Lipophilicity, Molecular Weight, and Drug Action: Reexamination of Parabolic and Bilinear Models

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Received October 4, 1979, from the *Section of Biomedicinal Chemistry, School of Pharmacy, University of Southern California, Los Angeles, CA 90033.* Accepted for publication January 7, 1980.

Abstract □ The effect of molecular weight on drug diffusion and drug action has been described based on the relation $D = (RT/6\pi\eta N)(\sqrt[3]{4\pi N/3M\bar{v}})$, an inverse relation between the clearance of drugs through artificial membranes and molecular weights, and apparent correlations between log (1/dose) and log mol. wt. for various central nervous system-acting drugs, anticancer drugs, and water-soluble vitamins. *In situ* rat jejunum permeability data of various drugs were correlated with log P (octanol–buffer) and log mol. wt. A parabolic equation of log P combined with log mol. wt. proposed previously was shown to give significant correlations for hydrolysis data of amides and antifungal data of amines. This model is mathematically simpler and easier to interpret than the more complex curvilinear and bilinear models.

Keyphrases □ Molecular weight—effect on drug diffusion and activity, parabolic model □ Diffusion—effect of molecular weight, parabolic model □ Structure–activity relationships—effect of molecular weight, parabolic model

While the importance of lipophilicity (partition coefficient) in drug action has been well recognized (1, 2), the effect of molecular weight on the biological activity of drugs has not been appreciated fully. This report discusses the rationale of including a log mol. wt. term in quantitative structure–activity correlations by using specific examples of drug absorption data and *in vitro* biological data. Statistical analysis is employed to assess the significant contribution of the log mol. wt. term above and beyond the contribution from lipophilicity (log P).

MATHEMATICAL MODELS

Few of the various mathematical models developed (3–12) include the effect of the change in molecular weight among homologs, analogs, or congeners (13, 14). Several of these models are discussed here.

Model A—A parabolic model based on a nonsteady-state theory (3–5):

$$\log 1/C = -k(\log P)^2 + k' \log P + k'' \qquad \text{(Eq. 1)}$$

where C is the drug concentration required to produce a standard biological response (*e.g.*, ED_{50} and I_{50}), P is the 1-octanol–water partition coefficient, and k, k', and k'' are derived by the least-squares method.

Model B—The curvilinear model of Franke and Oehme (7):

$$\log 1/C = a \log P + b \qquad \text{for } \log P < \log P_x \qquad \text{(Eq. 2a)}$$

$$\log 1/C = \alpha(\log P)^2 + \beta(\log P) + \gamma \qquad \text{for } \log P > \log P_x \qquad \text{(Eq. 2b)}$$

where α, β, and γ are derived by least-squares fit and P_x is the limit of the straight line.

Model C—A bilinear model (8, 9):

$$\log 1/C = a \log P - b \log(\beta P + 1) + c \qquad \text{(Eq. 3)}$$

where a, b, β, and c are coefficients derived from the regression analysis.

Model D—The Hyde model (10):

$$\log C = \text{constant} + \log(a + 10^{-\pi}) \qquad \text{(Eq. 4)}$$

where π is the Hansch π constant.

Model E—The Higuchi–Davis model (equilibrium model) (11):

$$D = C_w V_w + \sum_{i=1}^{i=t} C_i V_i \qquad \text{(Eq. 5)}$$

$$C_w = \frac{D}{V_{aq} + P_i V_i} \qquad \text{(Eq. 6)}$$

$$C_r = C_w P_r = \frac{DP_r}{V_w + \sum_{i=1}^{i=t} P_i V_i} \qquad \text{(Eq. 7)}$$

where D is the amount of drug, C_w is the concentration in the water phase, C_r is the drug concentration on the receptor, and $P_i = C_i/C_w$.

Model F—The asymptotic model of Ho *et al.* (12):

$$P^*_{app} = \frac{1}{\frac{1}{P^*_{aq}} + \frac{1}{P^*_p + P^*_{e,lipid}}} \qquad \text{(Eq. 8)}$$

where P^*_{app} is the predicted apparent permeability coefficient; P^*_{aq}, P^*_p, and $P^*_{e,lipid}$ are the permeability coefficients of the aqueous diffusion layer, aqueous pores, and lipid membrane diffusion–bioconversion pathway, respectively; and $P^*_{e,lipid} = (10^{n\pi}/X_s)$, where X_s is the fraction of the undissociated form.

Model G—The Lien model (13):

$$\log \%\,\text{Abs. or } \log k = -k_1(\log P)^2 + k_2(\log P) + m[\log(U/D)] + n(\log \text{mol. wt.}) + q(\log \chi) + k_3 \qquad \text{(Eq. 9)}$$

where U/D = (pKa − pH) for acids and χ is a parameter to account for branching or stereochemical factors.

Regardless of the fact that in many instances there is a high degree of covariance between the partition coefficient (log P) and the molecular weight (log mol. wt.) while in other cases there may not be a wide spread in the molecular weight, the molecular weight may affect both *in vitro* drug diffusion and *in vivo* drug action in the following ways:

1. An inverse relationship exists between the diffusion coefficient (D) and the molecular weight [(mol. wt.)$^{1/3}$] according to the Sutherland and Einstein equation:

$$D = \frac{RT}{6\pi\eta r N} = \frac{RT}{6\pi\eta N}\sqrt[3]{\frac{4\pi N}{3M\bar{v}}} \qquad \text{(Eq. 10)}$$

where η is the viscosity of the solution, r is the radius of the spherical particle, N is Avogadro's number, $\bar{v}$ is the partial specific volume in cubic centimeters per gram of the solute, and M is the molecular weight (15, 16).

2. An inverse relationship exists between log clearance and log mol. wt. for clearance through artificial membranes and possibly through biological membranes and the kidneys as well according to (17):

$$\log \text{clearance} = -0.432 \log \text{mol. wt.} + 2.701 \qquad n = 6 \quad r = 0.997 \quad s = 0.016 \qquad \text{(Eq. 11)}$$

for drugs with molecular weights less than 1000.

3. Direct apparent correlations appear to exist between log (1/dose) and log mol. wt. of various central nervous system-acting drugs, anticancer drugs, and water-soluble vitamins (14).

Accumulated data have shown that in many cases where a bilinear model gives a better correlation than a parabolic model, one can obtain equally good correlation simply by including a log mol. wt. term in the equation. Furthermore, when log $1/C$ or log K is corrected for the difference in log mol. wt., a bilinear dependence on log P usually is restored to a parabolic dependence (or only part of a parabola) (Eqs. 12–21 and Figs. 1–3).

RESULTS AND DISCUSSION

The biological data and the physicochemical constants used in the regression analysis are summarized in Tables I–III.

Equations 12–17 were derived from the data of Ho *et al.* (12). Since

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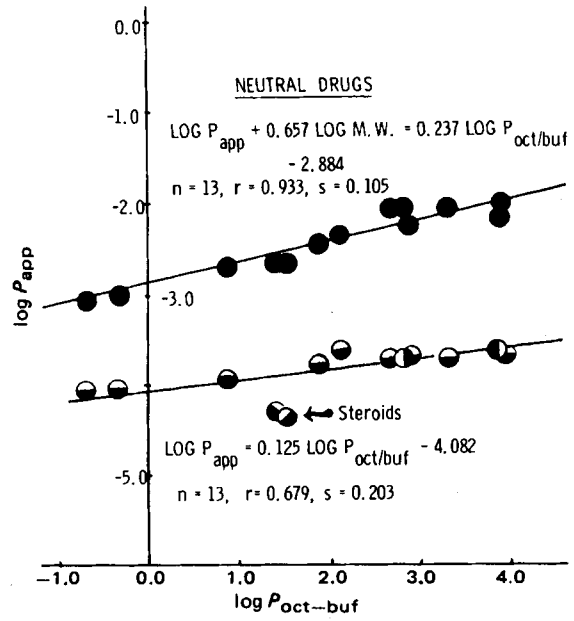

Figure 1—*Linear dependence of the apparent permeability coefficient on the uncorrected octanol–buffer (pH 6.0) partition coefficient for 13 neutral compounds. Lower permeability coefficients (log P_{app}) for the steroids result when the log mol. wt. term is not included.*

the uncorrected octanol–buffer (pH 6.0) partition coefficients were used, no apparent correlation could be obtained when both neutral and acidic drugs were included. When these two groups were separated, statistically highly significant correlations were obtained, as judged from the correlation coefficient r and the standard deviation s of the regression for permeability (log P_{app}) through the rat jejunum with high stirring (12).

For both neutral and acidic drugs, the equations are:

$$\log P_{app} = 0.090 \log P_{(oct\text{-}buf)} - 3.967$$
$$n = 24 \quad r = 0.407 \quad s = 0.258 \qquad \text{(Eq. 12)}$$

$$\log P_{app} = 0.183 \log P_{(oct\text{-}buf)} - 0.689 \log \text{mol. wt.} - 2.627$$
$$n = 24 \quad r = 0.740 \quad s = 0.195 \qquad \text{(Eq. 13)}$$

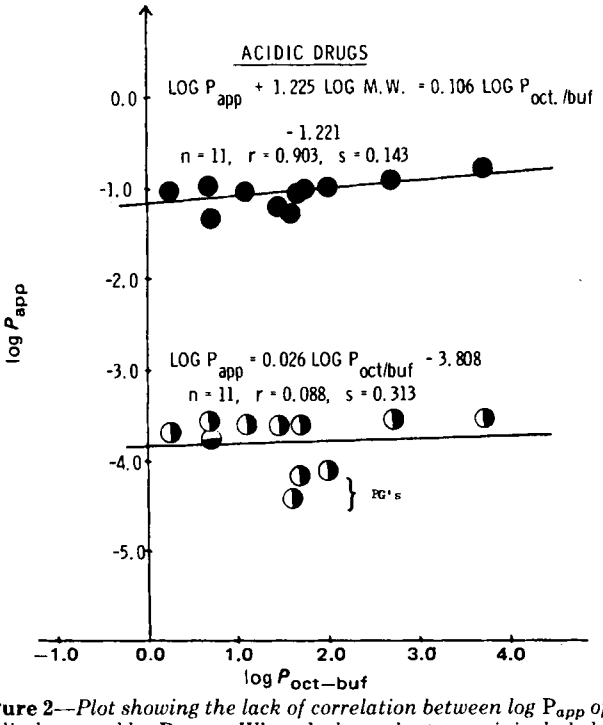

Figure 2—*Plot showing the lack of correlation between log P_{app} of 11 acidic drugs and log $P_{oct\text{-}buf}$. When the log mol. wt. term is included, the correlation becomes statistically significant.*

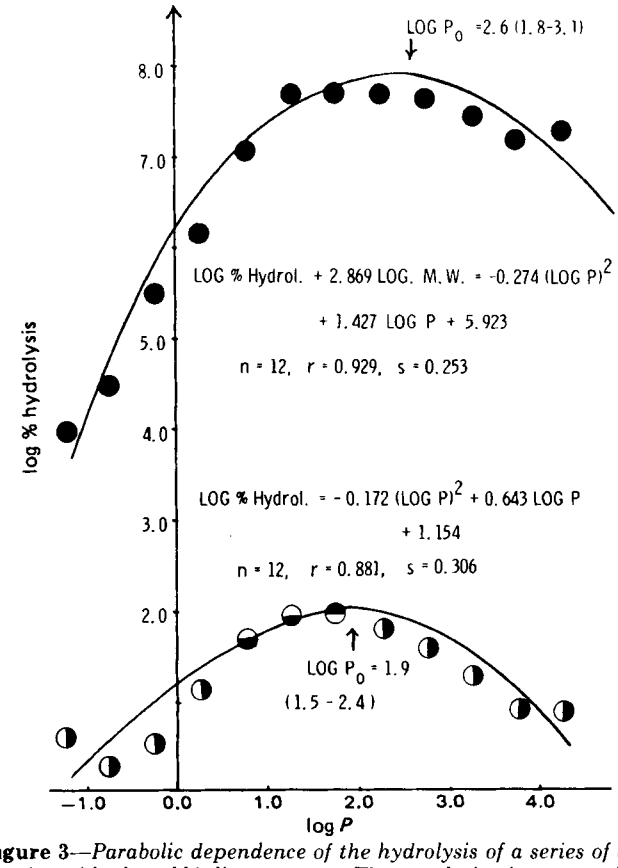

Figure 3—*Parabolic dependence of the hydrolysis of a series of aliphatic amides by rabbit liver extracts. The correlation improves when the log mol. wt. term is included.*

For neutral drugs only, they are:

$$\log P_{app} = 0.125 \log P_{(oct\text{-}buf)} - 4.082$$
$$n = 13 \quad r = 0.679 \quad s = 0.203 \qquad \text{(Eq. 14)}$$

$$\log P_{app} = 0.237 \log P_{(oct\text{-}buf)} - 0.657 \log \text{mol. wt.} - 2.884$$
$$n = 13 \quad r = 0.933 \quad s = 0.105 \qquad \text{(Eq. 15)}$$

For acidic drugs only, they are:

$$\log P_{app} = 0.026 \log P_{(oct\text{-}buf)} - 3.808$$
$$n = 11 \quad r = 0.088 \quad s = 0.313 \qquad \text{(Eq. 16)}$$

$$\log P_{app} = 0.106 \log P_{(oct\text{-}buf)} - 1.225 \log \text{mol. wt.} - 1.221$$
$$n = 11 \quad r = 0.903 \quad s = 0.143 \qquad \text{(Eq. 17)}$$

The log mol. wt. term is significant at the 99.95 percentile level in Eqs. 15 and 17 as indicated by an F test ($F_{1,10} = 31.4$ and $F_{1,8} = 35.1$, respectively).

For the limited data available, addition of the $(\log P)^2$ term did not result in significant improvement in the correlation.

Equations 18 and 19 were derived from the data of Bray *et al.* (18) on the hydrolysis of aliphatic amides by amidase from rabbit liver extract:

$$\log \% \text{ hydrolysis} = -0.172 (\log P)^2 + 0.643 \log P + 1.154$$
$$n = 12 \quad r = 0.881 \quad s = 0.306 \qquad \text{(Eq. 18)}$$

$$\log \% \text{ hydrolysis} = -0.274 (\log P)^2 + 1.427 \log P - 2.869 \log \text{mol. wt.} + 5.923$$
$$n = 12 \quad r = 0.929 \quad s = 0.253 \qquad \text{(Eq. 19)}$$

The addition of the log mol. wt. term to the parabolic equation of log P again significantly improves the correlation at the 90 percentile level ($F_{1,8} = 5.12$).

Equations 20 and 21 were derived from the antifungal data of a series of aliphatic amines against *Rhinocladium beurmanni* (19):

$$\log 1/C = -0.199 (\log P)^2 + 2.119 \log P - 1.382$$
$$n = 15 \quad r = 0.967 \quad s = 0.354 \qquad \text{(Eq. 20)}$$

Table I—*In Situ* Permeability Coefficients and Physicochemical Constants Used in the Regression Analysis for Rat Jejunum Data

Compound	log P_{app}, cm/sec Exp.[a]	log P_{app}, cm/sec Calc.[b]	log mol. wt.	log P (oct–buf)[a]
Neutral				
Methanol	−4.036	−4.029	1.506	−0.66
Ethanol	−4.081	−4.052	1.663	−0.32
Butanol	−3.896	−3.904	1.870	0.88
Hexanol	−3.726	−3.758	2.009	1.88
Octanol	−3.609	−3.591	2.115	2.88
Decanol	−3.597	−3.414	2.205	3.88
Hydrocortisone	−4.310	−4.202	2.559	1.53
Prednisolone	−4.292	−4.227	2.557	1.42
Progesterone	−3.635	−3.601	2.498	3.90
Benzene	−3.558	−3.623	1.893	2.13
Acidic				
Prostaglandin F_2	−4.377	−4.175[c]	2.550	1.60
Prostaglandin E_2	−4.167	−4.162	2.547	1.69
Prostaglandin E_1	−4.081	−4.133	2.550	2.00
Butyric acid	−3.726	−3.525	1.945	0.74
Hexanoic acid	−3.578	−3.566	2.065	1.74
Octanoic acid	−3.530	−3.575	2.159	2.74
Decanoic acid	−3.506	−3.564	2.236	3.74
Phenol	−3.616	−3.484	1.974	1.46
Benzoic acid	−3.587	−3.660	2.087	1.11
Phenylacetic acid	−3.585	−3.761	2.134	0.70
Salicylic acid	−3.668	−3.813	2.140	0.28

[a] Taken from Ref. 12. [b] Calculated from Eq. 15. [c] Calculated from Eq. 17.

Table II—Hydrolysis of Aliphatic Amides by Rabbit-Liver Extracts and Physicochemical Parameters Used in the Regression Analysis

Amide	log % Hydrolysis Exp.[a]	log % Hydrolysis Calc.[b]	log mol. wt.	log P (oct–water)[c]
CH_3	0.602	0.418	1.177	−1.21
C_2H_5	0.301	0.574	1.463	−0.71
C_3H_7	0.544	0.617	1.741	−0.21[d]
C_4H_9	1.114	1.273	1.757	0.29
C_5H_{11}	1.748	1.566	1.852	0.79
C_6H_{13}	1.964	1.605	1.988	1.29
C_7H_{15}	1.964	1.873	1.996	1.79
C_8H_{17}	1.806	1.860	2.054	2.29
C_9H_{19}	1.597	1.731	2.105	2.79
$C_{10}H_{21}$	1.255	1.481	2.150	3.29
$C_{11}H_{23}$	0.903	1.106	2.191	3.79
$C_{12}H_{25}$	0.903	0.602	2.229	4.29

[a] Taken from Ref. 18. [b] Calculated from Eq. 19. [c] Calculated from the value of $C_3H_7CONH_2$ by subtracting or adding 0.50 for each CH_2 unit. [d] Experimentally determined value taken from A. Leo, C. Hansch, and D. Elkins, *Chem. Rev.*, **71**, 525 (1971).

$$\log 1/C = -0.499 (\log P)^2 + 8.010 \log P - 42.691 \log \text{mol. wt.} + 74.281$$
$$n = 15 \quad r = 0.994 \quad s = 0.161 \qquad \text{(Eq. 21)}$$

The log mol. wt. term in Eq. 21 is significant at the 99.95 percentile level ($F_{1,11} = 46.7$). The relatively large coefficient associated with the log mol. wt. term and the large constant term in Eq. 21 probably are due to the fact that the log mol. wt. values range only from 1.864 to 2.431. Similarly, high coefficients were obtained for many other sets of antimicrobial data from the same and other sources. In some cases when the parabolic equation of log P gave an almost perfect correlation ($r \geq 0.97$), the addition of the log mol. wt. term did not further improve the correlation. In reality, when one considers the experimental errors involved, a correlation coefficient of ~0.95–0.97 (r^2 of ~0.90–0.94) probably is the maximum limit one should expect.

The data suggest that the semiempirical model of Lien (13) can be used when there is a fairly wide spread in the molecular weights of the drug molecules. The advantages of this model are the simplicity of the mathematical equation (one can use any standard linear or nonlinear regression programs) and the more understandable physical meaning linking diffusion and molecular weight.

Table III—Antifungal Activities of Aliphatic Amines against *Rhinocladium beurmanni* and Physicochemical Constants Used in the Correlation

Amine	log 1/C, M Exp.[a]	log 1/C, M Calc.[b]	log mol. wt.	log P (oct–water)[c]
C_4H_9	0.663	0.866	1.864	0.81
C_5H_{11}	1.190	1.098	1.940	1.31
C_6H_{13}	1.675	1.551	2.005	1.81
C_7H_{15}	2.151	2.095	2.062	2.31
C_8H_{17}	2.621	2.732	2.111	2.81
C_9H_{19}	3.075	3.290	2.156	3.31
$C_{10}H_{21}$	3.536	3.770	2.197	3.81
$C_{11}H_{23}$	3.983	4.171	2.234	4.31
$C_{12}H_{25}$	4.388	4.451	2.268	4.81
$C_{13}H_{27}$	4.629	4.567	2.300	5.31
$C_{14}H_{29}$	4.709	4.562	2.329	5.81
$C_{15}H_{31}$	4.397	4.350	2.357	6.31
$C_{16}H_{33}$	3.882	3.974	2.383	6.81
$C_{17}H_{35}$	3.307	3.434	2.407	7.31
$C_{18}H_{37}$	2.530	2.645	2.431	7.81

[a] Taken from Ref. 19. [b] Calculated from Eq. 21. [c] Taken from E. J. Lien, C. Hansch, and S. M. Anderson, *J. Med. Chem.*, **11**, 430 (1968); higher homologs were calculated by adding 0.50 for each CH_2 unit.

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ACKNOWLEDGMENTS

Presented in part at the APhA Academy of Pharmaceutical Sciences, Washington, D.C. meeting, April 1980.

Supported in part by National Institutes of Health Biomedical Research Support Grant 5 S07 RR05792 03.