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Understanding and Estimating Membrane/Water Partition Coefficients: Approaches To Derive Quantitative Structure Property Relationships

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In the current study we describe three approaches to derive quantitative structure property relationships (QSPRs) that give insight in the interactions that are important in membrane/water partitioning. In the first model only semiempirically (AM1) calculated descriptors are used to model membrane/water partition coefficients. Additionally, differences between the *n*-octanol/water and membrane/water partition coefficients are explored using a small selection of calculated descriptors. The results from both these models show that besides the partitioning between an organic phase and water, additional hydrogen-bonding parameters (ϵ_{LUMO}, Q^-, and Q^+) should be taken into account. Finally, using structural fragment values, a QSPR was derived to correct the *n*-octanol/water partition coefficient to obtain membrane/water partition coefficients, in case that obtaining AM1 descriptors is not feasible. The QSPRs that are presented here include only alcohols, benzenes, anilines, phenols, nitrobenzenes, quinoline, esters, and amines. Due to the data limitation, the models should be regarded preliminary for other structures, and caution is necessary when modeling charged species.

Introduction

In pharmacology, properties of drugs are optimized to give a maximum effect, while in toxicology these properties are used to explain processes involved in the toxic action. The pharmacological or toxicological effect of a chemical is the result of both kinetic factors, i.e., transport to the target, as well as dynamic factors, i.e., the affinity for the receptor compared to the solvating medium, e.g., blood or interstitial water. An increase in affinity and even specificity can be achieved by modifying the chemical structure, thereby changing chemical and physicochemical properties, to increase energetically favorable interactions of a chemical with its receptor.

Interactions may vary from very specific to nonspecific and from hydrogen bonding to hydrophobic binding. Hydrophobicity, i.e., the aversion of a chemical to reside in an aqueous phase, can be interpreted in pharmacology and toxicology as the tendency of a chemical to interact

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nonspecifically with an energetically more favorable phase. It is well-known that hydrophobicity determines interactions with hydrophobic pockets in proteins, lipoid phases in tissue, or the hydrophobic core in cell membranes. Therefore, hydrophobicity parameters are of great interest for toxicodynamic as well as toxicokinetic studies of xenobiotics.

As early as 1899, Meyer (*1*) and Overton (*2*) discovered that general anesthetic potency of simple compounds showed a good correlation with the olive oil/water partition coefficient. Ever since that time, partition coefficients have been used as a general parameter in pharmacological as well as toxicological studies to model effect-concentrations and kinetic behavior in biological systems (*3, 4*). In general, partition coefficients can be interpreted as parameters that reflect the interaction of a chemical with the target site on the receptor, or the concentration ratio between the target and the aqueous phase. Since numerous solvents with widely differing physicochemical properties are available, it should not come as a surprise that different partition coefficients can be used to describe different processes or interactions, as elegantly shown by Leahy et al. (*5*−*7*). Nevertheless, partition coefficients are mostly used to model the hydrophobic nature of chemicals.

The most frequently used partition coefficient by far is that between *n*-octanol and water, log K_{ow}. This parameter has been shown to correlate with numerous physical and biological processes: interactions with proteins (*3, 8*), kinetics and partitioning between aqueous and lipoid phases (*5, 9, 10*), partition coefficients for dissolved organic matter (DOC)/water (*11*), partition coefficients between tissue and blood for physiologically based pharmacokinetic (PBPK) modeling (*12*), and of course partition coefficients between biological membranes and water (*13, 14*). The latter is of major importance in toxicology, since it is directly related to membrane permeation rates and narcotic toxicity of various chemicals (*4, 15, 16*).

In the current study we want to focus on the modeling of membrane/water partition coefficients. We have already shown that membrane/water partition coefficients can be used to predict the toxicity of both polar and nonpolar chemicals with a nonspecific mode of action, to fish (*17*). Additionally, Cantor described a physical mechanism of general anesthesia involving protein inhibition through accumulation into membranes (*18*).

Recently, we showed that the assumption that log K_{ow} is a good surrogate parameter for membrane/water partitioning (log $K_{DMPC,water}$) should be used with caution, especially with polar chemicals (*19*). Nevertheless, several papers have been published that describe the successful use of log K_{ow} for modeling membrane/water partition coefficients (*13, 14, 20*). The explanation for these successful efforts in the past lies mostly in the use of homologous series and relatively simple molecular structures, thereby excluding polar groups.

In this paper we want to show the results of a more in-depth survey, performed to gain insight in the fundamental processes that are responsible for differences in membrane/water partition coefficients of molecules with a variety of substructures. In addition, we will explore causes of differences between log K_{ow} and log $K_{DMPC,water}$. Models will be presented to predict the membrane/water partition coefficient using log K_{ow}, semiempirically calculated parameters, and structural fragment values.

Theory

In this paper, three modeling approaches will be discussed. First, membrane/water partitioning will be described in terms of only quantum chemically calculated descriptors, to gain information on relative importances of different interactions. Subsequently, a comparison will be made between *n*-octanol/water and membrane/water partition coefficients using a limited set of selected calculated descriptors. Last, structural fragment values will be derived to complement currently used algorithms to calculate log K_{ow} and make them applicable to calculate log $K_{DMPC,water}$. The theoretical background of these three approaches is presented below.

Modeling Membrane/Water Partition Coefficients. The partitioning of a molecule between two phases is a direct consequence of the difference between the Gibbs free energy of solvation of said molecule in these phases. For example, the Henry's constant of a compound is directly related to the free energy difference between the vapor 'dissolved in air' and the aqueous solvated phase. The difference of the Gibbs free energy between two solvated states is due to differences in favorable and unfavorable interactions between the media and the solute.

Several authors have tried to explain and quantify different interactions between molecules. Hammett introduced the substituent constant σ as an electronic parameter (*21*), and later Hansch et al. developed, with a similar approach, the hydrophobicity substituent constant π (*22*), while Taft (*23*) devised the steric parameter E_S. More recently, Abraham et al. (*24, 25*) introduced overall hydrogen bond acidity (α_2^H) and basicity (β_2^H) parameters to account for hydrogen-bonding interactions of solutes. Although all these parameters are actively used in quantitative structure−activity relationship (QSAR) analyses, in recent years there has been a shift from purely empirical descriptors to quantum chemically calculated molecular properties. The advantage of theoretically calculated descriptors over the earlier mentioned empirical parameters is the possibility to calculate the parameters and to apply them to sets of structurally diverse compounds, including hypothetical compounds. We will study the possibility to use semiempirically calculated molecular properties and solvation energies to model membrane/water partition coefficients.

Using solvation energies and free energy cycles, partition coefficients can be calculated according to (*26*):

$$\log K_{A/B} = \frac{\Delta G_B - \Delta G_A}{2.303RT} \qquad (1)$$

where ΔG_A, ΔG_B, and $K_{A/B}$ are the solvation free energies in solvent A and in solvent B and the partition coefficient between solvent A and B, respectively.

Since the denominator in this expression is a constant, we can approach the particular case for the membrane/water partition coefficient that is described here as follows:

$$\log K_{DMPC,water} \propto \Delta G_{S,aq} - \Delta G_{S,DMPC} \qquad (2)$$

Thus, the membrane/water partition coefficient is directly proportional to the difference between the aqueous ($\Delta G_{S,aq}$) and membrane ($\Delta G_{S,DMPC}$) solvation energies. Hawkins et al. (*27*) reported a parametrized model to calculate aqueous solvation energies ($\Delta G_{S,aq}$) using

semiempirical Hamiltonians. Recently, we reported a model to calculate membrane solvation energies semiempirically (*28*), using a modified model from Giesen (*26*). This model, however, does not give explicit information about the relative importances of different interactions that are described hereafter. Therefore, we will derive an expression to model the relative importances of favorable and unfavorable interactions that play a role in membrane/solute interactions.

Recently, Jin and Hopfinger (*29*) characterized the structure of phospholipid membranes using molecular dynamics simulations. They described the membrane as a three-zone liquid, where each zone showed different diffusion characteristics. In the first or outermost zone, which includes the polar headgroups, hydrogen bonding may play a role in the diffusion process. The second intermediate zone mainly consists of hydrocarbon chains with a high conformational order, and therefore the density and size of free volume sites are limited. The most internal zone, zone 3, exhibits properties similar to hydrocarbon solvents. On the basis of this model, and assuming that diffusion at equilibrium is governed by these same processes, we will formulate a basic approach to model membrane/water partitioning in terms of calculated descriptors only.

Analogous to Cramer et al. (*30*), hydrogen-bonding properties of the first zone can be described using four parameters that together form a complete set of theoretically possible hydrogen-bonding interactions. Q^+ and Q^-, the most positive charge on any hydrogen atom and the most negative charge on any non-hydrogen atom in the molecule, respectively, are used to describe the ionic contribution of the solute to hydrogen bonding. In addition, ϵ_{LUMO} and ϵ_{HOMO}, i.e., the energy of the lowest unoccupied molecular orbital and the energy of the highest occupied molecular orbital, respectively, describe the energies of electron-accepting and -donating orbitals, and therefore these energies will be used to describe the covalent part of hydrogen bonding. In the intermediate zone, where because of the high conformational order crowding is a major issue according to Jin and Hopfinger (*29*), the volume of the solute might be the most important factor determining the solvation process. The interactions in the internal zone will be described by calculating the solvation energy ($\Delta G_{S,C16}$) for *n*-hexadecane (*31*), since membrane properties at this location are similar to those of hydrocarbon solvents.

All these separate interactions can be considered to contribute to the overall interaction with the membrane phase. None of these interactions plays a role in the gas phase. Therefore, a linear combination of these parameters, analogous to Cramer et al. (*30*), will be used to model the membrane solvation energy. Although there is no a priori information about the linearity of all these parameters in this partition process, these parameters have been used successfully before in linear regression analyses (*30, 32*). Substituting in eq 2 gives

$$\log K_{DMPC,water} = a \times \Delta G_{S,aq} - (b \times \Delta G_{S,C16} + c \times \epsilon_{HOMO} + d \times \epsilon_{LUMO} + e \times MV + f \times Q^- + g \times Q^+ + h) \quad (3)$$

where the term in parentheses can be considered as the membrane solvation energy.

Since no information on the relative importance of the separate interactions in the different zones exists, we have chosen to use a linear multivariate analysis, using experimentally determined partition coefficients, to estimate these regression coefficients.

Comparison between *n*-Octanol/Water and Membrane/Water Partition Coefficients. As we described earlier (*19*), the main differences between *n*-octanol and phospholipids, besides of course that of a bulk solvent versus a highly organized bilayer structure, are in the polar headgroups and the length of the alkyl chain. Differences between the polar headgroups will involve mainly hydrogen-bonding properties. These differences should be reflected in the importances of the four hydrogen-bonding parameters devised by Cramer et al. (*30*). Differences in interactions with the linear alkyl chains should be taken care of by the molecular volume of the solutes. Altogether, we have chosen to use a multivariate analysis to describe the differences between log $K_{DMPC,water}$ and log K_{ow}, using log K_{ow}, ϵ_{LUMO}, ϵ_{HOMO}, MV, Q^-, and Q^+ as independent and log $K_{DMPC,water}$ as dependent variables.

Modeling Membrane/Water Partition Coefficients Using log K_{ow} and Structural Fragment Values. Several programs have already been developed to predict log K_{ow}, using structural fragments (*33, 34*). These algorithms are based on the assumption that the contribution of a structural fragment to log K_{ow} is basically independent of the compound. On many occasions interaction effects between fragments are taken into account as well. Despite the relative simplicity of the structural fragment methods, the performance of these methods is unsurpassed (*34*). Unfortunately, due to lack of data there do not exist any structural fragment methods to predict log $K_{DMPC,water}$. The extensive use of log K_{ow} as a model for membrane/water partition coefficients and the fact that it was recently shown that log K_{ow} and log $K_{DMPC,water}$ can differ considerably, together with the availability of a small but consistent dataset, made it feasible as well as worthwhile to derive structural fragments for log $K_{DMPC,water}$ for a limited amount of structural fragments.

Analogous to the Fujita-Ban (*35*) modification of the Free−Wilson analysis on biological data, we formulate the following model:

$$\log K_{DMPC,water} - \log K_{ow} = \sum_j b_j X_j \quad (4)$$

where b_j is the value of structural fragment j, where j runs over all structural fragments that occur X times in the molecule. Since we only derive fragment values for the difference between log $K_{DMPC,water}$ and log K_{ow}, we may assume that interaction effects will not be significantly different in *n*-octanol from DMPC and therefore they will not be taken into account explicitly in the analysis. Regression analysis on the **X**-matrix, using the difference between the two partition coefficients as *Y*-variable, will give the structural fragment values (*35*).

The original Free−Wilson approach was developed for compounds with a similar backbone structure. In the current study we use a modification on this method for compounds that do show differences in backbone structure, i.e., aliphatic as well as aromatic compounds are included in the dataset. Since we will perform a multivariate analysis on the difference between log $K_{DMPC,water}$ and log K_{ow}, using a limited set of structural fragments,

an inherent assumption is that the backbone structure is not of any influence on said difference.

Experimental Procedures

Measuring DMPC/Water Partition Coefficients. L-α-Dimyristoylphosphatidylcholine (DMPC)/water partition coefficients for nineteen compounds were taken from Vaes et al. (*19*). More diverse structures were included in the set to make a wider application of the models feasible. Seven esters were selected by a statistical design procedure similar to the one described by Urrestarazu Ramos et al. (*36*), using the dataset from Veith et al. (*37*). Selected esters were diethyl adipate, diethyl malonate, propyl acetate (Sigma, St. Louis, MO), methyl 4-chloro-2-nitrobenzoate, dimethyl aminoterephthalate, dibutyl *o*-phthalate (Aldrich, Steinheim, Germany), and dibutyl succinate (Merck, Darmstadt, Germany). In addition, *n*-butylamine and *n*-octylamine (Sigma) were selected to study the behavior of positively charged amines (pK_a=10.6, more than 99% ionized under experimental conditions).

Small unilamellar vesicles were prepared as described earlier (*19*). Partition coefficients DMPC (Sigma)/water were determined as described before (*19*). In short, chemicals were dissolved in 0.1 M phosphate buffer (pH 7.4) and stirred for at least 24 h to achieve complete dissolution. Two series of samples with increasing concentrations were prepared, one series served as calibration standards while in the other small unilamellar vesicles (SUV) of DMPC were added. The samples were placed at 35 °C and equilibrated for at least 30 min, after which the free concentration was determined using a negligible depletion SPME procedure (*38*). The decrease in free concentration of the chemical in the samples containing the vesicles was assumed to be solely caused by partitioning to the membranes. From the decrease in free concentration, the initial concentration, and the concentration of DMPC, the partition coefficient was calculated (*19*). For the analysis of the samples a Varian 3600CX gas chromatograph equipped with a thermostated (35 °C) 8200CX SPME autosampler and flame ionization detector (FID) was used. The autosampler was used in agitation mode and sampling time was set at 1 min.

It should be noted that aliphatic amines are ionized at physiological pH. Since using the negligible depletion SPME method a decrease in free concentration is measured, it would be more appropriate to refer to distribution coefficients than to partition coefficients in the case of these ionized compounds.

Retrieval of Descriptors. *n*-Octanol/water partition coefficients were taken from the MedChem StarList or, if unavailable, calculated by the MedChem $CLOGP_3$ algorithm (*33*). All quantum-chemical descriptors, viz., ϵ_{HOMO} (energy level of the highest occupied molecular obital), ϵ_{LUMO} (energy level of the lowest unoccupied molecular orbital), MV (molecular volume), Q^- (most negative charge on any non-hydrogen atom), and Q^+ (most positive charge on any hydrogen atom), were calculated using the quantum-chemical package Spartan (*39*), running on an IBM RS/6000 workstation. Molecular structures were entered directly in Spartan and minimum-energy structures generated by preoptimizing all possible conformers using the built-in force-field optimizer. The conformer with the lowest energy was submitted to a quantum-chemical optimization run using the eigenvector following (EF) minimization procedure (*40*) and the semiempirical AM1 (*41*) Hamiltonian. Descriptors, ϵ_{HOMO} and ϵ_{LUMO}, were taken from the self-consistent field wave function of the energy-minimized structure. MV was calculated using van der Waals radii. Q^- and Q^+ were taken from charge lists of partial charges that were calculated using an electrostatic potential fit. Quantum-chemical calculations for the amines were performed for the positively charged species, since under experimental conditions they are more than 99% ionized. All calculations were performed for the molecules in the gas phase.

Solvation energies were calculated using the AMSOL version 6.0 package (*42*) running on an IBM RS/6000 machine. Output files from Spartan energy-minimized structures were modified into input files for the AMSOL program. Keywords used were AM1 CART HFOPT=x TRUES SM5.4A and SOLVNT=WATER for the $\Delta G_{S,aq}$ calculation and AM1 CART HFOPT=x TRUES SM4 and SOLVNT=N16ANE for the $\Delta G_{S,C16}$ calculation. These keywords designate the Hamiltonian, Cartesian coordinates to be read in, energy of gas-phase-optimized structure (where the energy *x* was retrieved from the Spartan calculation), and calculation of energy of solvation, used solvation model, and solvent, respectively. Again the EF routine was used to optimize geometry. Solvation energies for the amines were calculated for the ionized species, thus including the CHARGE=1 keyword. For each solvation energy calculation, an average of 10 min of CPU time was required.

Table 1. Results from the PLS Analysis Using Only Calculated Descriptors to Predict log $K_{DMPC,water}$

	with amines		without amines	
descriptor	importance[a]	PRC[b]	importance	PRC
constant		1.185		1.169
$\Delta G_{S,aq}$	3.546	0.2471	0.5500	0.2951
$\Delta G_{S,C16}$	−3.077	−0.4230	−0.6838	−0.4228
ϵ_{LUMO}	−0.7011	−0.4609	−0.5546	−0.4646
Q^-	0.5398	2.983	0.4582	2.686
Q^+	0.6043	6. 580	0.6475	6.813
R^2	0.87		0.87	
Q^2	0.81		0.77	
LV[c]	5		5	

[a] Regression coefficients on autoscaled variables. [b] Pseudoregression coefficients, i.e., results from the autoscaled PLS analysis back-transformed to the original variables. [c] Number of latent variables.

Structural fragments were chosen from the molecular structures, taking all polar fragments. Chosen structural fragments were alcohol (alOH), phenol (arOH), aliphatic amine ($alNH_3^+$), aromatic amine ($arNH_2$), aromatic nitro group ($arNO_2$), aliphatic ester [alC(=O)O], and aromatic ester [arC(=O)O]. Structural fragment values were entered in the data matrix as dummy variables counting the occurrence of each structural fragment in each molecule. Retrieved log K_{ow} values were subtracted from their respective measured log $K_{DMPC,water}$. This difference was modeled using the structural fragment values.

Data Analysis. To develop quantitative structure property relationships (QSPR) partial least-squares (PLS) regressions were used for the analysis. All models were internally validated using the cross-validated correlation coefficient Q^2, calculated as 1-PRESS/SS_Y (*43*). The number of latent variables in the current study was not restricted, i.e., the model with highest Q^2 was chosen for the final result. All analyses were performed using the SCAN 1.1 package (Software for Chemometric Analysis, Minitab Inc., State College, PA) running on an IBM personal computer equipped with an Intel Pentium 133 processor.

The measured membrane/water partition coefficients, log K_{ow}, all calculated descriptors, and the dummy values for the structural fragments are given as Supporting Information.

Results and Discussion

Data Analysis. Clark and Cramer (*44*) showed that when using PLS with much less descriptors than subjects, the probability of chance correlation is reduced to negligible numbers. They used an unrestricted number of latent variables, as in this study. PLS was chosen as the multivariate analysis technique because of its stable models in comparison to multiple linear regression, and not specifically to reduce the number of dimensions. Altogether we find it justified to include more latent variables than was originally devised by Geladi and Kowalski (*43*).

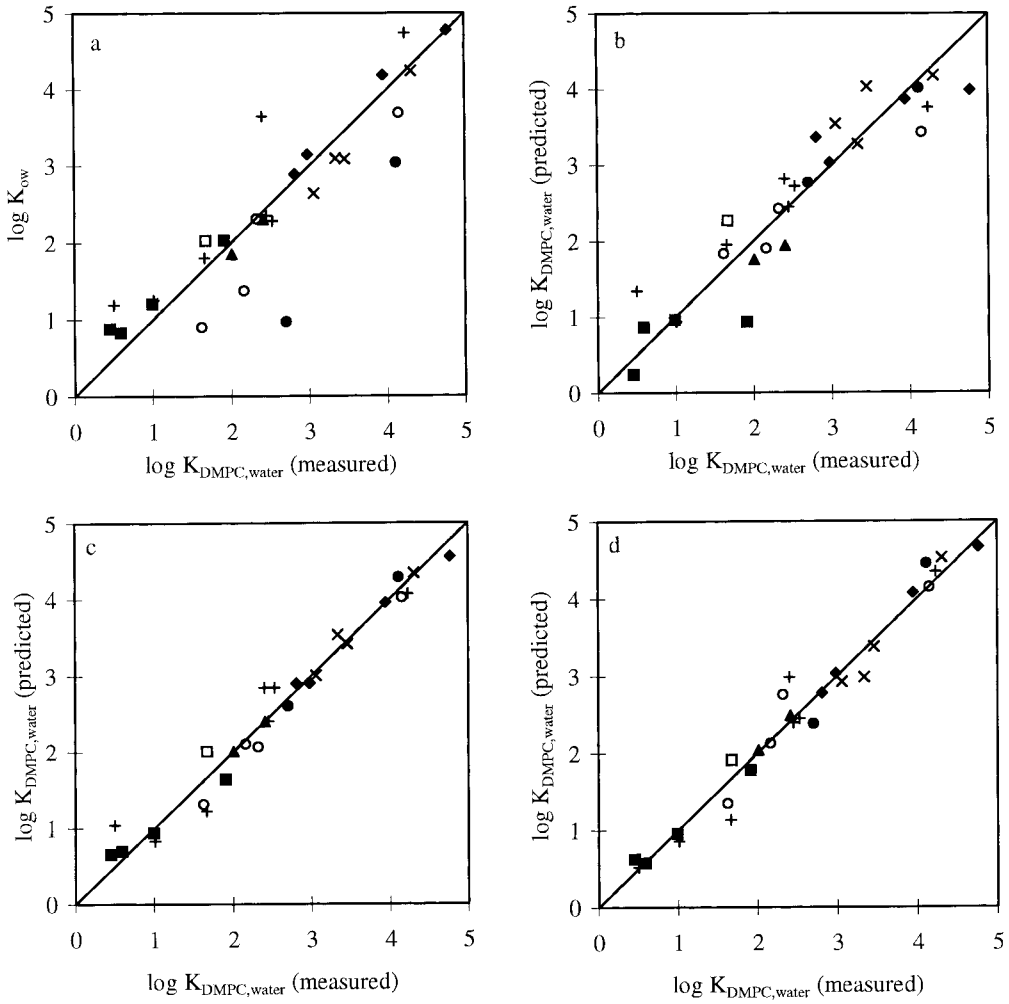

Figure 1. Measured versus predicted log $K_{DMPC,water}$ values from models using only log K_{ow} (a), only calculated descriptors (b), log K_{ow} and calculated descriptors (c), and log K_{ow} with the derived structural fragment values (d). Data are shown for benzenes (◆), alcohols (■), anilines (○), phenols (×), nitrobenzenes (▲), quinolines (□), esters (+), and amines (●).

Modeling Membrane/Water Partition Coefficients. In Table 1, the results of the PLS analysis with only calculated descriptors are given. Figure 1b shows these predicted versus measured partition coefficients. MV and ϵ_{HOMO} had a low contribution to the model (importances of −0.08947and −0.1913, respectively), and leaving them out of the PLS analysis gave appreciably better results. With five descriptors remaining, a sufficient model was developed with good predictive capabilities ($Q^2 = 0.81$). The main purpose of this model was to gain insight in the relative contributions of the different interactions in the partitioning process. The best way to deal with this is to use the autoscaled pseudoregression coefficients. Rewriting eq 3 in autoscaled pseudoregression coefficients gives for the membrane/water partition coefficient:

$$\log K_{DMPC,water}(\text{autoscaled}) = 3.546 \times \Delta G_{S,aq} - 3.077 \times \Delta G_{S,C16} - 0.7011 \times \epsilon_{LUMO} + 0.5398 \times Q^- + 0.6043 \times Q^+ \quad (5)$$

A negative coefficient of $\Delta G_{S,C16}$ indicates that it is inversely related to the membrane/water partition coefficient. Besides, the autoscaled pseudoregression coefficient shows that $\Delta G_{S,C16}$ is the dominant factor in describing the membrane solvation energy, and therefore the largest portion of partitioning is governed by the hydrophobic regions (mostly the inner zone and probably partly the intermediate zone). The three remaining parameters (ϵ_{LUMO}, Q^+, and Q^-) were defined as zone 1 (interface) interactions. The negative coefficient for ϵ_{LUMO} shows that good electron-accepting capabilities of the solute (low ϵ_{LUMO}) increase the membrane/water partition coefficient. Additionally, the positive coefficient for Q^+ indicates that good proton-donating capabilities (high Q^+) also interact favorably with the membrane, thereby increasing log $K_{DMPC,water}$. The negatively charged groups in the phospholipid, i.e., the carbonyl groups and the phosphorus group, thus interact favorably with acidic protons of the solute. On the other hand, a highly negative Q^- will probably result in repulsions due to the highly negatively charged groups in DMPC and decrease the membrane/water partition coefficient. Concluding, high membrane/water partition coefficients will result from hydrophobic chemicals (low $\Delta G_{S,C16}$ and high $\Delta G_{S,aq}$) with good hydrogen bond-donating capabilities (low ϵ_{LUMO}, high Q^+) and low hydrogen bond-accepting capabilities (low absolute value of Q^-).

Molecular volume did not improve the model. It should be noted that the SM4 and SM5.4 solvation models, which are used in this study, take the molecular volume (in fact, solvent-accessible surface area) explicitly into

Table 2. Results from the PLS Analysis Using log K_{ow} and a Selected Set of Calculated Descriptors To Predict log $K_{DMPC,water}$

descriptors	importance[a]	PRC[b]
constant		0.2275
log K_{ow}	0.9020	0.9256
ϵ_{HOMO}	0.005793	−0.005027
ϵ_{LUMO}	−0.3669	−0.2412
MV	−0.1054	−0.002968
Q^-	0.1012	0.5590
Q^+	0.2849	3.102
R^2	0.97	
Q^2	0.94	
LV[c]	5	

[a] Regression coefficients on autoscaled variables. [b] Pseudoregression coefficients, i.e., results from the autoscaled PLS analysis back-transformed to the original variables. [c] Number of latent variables.

account (*27*, *30*), and therefore MV is actually already included in both solvation energies. Hydrogen bonding is implemented as an atomic surface tension parameter in the aqueous SM5.4 but not in the organic SM4 model. Since the solvation energies that were calculated using the organic SM4 model were defined as a zone 3 interaction, additional hydrogen-bonding parameters were incorporated for zone 1 interactions.

In Table 1, the results are also given for a model where the amines were excluded from the analysis. The models with and without amines give comparable results in their pseudoregression coefficients, which suggests that quantum-chemical calculations of ionized species may be used in calculations on partition coefficients. Differences in autoscaled pseudoregression coefficients between the two models are only due to differences in mean and standard deviations.

Diffusion rates of amines over membranes have been shown to be pH-dependent and completely determined by the uncharged form (*45*). A clear distinction between diffusion and partitioning in membranes seems appropriate here. Partitioning of organic solutes only involves entering the membrane, while diffusion comprises both entering the membrane and subsequently passing the hydrophobic interior. The latter is highly improbable for charged species. Nevertheless it is reasonable to assume that interactions of positively charged amines with negatively charged phospholipid headgroups are energetically favorable. Therefore, the pH-dependent diffusion rates of amines can be explained by the pH-dependent concentration of the un-ionized form. Note that only two amines were included in the dataset, and thus results concerning calculations on charged species are highly preliminary.

Comparison between *n*-Octanol/Water and Membrane/Water Partition Coefficients. In Table 2, results are given from the PLS analysis using log K_{ow}, MV, and hydrogen-bonding capabilities to model log $K_{DMPC,water}$. Figure 1a,c shows the predicted versus measured partition coefficients for only log K_{ow} and for the model from Table 2, respectively. These results show that it is possible to correct for the differences in partitioning behavior between *n*-octanol and DMPC, using calculated descriptors. The model shows good predictive capabilities ($Q^2 = 0.94$). In addition, the model shows very clearly that the differences between *n*-octanol and DMPC are governed by hydrogen-bonding interactions. A low ϵ_{LUMO} and a high Q^+ show a more favorable interaction with DMPC than with *n*-octanol, while Q^- interacts weakly and unfavorably with DMPC. This implies that DMPC is a better electron donor than *n*-octanol, while the opposite is valid for the electron-accepting capabilities. *n*-Octanol does carry an acidic proton which might interact favorably with negative groups on the solute. Since DMPC does not have any acidic hydrogen that can be shared by electron donation of a solute, the positive sign of the coefficient of Q^- makes sense. In addition the negative sign of the coefficient of MV shows that a higher molecular volume has a negative influence on the membrane/water partition coefficient, which is in accordance with the expectations for zone 2, as outlined in the theoretical section.

Table 3. Results from the PLS Analysis Using Structural Fragments To Predict log $K_{DMPC,water}$

descriptors	PRC[a]
log K_{ow}	1.000
alOH	−0.1698
arOH	0.3565
$alNH_3^+$	1.482
$arNH_2$	0.5807
$arNO_2$	0.2809
alC(=O)O	−0.2890
arC(=O)O	−0.1710
R^2	0.91
LV[b]	3

[a] Pseudoregression coefficients, i.e., results from the autoscaled PLS analysis back-transformed to the original variables. [b] Number of latent variables.

Modeling Membrane/Water Partition Coefficients Using log K_{ow} and Structural Fragment Values. The results from the PLS analysis using log K_{ow} and structural fragments are given in Table 3. Using the structural fragments from Table 3 to predict log $K_{DMPC,water}$ gives an $R^2 = 0.91$ between measured and predicted values. Figure 1d clearly shows the improvement introduced by these structural fragment values compared to log K_{ow} alone, as in Figure 1a.

Phenols and aliphatic and aromatic amines present a higher log $K_{DMPC,water}$ than log K_{ow}. As we know from the earlier models, this is probably due to the high Q^+ and low ϵ_{LUMO} and thus favorable hydrogen-bonding interactions. On the other hand, aliphatic alcohols have a lower log $K_{DMPC,water}$ than log K_{ow}. An inspection of the hydrogen-bonding parameters for these alcohols shows that Q^+ is relatively high, but the ϵ_{LUMO} is much higher than that for the former structures. Thus although there is a high positive charge, the electron-accepting orbital seems to be of too high energy to turn the hydrogen bonding into a favorable interaction. A similar reasoning applies for the aliphatic esters where the negative charge causes a repulsion that has a negative influence on the membrane/water partition coefficient. The same would be expected for aromatic nitro groups and chlorines, but these seem to have favorable interactions with the phospholipids, probably due to the low LUMO energy. The structural fragment values that we discussed here should be used with caution, since there were only 28 compounds available, with a limited number of functional groups, to parametrize these values. Nevertheless, for fairly similar structures these values can be used to get a better estimate of log $K_{DMPC,water}$ than solely based on log K_{ow}.

One should keep in mind though that whenever it is possible to calculate the quantum-chemical parameters,

the models containing these parameters should be preferably used. The theoretical basis for these models is better since they use parameters that describe molecular properties rather than particular group substitutions.

General Remarks. The models that are presented in this contribution are all based on differences between the Gibbs free energy of solvation in two phases. While the first model uses explicitly calculated free energies, the latter two models use octanol/water partition coefficients, i.e., the measured difference between the free energies in these two phases. None of the models give information about the relative contributions of entropy and enthalpy. It is expected that solutes with single or multiple torsion angle degrees of freedom will give different contributions of the entropy to the partitioning process. Nevertheless, there are no validated semiempirical methods available to calculate these entropies explicitly in the solvated state. Therefore, we assume that the contributions of both enthalpy as entropy are implicitly incorporated in the models.

Conclusions

The partitioning behavior of organic chemicals to phospholipids can be modeled using physicochemical and quantum-chemical descriptors that account for hydrophobicity as well as hydrogen-bonding capabilities. Differences between the *n*-octanol/water and membrane/water partition coefficients can be almost completely explained by differences in hydrogen-bonding capabilities of the solvents. The influence of one being a bulk phase and the other being a highly organized bilayer seems to be of minor importance. In addition, this study provides structural fragment values for adjusting log K_{ow} to obtain log $K_{DMPC,water}$ for phenol, aniline, nitrobenzene, alcohol, amine, and ester groups.

The QSPRs that are presented here include only alcohols, benzenes, anilines, phenols, nitrobenzenes, quinolines, esters, and amines. Due to the data limitation, the models should be regarded preliminary for other structures, and caution is necessary when modeling charged species.

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Supporting Information Available: Table of membrane/water partition coefficients, log K_{ow}, calculated descriptors, and dummy values (1 page). Ordering information is given on any current masthead page.

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