated from the p-aminobenzoic acid and benzyl alcohol data, respectively. The octanol calibration with benzyl alcohol gave an effective tube radius of 0.0455 cm. These values are close to the manufacturers stated tube radius of .0381 cm and indicate that contributions to the effective radius due to the injector and detector flow paths and connections are small. With these calibrations in place, the diffusion coefficients of a number of the test compounds in buffer and octanol were determined. A linear regression of 1/volume vs. diffusion coefficient for these compounds gave regression values for slope, intercept and r, respectively, of $4.93 \times 10^{-4}$, $3.1 \times 10^{-6}$ and 0.93 for the buffer and $1.36 \times 10^{-4}$, $4.28 \times 10^{-7}$ and 0.86 for the octanol. The diffusion coefficients of the remaining compounds in buffer and octanol were determined from these regression results and calculated molecular volumes. The measured and calculated (from the regression data) diffusion coefficients are given in Table I.

### Unstirred Layer Thickness Determinations

The unstirred layer thicknesses were determined using a resistance summation approach (16). The total resistance ($R_T$) to transport from the bulk donor phase to the bulk receiver phase is composed of the sums of the resistances of the two unstirred diffusion

$$R_T = 2R_{udl} + R_f \tag{2}$$

layers, $R_{udl}$, and the resistance offered by the liquid filled pores of the filter, $R_f$ as given in Equation 2. The resistances can be further described as in Equation 3 in terms of

$$R_T = \frac{1}{P} = \frac{2h_{udl}}{D} + \frac{h_f}{\alpha D} \tag{3}$$

permeability, P, thicknesses, h, and diffusion coefficients in the solvent used, D. The porosity, $\alpha = 0.157$, accounts for the effective cross sectional area of the membrane. In the current diffusion cell setup, the thickness of the filter ($h_f$) was 0.001 cm, tortuosity was assumed to equal one, and the solvent diffusion coefficients were $6.82 \times 10^{-6}$ cm$^2$/s for mannitol in water (14) or $1.96 \times 10^{-6}$ cm$^2$/s for butanol in octanol (6). Permeabilities were calculated from the donor phase concentrations and the steady state fluxes into the receptor phases. From the permeability values of mannitol in water and in buffer, thicknesses of the unstirred aqueous diffusion layer were calculated to be 176 ± 56 μm (n = 6) and 176 ± 22 μm (n = 6), respectively. The butanol permeability data gave an unstirred octanol diffusion layer thickness of 97.6 ± 9.6 μm (n = 5). This smaller value indicates that the increased mixing in the octanol half-cells more than compensates for the difference in viscosity between octanol and water.

### Interfacial Transport Studies

The flux data of the compounds into the receptor half-cells were treated according to a model based on the resistance summation approach. Permeabilities (P) were calculated from the linear portions of the flux data (assumed steady-state) and used in reciprocal form as the measured total resistance ($R_T = 1/P$). Equation 4 was then used for compounds with distribution coefficients > 1 to describe the transfer of compound from a buffer donor half-cell across the interface to the octanol receptor half-cell. This is similar to the approach used in

$$\frac{1}{P} = \frac{h_{aq}}{D_{aq}} + \frac{h_f}{\alpha D_{aq}} + \frac{1}{\alpha k_1} + \frac{h_o}{D_o K} \tag{4}$$

the rotating diffusion cell (8). The terms in Equation 4 that are summed, describe in order, the individual resistances ascribed to diffusion through the unstirred diffusion layer in

Table I. Physical Parameters Measured or Calculated for Model Compounds

| Compound | Diffusion Coefficient ($\times 10^6$ cm$^2$/s) Buffer | Octanol | Interfacial Constant ($\times 10^3$ cm/s) $k_1$ | Distribution Coefficient K | Molecular Volume (Å$^3$) |
|---|---|---|---|---|---|
| PABA | 7.62[a] | 1.07[a] | — | — | 101 |
| Benzyl Alcohol | 9.37[a] | 1.79[a] | — | — | 90.3 |
| Mannitol | 7.04[b] | 1.47[b] | 0.00173 | 0.00155 | 125 |
| Tyrosine | 6.42[a] | 1.41[b] | 0.00873 | 0.0077 | 137 |
| Phenylalanine | 6.56[a] | 1.46[b] | 0.0255 | 0.024 | 127 |
| Phe-Phe | 5.35[a] | 1.16[b] | 0.0673 | 0.0462 | 234 |
| l-Dopa | 5.89[a] | 1.40[b] | 0.0754 | 0.0634 | 140 |
| Enalapril Maleate | 5.54[a] | 1.04[b] | 0.207 | 0.186 | 270 |
| Caffeine | 7.21[a] | 1.53[a] | 0.834 | 0.68 | 138 |
| Phe-Phe-Phe | 4.56[a] | 1.04[b] | 0.856 | 0.838 | 347 |
| Butanol | 10.4[b] | 2.04[b] | 1.66 | 7.83 | 67.7 |
| Dexamethasone | 4.82[b] | 1.09[b] | 2.32 | 21.3 | 287 |
| Propranolol | 5.13[a] | 1.43[a] | 2.53 | 25.9 | 207 |
| Estrone | 5.39[b] | 1.04[a] | 1.57 | 46.6 | 215 |

[a] Measured value
[b] Regressed value

the aqueous (aq) donor half-cell, the solvent filled pores of the filter (f), the interface, and the unstirred diffusion layer in the octanol (o) receiver half-cell. By substituting known values for the various barrier thicknesses, h, diffusion coefficients, D, and distribution coefficient, K, the equation can be solved for $k_1$, the interfacial buffer-to-octanol transfer rate constant. The units of $k_1$ are distance/time which are the same as for permeability. Equation 5 is the

$$\frac{1}{P} = \frac{h_o}{D_o} + \frac{1}{\alpha\, k_2} + \frac{h_f K}{\alpha\, D_{aq}} + \frac{h_{aq} K}{D_{aq}} \qquad (5)$$

analogous equation for transfer from octanol to buffer where $k_2$ is the interfacial octanol to buffer transfer rate constant. This equation was used for compounds with $K < 1$ and octanol donor phases. With one interfacial rate constant known, the other was calculated from the relationship $K = k_1/k_2$. In both equations, the membrane is assumed to contain the buffer phase. The $k_1$ constants determined from the method are given in Table I and show a trend with the distribution coefficient data.

This relationship between observed interfacial rate constants and distribution coefficients was first observed by Kubinyi (17) who developed equations that described the behavior. The equations were refined by Van de Waterbeemd et al. (18) to give the forms shown in Equations 6–8. The term log $k_{aq}$ is the plateau value that log $k_1^{obs}$ approaches at high values of PC, the partition coefficient. Similarly, log $k_2^{obs}$ approaches log $k_{org}$ at low values of PC.

$$\log k_1^{obs} = \log PC - \log (\beta * PC + 1) + \log k_{org} \qquad (6)$$

$$\log k_2^{obs} = -\log (\beta * PC + 1) + \log k_{org} \qquad (7)$$

$$\beta = \frac{k_{org}}{k_{aq}} \qquad (8)$$

The distribution coefficients and interfacial rate constants given in Table I were fit to Equations 6 and 7 using the nonlinear least squares regression option in *Scientist*. Values of −2.900 and 0.558 were determined for the floated terms log $k_{org}$ and β, respectively. These values are used with equations 6 and 7 to generate the solid lines overlaying the interfacial transfer constant data in Figure 1.

Two additional models were evaluated for generation of interfacial transfer constants from the flux data. One model accounted for the individual barriers in terms of reversible steps for which differential equations were written that described the mass flux. The other model was a simple A ⇄ B reversible system which used macro constants for the transfer of mass to and from the donor and receptor compartment. Both models generated transfer constants with units of reciprocal time. Although detailed results for the other two models are not presented in this report, all three models performed well in the determination of the interfacial transfer constants. A fitting of these two sets of data to the theoretical Equations 6 and 7 gave log $k_{org}$ values of −4.136 and −3.770, and β values of 0.674 and 0.482 for the multi-equation and A ⇄ B models, respectively. For all three models, the fit of the data to Equations 6 and 7 was good ($r^2 >$ 0.999) although it must be remembered that the relationship $K = k_1/k_2$ was assumed and used to calculate one of the constants for each compound.

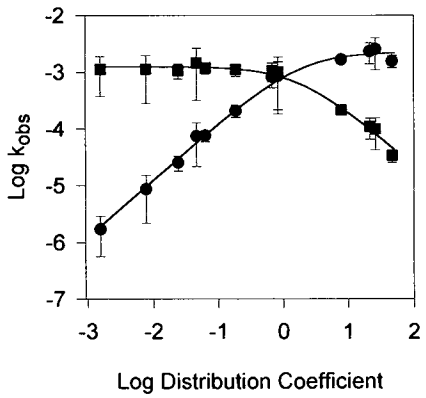


Figure 1. Interfacial $k_1$ (●) and $k_2$ (■) transfer constants (±s.d.) from Model I. Solid lines are the best fit of the data to Equations 6 and 7.

An interpretation of the significance and physical descriptions of the parameters $k_{org}$, $k_{aq}$, and β has been put forth in the literature (19). The term β is described as reflecting a ratio of diffusion rate constants associated with the hydration-solvation process at the interface. For systems such as the A ⇄ B model, $k_{org}$ and $k_{aq}$ (and so β) are system parameters independent of the solute. They depend on temperature, stirring rate and the solvents used. Van de Waterbeemd (19) has determined values for these system parameters in a number of solvent systems using a two phase transfer cell. For a series of sulfonamides in an octanol-water system (18), values of 0.406 and −3.996 were found for β, and log $k_{org}$ respectively. Comparing these values to those for the A ⇄ B model (comparable system) shows reasonable agreement. The deviation in values probably represent differences in the hydrodynamics of the apparatus used. For further comparisons or interpretation of the parameters, the reader is referred to the literature (19,20,21,22).

## CONCLUSIONS

Results of this study suggest that the side-by-side diffusion cell setup is a viable alternative to existing methods for the determination of interfacial transfer constants. Its utility is enhanced due to commercial availability of the apparatus, fixed interfacial surface area and measurable hydrodynamics. Flux data generated by the cell setup can be successfully handled by several models with the choice being determined by the nature of the data (steady state or not) and the type of output desired (macro- or micro-constants and units).

## ACKNOWLEDGMENTS

I wish to thank Mr. John Breth, Ms. Geri Kay Hart, and Mr. Trenton Knewtson for their technical assistance.

## REFERENCES

1. G. L. Flynn, and R. W. Smith. Membrane diffusion. 3. Influ-

ence of solvent composition and permeant solubility on membrane transport. *J. Pharm. Sci.* **61**,61–66 (1972).
2. R. W. Schrage. *A Theoretical Study of Interphase Mass Transfer;* Columbia University Press, New York, 1953.
3. R. H. Guy and D. H. Honda. Solute transport resistance at the octanol-water interface. *Int. J. Pharm.* **19**:129–137 (1984).
4. D. M. Miller. The measurement of the rate of transport of solutes in both directions across the aqueous-nonaqueous liquid interface and its significance to membrane permeability. *Biochim. Biophys. Acta* **856**:27–35 (1986).
5. K. M. S. Fahelelbom, J. M. Quigley, R. F. Timoney, and O. I. Corrigan. Thermodynamics of the distribution and interfacial transfer kinetics of antimicrobial iminophenazines in a two-phase system of n-octanol/aqueous buffer. *Proc. R. Ir. Acad.* **89B**:287–298 (1989).
6. D. M. Miller. Determination of the thickness of the unstirred layers in the moving-drop method for measuring aqueous-nonaqueous interfacial transport rates. *Biochim. Biophys. Acta* **1065**:69–74 (1991).
7. P. R. Byron, and M. J. Rathbone. Prediction of interfacial transfer kinetics. II. Solute ionization and aqueous phase ionic strength effects in two-phase transfer and rotating diffusion cells. *Int. J. Pharm.* **29**:103–111 (1986).
8. W. J. Albery, J. F. Burke, E. B. Leffler, and J. Hadgraft. Interfacial transfer studies with a rotating diffusion cell. *Chem. Soc. Faraday I* **72**:1618–1626 (1976).
9. D. F. Sears. Solute transfer across liquid-liquid interfaces. In L. M. Prince and D. F. Sears (eds.), *Biological Horizons in Surface Science,* Academic Press: New York, 1973.
10. G. I. Taylor. Dispersion of soluble matter in solvent flowing slowly through a tube. *Proc. R. Soc. London, Ser. A* **219**:186–203 (1953); Conditions under which dispersion of a solute in a stream of solvent can be used to measure molecular diffusion. *Ibid.* **225**:473–477 (1954).
11. R. Aris. On the dispersion of a solute in a fluid flowing through a tube. *Proc. R. Soc. London, Ser. A.* **235**:67–77 (1956).
12. K. C. Pratt and W. A. Wakeham. The mutual diffusion coefficient of ethanol-water mixtures: determination by a rapid, new method. *Proc. R. Soc. London, Ser. A* **336**:393–406 (1974); The mutual diffusion coefficient for binary mixtures of water and the isomers of propranolol. *Ibid.* **342**:401–419 (1975).
13. E. Grushka and J. Kikta Jr. Extension of the chromatographic broadening method of measuring diffusion coefficients to liquid systems. I. Diffusion Coefficients of some alkylbenzenes in chloroform. *J. Phys. Chem.* 78:2297–2301 (1974).
14. D. R. Lide (ed.). *C.R.C. Handbook of Chemistry and Physics, 53rd ed.,* CRC Press: Boca Raton, FL, 1985 section 6 p. 151.
15. D. M. Miller. Evidence that interfacial transport is rate-limiting during passive cell membrane permeation. *Biochim. Biophys. Acta* **1065**:75–81 (1991).
16. B. J. Zwolinski, H. Eyring, and C. E. Reese. Diffusion and membrane permeability. I. *J. Phys. Chem.* **53**:1426–1453 (1949).
17. H. Kubinyi. Lipophilicity and drug activity. In E. Jucker (ed.), *Progress in Drug Research,* Birkhäuser Verlag, Stuttgart, 1979.
18. J. T. M. Van de Waterbeemd, C. C. A. A. Van Boeckel, R. L. F. M. De Sévaux, A. C. A. Jansen, and K. W. Gerritsma. Transport in QSAR. IV. The interfacial drug transfer model. Relationships between partition coefficients and rate constants of drug partitioning. *Pharm. Weekbl. Sci. Edn.* 3:12–25 (1981a).
19. H. Van de Waterbeemd. The theoretical basis for relationships between drug transport and partition coefficient. In J. C. Dearden (ed.), *Quantitative Approaches to Drug Design,* Elsevier Science Publishers B. V., Amsterdam, 1983.
20. H. Van de Waterbeemd, S. Van Boeckel, A. Jansen, and K. Gerritsma. Transport in QSAR II. Rate-equilibrium relationships and the interfacial transfer of drugs. *Eur. J. Med. Chem.* **15**:279–282 (1980).
21. J. Th. M. Van de Waterbeemd and A. C. A. Jansen. Transport in QSAR. V. Application of the interfacial drug transfer model. *Pharmaceut. Weekbl. Sci. Ed.* 3:1081–1082 (1981).
22. H. Van de Waterbeemd, P. Van Bakel, and A. Jansen. Transport in quantitative structure-activity relationships. VI. Relationship between transport rate constants and partition coefficients. *J. Pharm. Sci.* 70:1081–1082 (1981b).