Universal Model Based on the Mobile Order and Disorder Theory for Predicting Lipophilicity and Partition Coefficients in All Mutually Immiscible Two-Phase Liquid Systems

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The quantitative thermodynamic development of the mobile order and disorder theory in H-bonded liquids has been extended in order to predict partition coefficients. The model enables "a priori" estimation of the partition coefficient (log *P*) of neutral solutes, not only in the conventional 1-octanol/water reference but also in all mutually saturated two-phase systems made up of largely immiscible solvents. The model is obtained from the thermodynamic treatment of the various physicochemical free energy processes encoded in the overall distribution process and accordingly provides a useful tool for better understanding both the origin and the factors, such as the solute molar volume, that determine the partition coefficient of nonelectrolytes in a given system. From the comparison of the relative magnitude of the processes contributing to the log *P* value, a lot of information can also be gained regarding the variation in log *P* of the same substance partitioned between different solvent systems. As a demonstration, the model has been successfully applied to predict the log *P* of a great number of chemicals of varying structure, size, and chemical nature partitioned in a large set of essentially immiscible solvent pairs, differing either by their nonpolar or by their polar phase. In the systems involving water as the polar phase, the hydrophobic effect is always the driving force that governs the distribution process irrespective of the interacting or noninteracting nature of the substances studied. In the other two-phase systems, the partitioning of complexing solutes in particular appears to be ruled rather by their hydrogen-bonding capabilities than by their hydrophobicities.

INTRODUCTION

In the course of the past 50 years, lipophilicity or "oil loving" has been widely recognized to be a prime physicochemical descriptor of the distribution and transport processes occurring in biochemical, pharmacological, and environmental systems (drug−membrane interaction, drug transport and absorption, blood−brain distribution, plasma protein and receptor binding, efficacy and drug resistance, aqueous solubility, bioconcentration in abiotic and biotic compartments, toxicity toward aquatic organisms, and soil and sediment sorption phenomena). Given furthermore its leading role in many quantitative structure−property/−activity relationships (QSPR and QSAR) used in today's practice of rational drug or agrochemical design methods (combinatorial chemistry), the parametrization of the chemical's lipophilic nature is of great relevance in many areas of natural sciences such as chemistry, biochemistry, medicinal chemistry, biology, toxicology, pharmacology, engineering, and environmental sciences. All organic compounds can be characterized as more or less lipophilic or lipophobic, and their aqueous solubility, a commonly determined property, is sometimes used as such a measure. However, being directly associated with the change in the free energy during the transfer from one solvent to another, the thermodynamic *D* distribution ratio of the solute partitioned beween two immiscible solvents has proven to be a more valuable operational measure of lipophilicity. According to the definition given by Berthelot and Jungfleisch[1] in 1872, the distribution ratio is the equilibrium concentration of a solute in the lipophilic or nonpolar phase divided by the corresponding concentration of the same species in the polar or lipophobic phase when distributed between two immiscible solvents. [The term "immiscible" does not preclude the two phases from displaying partial miscibility. For example, the saturation mole fractions are at 25 °C: water in 1-octanol, 0.275, and 1-octanol in water, 7.5×10^{-5}. On a mole fraction basis, therefore, the solubility of 1-octanol in water in several orders of magnitude smaller than that of water in 1-octanol.] A literature survey, however, shows that the polar phase is almost invariably water, while, among the wide variety of solvents used as lipophilic phases, 1-octanol has become firmly established as the nonpolar organic phase of choice for the determination of biologically relevant partition coefficients. As a matter of fact, the mutually saturated 1-octanol/water solvent pair is now currently accepted as an arbitrary standard, and lipophilicity is conventionnaly expressed by the logarithm of the 1-octanol/water distribution ratio (log D_{oct}). A positive value of log D_{oct} reflects a preference of the substance for the lipid phase (lipophilic substance), whereas a negative value indicates a larger affinity for water (lipophobic substance). When the substance

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is present in the same neutral molecular form in both phases and when no association occurs, the equilibrium ratio does not change with concentration according to Nernst's distribution law[2] and is then called the "*partition coefficient*", *P*. Moreover, by convention, when ionizable compounds are concerned, *P* refers to the neutral species, whereas what is actually measured may be the distribution coefficient *D*. In this case, the *distribution coefficient or apparent partition coefficient* corresponds rather to the ratio of the total concentrations of ionized, nonionized, and associated species across both phases.

The reasons why, for the past decades, 1-octanol/water has progressively emerged as the standard system[3] include, among others, easy determination and H-bonding characteristics which are relatively similar in each phase. Water, like 1-octanol (which itself contains a considerable amount of dissolved water), displays hydroxyl groups able to interact comparably and specifically with the polar and H-bonding sites of the partitioned chemical. As a result, it is believed that the 1-octanol/water partition coefficient essentially emphasizes differences in the nonspecific interactions that the solute hydrocarbon moieties may develop in lipophobic (water) and lipophilic (1-octanol) environments. However, if the 1-octanol/water partition coefficient can most often be regarded as a good indicator for correlating chemical structures and biological effects, the attempts to apply this reference solvent pair universally to all biodistribution phenomena and all sets of molecules have not always led to favorable results.[4−6] Due to the varying biophysical characteristics of the diverse biological membranes (intestine, skin, blood−brain barrier) which a drug, for instance, must cross to reach its site of action, it is not suprising that, instead of 1-octanol, numerous organic solvents with widely varying physicochemical properties and H-bonding capabilities might successfully be used to model some distribution and transport processes. For example, alkane/water partition coefficients proved their value in modeling the blood−brain barrier crossing and the ability of drugs to reach the central nervous system.[7] It has furthermore been evidenced[8−11] that, for some systems, a H-bonding parameter (rather than a solute volume effect) was better suited in estimating transport potential. Even if, up to now, the 1-octanol/water system has had no serious challenger, the search for alternative water/insoluble organic solvent partitioning systems is open. With this perspective, Leahy et al.[12] suggested grouping all solvents into four highly contrasted solvent/water partitioning systems called the "critical quartet": (1) amphiprotic solvents such as 1-hexanol and 1-octanol, (2) proton-acceptor or basic solvents such as propylene glycol dipelargonate (PGDP), dibutyl ether, or butyl acetate, (3) proton-donor or acid solvents such chloroform, and (4) apolar aprotic inert solvents such as *n*-alkanes or cyclohexane. Although partition coefficients measured in these solvent systems have not yet met substantial applications in QSAR studies, their knowledge, however, would be interesting since they are expected to encode very different structural information related, in particular, to the solute/solvent and solute/water interactions. The capacity of evaluating a priori these interactions in a range of eligible solvents would be particularly helpful, for instance, to environmentalists in order to rationally predict the behavior of chemicals with respect to particular environments, or to chemical engineers in order to rapidly select the appropriate solvent for the extraction of certain solutes from multicomponent aqueous solutions (liquid−liquid extraction).

The outstanding importance of lipophilicity (partition coefficient) in correlating numerous biophysical and biological properties such as narcotic, bactericidal, fungicidal, hemolytic, and toxic properties underlines the large interest and effort that have been devoted to the development of reliable and quick procedures to acquire information on this property. In turn, the ability to predict the log *P* value from simple structure-based methods greatly assists and eases the formulation development effort toward the design of better compounds by enabling the elimination of many of the unsuitable candidates from synthesis and extensive experimentation. Calculation methods also offer new insight into the dependence of compound properties on structural features; hence, they really bring valuable guidelines to the design of potentially interesting molecules. The emphasis on estimating partition coefficient theoretically is furthemore driven by the advantage of having a rough estimate of the unknown partition coefficient value when the optimal conditions are selected for its experimental determination.

By now, a large number of calculation methods and programs[13−18] have been developed for the estimation of the 1-octanol/water partition coefficient with varying success and applicability. The most current approaches may essentially be grouped into three classes: the "fragment or group" contribution, the "atomistic" (the atom-centered fragments), and the "whole molecule" methods. Although fragment or atom-based methods are reasonably accurate and very fast, they suffer from serious limitations, such as (a) the need for a large array of parameters and correction factors, (b) the difficulty of defining unambiguously valuable group contributions, and (c) the inhability to calculate log *P* for structures containing novel atom types or fragments which have not yet been parametrized. To overcome these problems, a great deal of effort has been made to calculate log *P* directly from correlations involving the partition coefficient and one or several molecular properties of the solute molecule such as molar volume and solvatochromic parameters,[19−20] molar refraction,[21] aqueous solubility,[22] molecular surface area, volume and weight,[23−26] solvent-accessible surface area,[27] molar polarizability,[28] and molecular orbital indices such as charge densities, electrostatic potentials, dipole moments, ionization potentials, and highest occupied and lowest unoccupied molecular orbital energies.[29−31] Although these approaches obviate the necessity to define and justify fragments, and allow estimation of log *P* for different conformers of the same chemical, their predictive accuracy is only as good as the data from which they are derived, and predictions for compounds outside the chemical training sets are unlikely to be accurate. These methods are moreover class-specific, yielding the best results when applied to homologous series of chemicals or chemically related compounds. Even if some of the "whole molecule" approaches entail some theoretical basis, all above empirically derived methods contain limited thermodynamic information and do not lead to any significant understanding of the factors that determine log *P* values since they offer no insight into the physical aspects of the partitioning process (no or little physical significance being attached to the regression coefficients or fitting constants). As a result, their uses remain

essentially empirical, and because they are specifically designed to estimate log *P* in a particular biphasic system, currently 1-octanol/water, these methods have a limited range of applicability and are accordingly not "*universal*". Indeed, in comparison with the large number of works undertaken to establish predictive 1-octanol/water partition coefficient models, much less effort has been put into the development of similar methods to account for the partitioning of solutes in two-phase systems made of a lipophilic solvent other than 1-octanol and/or a lipophobic solvent different from water.

The objective of this work is precisely to derive a universal predictive method which, based on sound thermodynamic grounds, provides (1) a comprehensive understanding of what elementary processes are implied when a solute is distributed between two immiscible phases and (2) a clear basis of how these processes are affected and modified by the solute structural features as well as by the physicochemical properties of the cosolvent for different solvent/water distribution systems. In the present study, the partition coefficients and the lipophilicity in particular (traditionally expressed by the 1-octanol/water log $P_{o/w}$ value) are evaluated a priori from a simple, although general, method derived from the thermodynamics of the mobile order and disorder (MOD) theory in H-bonded liquids. The ability of the method to yield correct log *P* values is demonstrated from the comparison of the observed versus predicted data obtained with compounds of varying chemical nature partitioned in a large number of immiscible binary solvent systems. Attempts to rationalize the cosolvent effects on the partitioning process is furthermore deeply investigated from the comparison of the relative magnitude of the various contributions encoded in the log *P* values of the same solute distributed in a variety of systems consisting essentially of water and an immiscible organic cosolvent. Conversely, the influence of the solute features, such as the molar volume, on its distribution in a given partitioning system is analyzed, and the results are compared between various partitioning systems. The present study also evidences the importance of the hydrophobic effect in being responsible, in aqueous environments, for the high lipopihlic nature (high log *P* value) of nonpolar or slightly polar chemicals. This effect was already shown to be at the very origin of the poor aqueous solubility of these chemicals (their hydrophobic nature, i.e., their aversion to reside in an amphiphilic environment or more correctly the tendency of water and all H-bonded solvents to not accept such solutes within their H-bond networks).[32−35]

PARTITION COEFFICIENT AND MOD THERMODYNAMICS

In order for a model to describe phase equilibrium adequately, proper weighting must be assigned to the relative importance of the various physical phenomena that determine the partitioning process at the molecular level. The partition coefficient, the ratio of two equilibrium concentrations, is a free energy related term and represents the change in the Gibbs free energy during the transfer of the solute from one phase to the other: it arises from differences in the stabilization of the compound between phases. Such a definition therefore implies that, besides the enthalpic component on which most log *P* approaches described in the literature mainly focus and which is related to differences in the interactions between the solute and the surrounding solvent molecules in each phase, the partition coefficient also encodes an entropic part. The entropic aspects of the partition coeffcient account for the differences between the two phases in the solute/solvent mixing entropy and the tendency of the H-bonded solvents to induce a hydrophobic effect toward the solute.

Thermodynamically, a comprehensive understanding of the partition coefficient can be achieved more adequately by examining each phase separately rather than by studying the overall complex partition system, where it is never easy to ascribe a particular effect to one or the other phase or to a combination of effects. In this aim, the partition coefficient can be regarded not only as the ratio of concentrations at equilibrium but also as the ratio of saturation concentrations or solubilities. Therefore, written in logarithmic form, the partition coefficient of a substance B may advantageously be obtained from the difference of its volume fraction solubility between the less polar (index 1) and the more polar (index 2) phases.

$$\log P = (\ln 10)^{-1}[\ln \Phi^1{}_B - \ln \Phi^2{}_B] \qquad (1)$$

To go beyond just obtaining the log *P* value, and to obtain separate information about both enthalpic and entropic components encoded in the partition coefficient value, the saturation volume fraction solubilities are expressed, in the frame of the MOD theory,[36−38] in terms of the various free energy contributions accompanying the solution process in each phase. These contributions, whose quantitative expressions have been derived and reported in earlier papers,[39−41] are as follows: (i) the fluidization of the solute or the ideal solubility; (ii) the departure from ideality of the entropy of mixing between the solute and solvent molecules in solution; (iii) the change in the solute/solute, solvent/solvent, and solute/solvent nonspecific cohesion forces upon mixing; (iv) the so-called hydrophobic effect,[42,43] giving rise to the segregation between the solute and solvent molecules in the case of H-bonded solvents; (v) the H-bond formation between proton-acceptor sites on the solute and proton-donor solvents; and (vi) the various effects related to the interactions caused by the presence of amphiphilic groups on the solute.

Note that, by explicitely accounting for both nonergodicity and the mobility of the H-bonds in liquids, the present thermodynamics derived from the MOD theory differs completely from the classical multicomponent treatments of H-bonded liquids in two characteristics: (a) the equilibria are explicited in terms of the time fractions for the time schedule that a given molecule in the ensemble is "free" or "bonded", and not in terms of the classical fractions (concentrations) of the different *i*-mer species present in the solution at a given instant; (b) the mobile molecular domains replace the quasi-lattice model of Flory[44] for the calculation of the entropy of mixing.

Unlike solubility, the universal predictive equation for log *P* does not depend any longer on the melting properties of the solute, and five components at the most contribute to the Gibbs free energy of partition of a molecule in a biphasic system made of two essentially immiscible solvents.

$$\log P = \Delta B + \Delta D + \Delta F + \Delta O + \Delta \mathrm{OH} \qquad (2)$$

with

$$\Delta B = \frac{1}{\ln 10}\left[0.5V_B\left(\frac{1}{V_1^*} - \frac{1}{V_2^*}\right) + 0.5\ln\left(\frac{V_2^*}{V_1^*}\right)\right] \quad (3)$$

$$\Delta D = \frac{1}{\ln 10}\left[\frac{V_B}{RT}\left(\frac{(\delta'_B - (\delta'_2)^*)^2}{1.0 + (\max(K^2_{O_i}, K^2_{OH_i}))/V_2^*} - \frac{(\delta'_B - (\delta'_1)^*)^2}{1.0 + (\max(K^1_{O_i}, K^1_{OH_i}))/V_1^*}\right)\right] \quad (4)$$

$$\Delta F = \frac{1}{\ln 10}\left[V_B\left(\frac{r^*_2}{V^*_2} - \frac{r^*_1}{V^*_1}\right) + \sum_i \nu_{OH_i}\{r^*_1 - (r^*_2 + b)\}\right] \quad (5)$$

$$\Delta O = \frac{1}{\ln 10}\sum_i \nu_{O_i} \ln\left[\frac{1 + K^1_{O_i}/V^*_1}{1 + K^2_{O_i}/V^*_2}\right] \quad (6)$$

$$\Delta OH = \frac{1}{\ln 10}\sum_i \nu_{OH_i} \ln\left[\frac{1 + K^1_{OH_i}/V^*_1}{1 + K^2_{OH_i}/V^*_2}\right] \quad (7)$$

In these expressions, V_B and δ'_B represent the molar volume and the modified nonspecific cohesion parameter, respectively, of solute *B*. The constants $K^{1or2}_{O_i}$ and $K^{1or2}_{OH_i}$ are the H-bond stability constants governing, in the nonpolar (index 1) or in the polar (index 2) phase, the interactions of the solvent molecules with a given proton-acceptor site (*O*), respectively a proton-donor site (OH), of type *i* on the solute. The quantities ν_{O_i} and ν_{OH_i} figure the number of identical and independent type *i* proton-acceptor and proton-donor, respectively, sites on the solute molecule. The constant *b* accounts for the primary (1.2), secondary (2.0), or tertiary (2.9) character of the proton-donor group on the solute provided that this group is a hydroxyl group and that the solubility is estimated in water.[45,46] The structuration factors, r^*_{1or2}, the modified nonspecific cohesion parameters, $(\delta')^*_{1or2}$, and the molar volume, V^*_{1or2}, of the mutually saturated solvent phases are assumed to depend linearly on the phase composition according to the following expressions:

$$r^*_{1or2} = X_1 r_1 + X_2 r_2 \quad (8)$$

$$(\delta')^*_{1or2} = \Phi_1 \delta'_1 + \Phi_2 \delta'_2 \quad (9)$$

$$\frac{1}{V^*_{1or2}} = \frac{\Phi_1}{V_1} + \frac{\Phi_2}{V_2} \quad (10)$$

Whereas the overall value of the partition coefficient can be estimated from eq 2, the comparison of the relative magnitudes of the different terms involved in the log *P* calculation provides the opportunity to understand more about the molecular origin and the factors that govern the partition coefficient. The mixing entropy-related term, ΔB, brings information about the difference between the two phases in the entropy of the solute/solvent exchange. The hydrophobic effect-related term, ΔF, accounts for the difference in the propensity between the two solvent phases to squeeze the solute out of the solution by hydrophobic effect. Both terms refer to entropic contributions and essentially depend on the molar volume of the partitioned chemical. The two H-bond interaction-related terms, ΔO and ΔOH [the H-bond interaction-related terms, ΔO and ΔOH, may be grouped into one single term called $\Delta(O+OH)$], express the difference in the strengths of the H-bonds that bind the solute and solvent molecules in each phase. Near infinite dilution, these terms only depend on the number and the type of the solute functional groups able to interact with the solvent phases, as well as on the stability constants that rule these interactions. Indeed, in opposition to the methods based on "solubility parameters" such as the equation used by Beerbower et al.[47] The present treatment of H-bonds is based on stability constants and on concentrations of the active sites, allowing one to take into account the important entropy effects involved in any H-bond formation. The last term, ΔD, is equivalent to the two previous ones, but accounts for the nonspecific forces only. Unlike the H-bonds, these forces are more conventionally treated using a Scatchard−Hildebrand type of equation with modified nonspecific cohesion parameters. However, as the difference of relatively small numbers (the *D* term was shown to be negligible in estimating the solubility in alcohols or in water[32,39,48]), this contribution is often neglected in estimating the 1-octanol/water partition coefficients.

Due to its a priori derivation, eq 2 can be regarded as the most general and comprehensive thermodynamic expression ever developed for calculating the partition coefficient of a solute in any given pair of immiscible or partially miscible solvents. This general predictive log *P* model, however, reduces to very simple linear equations relating the logarithm of the partition coefficient of a solute to its molar volume when the difference in the changes of the nonspecific forces is negligible ($\Delta D = 0$) and when no solute/solvent specific interaction takes place in either phase (ΔO and $\Delta OH = 0$). For instance, the following thermodynamic relationships are derived for the 1-octanol/water and *n*-hexane/water systems, respectively:

1-octanol/water:

$$\log P_{o/w} = \Delta B_{o/w} + \Delta F_{o/w} = -0.48122 + 0.03328V_B \quad (11)$$

n-hexane/water:

$$\log P_{h/w} = \Delta B_{h/w} + \Delta F_{h/w} = -0.43079 + 0.03764V_B \quad (12)$$

Issued from the strictly thermodynamic treatment and unspoiled by any regression coefficient, eq 11 in particular may be regarded as the fundamental basis of all empirical linear or multilinear equations reported in the literature,[21,23,26,49−54] correlating log $P_{o/w}$ values of chemicals to their molar volume or any related property (surface area, parachor, molar refraction, connectivity indices). Although the log $P_{o/w}$ formulation of eq 11 resembles most regression models in showing comparable linear dependence on the solute molar volume, the present thermodynamic equation has a completely different origin and entirely differs in essence.[55,56]

The oustanding feature of the present theory is that, provided that the nonspecific effects are negligible, a solute unable to complex with the organic phase will always exhibit

a more lipophilic character in the *n*-hexane/water than in the 1-octanol/water system ($\log P_{h/w} > \log P_{h/w}$). This conclusion can be deduced just by comparing eqs 11 and 12 while no estimation needs to be made.

RESULTS AND DISCUSSION

Very rapid and easy predictions of the partition coefficient are obtainable from the MOD theory. Whereas, for noninteracting substances, only the molar volume needs to be known, for polar complexing compounds, the calculation requires in addition the knowledge of the number of active sites as well as the stability constants characterizing the associations of solute/solvent functional groups in each solvent phase. Although the numbers of the active proton-donor and -acceptor sites on the solute are important, their estimations are obvious in most cases. Another great advantage of the present model is that the values of the stability constants required for the log *P* calculation are identical to those considered in our earlier works dealing with solubility predictions.

Although the contribution of the nonspecific cohesion forces (ΔD term) to the partitioning process remains generally negligible in the presence of specific solute−solvent H-bonding interactions, this term is nevertheless taken into account in all present log *P* estimations. Indeed, this contribution might appear particularly important for uncomplexing solutes distributed in systems in which the nonpolar phase is an inert liquid such as an aliphatic or aromatic hydrocarbon. To estimate the ΔD term from eq 4, the values of the modified nonspecific cohesion parameters, δ'_B, of the solutes have been calculated from the ratio between the dispersion component F_d of the molar attraction constant and the molar volume of the substance. Whereas the first quantity was obtained from the molecular structure according to the method of Van Krevelen,[57] the molar volume was calculated from an additive-constitutive group contribution method.[39,58] Remember that, for substances which are solid at room temperature, the molar volume of the solute to consider in estimating their solubility or partition coefficient is not that of the crystalline substance, but the volume of the molecule in its hypothetical supercooled liquid state. However, to account for a certain amount of volume contraction[59−61] due to the strong H-bonded complexes that some molecular groups may form with water, the obtained volumes of the molecules containing these particular groups were systematically decreased by 15% in the aqueous phase as was previously done for the water solubility predictions.[40,62]

Ability of the MOD Model To Predict the Partition Coefficient. To demonstrate the applicability of the present thermodynamic log *P* model, the partition coefficient of selected nonelectrolytes of varying chemical and structural nature were calculated in a large variety of partitioning two-phase systems differing from one another by the interacting capacity and/or the volume of the constituting solvent phases. These were chosen to cover all strengths of solute/solvent interactions ranging from nonspecific to highly specific, including hydrogen-bonding, and to display the largest variation in size effects. The changes in the solvent properties should obviously result, for the same chemical, in different partition coefficient values, differences which will then be analyzed and rationalized in the frame of the MOD log *P* model.

All log *P* estimations reported in this work were obtained from eq 2 using the standard values of the stability constants of Table 1 as well as the physicochemical properties of the nonaqueous phase liquids (NAPL) given in Table 2. Note that, in the calculations, the volume, the structuration factor, and the modified nonspecific cohesion parameter of the mutually saturated phases were actually assimilated into those of the solvents in their pure liquid state. Given the relatively low mutual miscibility of the solvent pairs taken as partitioning systems, this approximation should not substantially impair the quality of the predictions, except perhaps for the 1-octanol/water system.

A number of computed log *P* values are reported and compared to the experimental data in Tables 3 and 4. Whereas Table 3 is a collection of the partition coefficients of a set of 45 solutes distributed in the same six partitioning solvent pairs, Table 4 reports the partition coefficients (and their contributions) of selected chemicals distributed in solvent systems whose number and constituents vary from one solute to another. A larger set of predicted and experimental log *P* data is also provided as Supporting Information. A list of 1854 log *P* values corresponding to the distribution in 16 partitioning systems are reported in Tables 5 and 6 in the Supporting Information. The model prediction accuracy relevant to these log *P* values has been calculated for each separate distribution system, and the results are collected in Table 7. The overall performance of the MOD theory-derived model for predicting the partition coefficient is illustrated in Figure 1. The goodness of agreement is further characterized by a value of 0.55 log units of the overall standard deviation of the residuals [the standard deviation of the residuals is calculated as $\{[\sum_{i=1}^{n} (\log P^{calcd,i} - \log P^{expt,i})^2]/n\}$, with n being the number of log *P* estimations]. Although Table 7 reveals a relative variation in the prediction accuracy with respect to the partitioning solvent system considered, the agreement between all observed and predicted partition coefficients reported in this work (2297 data points) is, though not perfect, quite remarkable, keeping in mind (i) the broad variety of solute functionality studied and the number of different distribution systems considered (e.g., 55 in the case of phenol), (ii) the fact that the results correspond to a priori predictions, and (iii) the extreme simplicity of the thermodynamic model. Indeed, in its present state of development, the log *P* model does not apply any correction factor accounting, for instance, for the proximity effects, the electronic inductive and resonance effects linked to the ortho, meta or para aromatic substitution, or the presence of multiple functional groups on the solute.

Other theoretical and experimental reasons may also be invoked to explain the discrepancies observed between experimental and predicted values.

From the theoretical viewpoint, one part of the errors may undoubtedly be assigned to the use of rough "standard" stability constants of solute/solvent group interactions instead of using values depending on the chemical environment of the interacting sites. Moreover, in polyfunctional solutes, the calculation includes the contributions for all possible associations of solute/solvent functional groups. Such treatment is of course unrealistic and leads clearly to overestimation of the specific solvation of the solute molecule in at least the aqueous phase. A rule of thumb in H-bonding is indeed

Table 1. Standard Stability Constants of Solute/Solvent Group Association[a] at 25 °C

solute acceptor[b]	solvent donor	K_O, cm^3 mol^{-1}	solute acceptor[b]	solvent donor	K_O, cm^3 mol^{-1}
aliph tertiary amine	$CHCl_3$	600.0	aliph ester	$(CH_2Cl)_2$	300.0
aliph tertiary amine	$(CH_2Cl)_2$	600.0	aliph ester	CH_2Cl_2	300.0
aliph tertiary amine	alcohol	300.0	arom ester	$CHCl_3$	300.0
aliph tertiary amine[c]	water	7500.0	arom ester	$(CH_2Cl)_2$	300.0
arom tertiary amine	$CHCl_3$	300.0	aliph ester	alcohol	110.0
arom tertiary amine	$(CH_2Cl)_2$	300.0	aliph ester	water	3500.0
arom tertiary amine	alcohol	170.0	arom ester	alcohol	110.0
arom tertiary amine	water	1500.0	arom ester	water	2000.0
aliph nitrile	$(CH_2Cl)_2$	600.0	aliph ether	$CHCl_3$	300.0
aliph ketone	$CHBr_3$	300.0	aliph ether	alcohol	110.0
aliph ketone	$CHCl_3$	300.0	aliph ether	water	3500.0
aliph ketone	CH_2Cl_2	300.0	arom ether	$CHCl_3$	300.0
aliph ketone	$(CH_2Cl)_2$	300.0	arom ether	water	250.0
aliph ketone	$(CHCl_2)_2$	300.0	aliph aldehyde	alcohol	110.0
aliph ketone	$(CH_2Br)_2$	300.0	aliph aldehyde	water	1000.0
aliph ketone	$CHCl_2CH_3$	300.0	arom aldehyde	$CHCl_3$	300.0
aliph ketone	alcohol	170.0	arom aldehyde	water	250.0
aliph ketone	water	5000.0	arom disubst ester	alcohol	110.0
arom ketone	$CHCl_3$	300.0	arom disubst ester	water	1000.0
arom ketone	CH_2Cl_2	300.0	aliph nitrile	$CHCl_3$	300.0
arom ketone	$(CH_2Cl)_2$	300.0	aliph nitrile	alcohol	175.0
arom ketone	$(CHCl_2)_2$	300.0	aliph nitrile	water	3000.0
arom ketone	alcohol	170.0	arom nitrile	water	300.0
arom ketone	water	3000.0	aliph nitro	$CHCl_3$	300.0
arom tertiary amide	alcohol	600.0	aliph nitro	water	1000.0
arom tertiary amide[c]	water	5000.0	arom nitro	water	100.0
unsubst phenyl ring	water	80.0	chloromethoxybenzenes	water	50.0
double bond −C═C−	water	10.0	PAH	water	80.0
triple bond −C≡C−	water	80.0	PCB, PBB, TCBT	water	30.0
polychloroalkyl	water	50.0	PCDE	water	200.0
aliph ester	$CHCl_3$	300.0			

solute donor[b]	solvent acceptor	K_{OH}, cm^3 mol^{-1}	solute donor[b]	solvent acceptor	K_{OH}, cm^3 mol^{-1}
R−OH	arom ring	200.0	aliph COOH	arom ring	100.0
R−OH	haloarom	200.0	arom COOH	arom ring	500.0
R−OH	$CHBr_3$	300.0	aliph COOH	haloarom	100.0
R−OH	$CHCl_3$	300.0	aliph COOH	$CHCl_3$	300.0
R−OH	CH_2Cl_2	300.0	arom COOH	$CHCl_3$	500.0
R−OH	$(CH_2Cl)_2$	500.0	aliph COOH	$(CH_2Cl)_2$	500.0
R−OH	$(CHCl_2)_2$	500.0	arom COOH	$(CH_2Cl)_2$	500.0
R−OH	CCl_3CHCl_2	500.0	aliph COOH	CH_2Cl_2	300.0
R−OH	$(CH_2Br)_2$	500.0	aliph COOH	nitro	1000.0
arom OH	nitro	1500.0	aliph COOH	ester	5000.0
aliph OH	ester	2500.0	arom COOH	ester	15000.0
arom OH	ester	5000.0	aliph COOH	ether	5000.0
aliph OH	ether	2500.0	arom COOH	ether	15000.0
arom OH	ether	5000.0	aliph COOH	ketone	5000.0
arom OH	ketone	5000.0	aliph COOH	alcohol	15000.0
R−OH	alcohol	5000.0	arom COOH	alcohol	15000.0
R−OH	water	5000.0	aliph COOH[c]	water	15000.0
arom NH_2	arom ring	200.0	arom COOH[c]	water	15000.0
arom NH_2	haloarom	200.0	aliph NHR	$CHCl_3$	100.0
aliph NH_2	$CHCl_3$	200.0	aliph NHR	ester	0.0
arom NH_2	$CHCl_3$	500.0	aliph NHR	ether	0.0
arom NH_2	$(CH_2Cl)_2$	500.0	arom NHR	ester	0.0
arom NH_2	ether	500.0	arom NHR	ether	0.0
arom NH_2	ester	500.0	aliph NHR	alchohol	230.0
R−NH_2	alcohol	1500.0	aliph NHR[c]	water	1000.0
aliph NH_2	alcohol	230.0	arom NHR	alcohol	200.0
aliph NH_2	water	3000.0	arom NHR	water	600.0

[a] Most values were deduced from solubility or log *P* data of monofunctional systems.[35,40,45−46,62−66] [b] "arom" notation stands for aromatic or conjugated systems. R stands for both aliph and arom compounds. [c] When the solute contains this group, its aqueous molar volume is reduced by 15%.

that, with polyfunctional molecules, solvent fixation at one solute functional group weakens the strength of the other nearby interacting sites, and consequently sterically hinders/prevents or reduces solvent fixation at a second neighboring functional group. In this connection, the formation of the internal H-bond also lowers the real solvation process, whereas the actual predictions result again in an overestimation in this process. In this particular case, the two intramolecularly interacting substituents form a single larger "interaction center" with a reduced polarity, hence yielding weaker complexation with the surrounding solvent molecules. The internal interaction is particularly important for two

Table 2. Molar Volume and Modified Nonspecific Cohesion Parameter[a] of Non-Aqueous Phase Liquids

solvent	V_S cm^3 mol^{-1}	δ'_S, MPa$^{1/2}$	solvent	V_S cm^3 mol^{-1}	δ'_S, MPa$^{1/2}$
n-pentane	116.1	14.18	isopentyl acetate	148.8	19.27
n-hexane	131.6	14.56	*n*-hexyl acetate	165.8	19.15
n-heptane	147.5	14.66	*n*-heptyl acetate	182.1	18.77
n-octane	163.5	15.85	methyl decanoate	208.6	18.49
n-nonane	179.7	15.07	ethyl benzoate	142.9	17.56
n-decane	195.9	15.14	PGDP	390.1	16.00
n-dodecane	228.6	15.34	triolein	949.0	16.43
n-hexadecane	294.1	15.61	diethyl ether	104.8	18.78
3-methylpentane	129.8	14.50	diisopropyl ether	141.1	18.17
isooctane	165.1	15.32	dibutyl ether	170.3	17.45
cyclohexane	108.8	14.82	dipentyl ether	204.0	16.16
methylcyclohexane	128.3	15.00	2-butanone	90.2	20.90
decaline	156.9	18.90	diethyl ketone	106.4	20.13
iodomethane	62.3	17.00	methyl isobutyl ketone	125.8	19.95
CCl_4	97.1	17.04	dichloromethane	64.5	20.53
1,1,1-trichloroethane	99.7	17.05	chloroform	80.7	18.77
trichloroethylene	90.2	17.96	1,2-dichloroethane	78.8	20.99
tetrachloroethylene	101.1	19.19	1,2,3-trichloropropane	114.4	17.22
carbon disulfide	60.0	18.48	1,1,2,2-tetrachloethane	105.2	18.63
benzene	89.0	18.95	pentachloroethane	120.4	19.30
toluene	106.9	18.10	bromoform	87.3	19.81
ethylbenzene	123.1	18.02	1,2-dibromoethane	87.0	20.75
isopropylbenzene	139.4	16.86	1-butanol	92.0	17.16
n-butylbenzene	156.1	17.05	2-methyl-2-propanol	92.8	16.14
xylene	123.0	17.20	*sec*-butanol	92.4	16.60
mesytilene	138.9	17.00	1-pentanol	108.6	16.85
chlorobenzene	102.1	19.48	*sec*-pentanol	109.0	16.01
o-dichlorobenzene	113.1	18.77	*tert*-pentanol	109.5	15.92
1,2,4-trichlorobenzene	124.0	18.77	1-hexanol	125.2	16.40
bromobenzene	105.3	21.22	1-heptanol	141.9	16.39
iodobenzene	111.4	20.70	2-ethylhexanol	156.3	15.87
nitrobenzene	102.7	21.77	1-octanol	158.3	16.38
o-nitrotoluene	117.9	21.10	1-nonanol	174.3	16.37
m-nitrotoluene	118.5	21.00	1-decanol	191.6	16.35
ethyl acetate	98.5	20.79	oleyl alcohol	316.2	16.06
n-butyl acetate	132.5	19.66	ethylene glycol	55.8	19.90

[a] The values of the modified nonspecific cohesion parameter were taken from previous published compilations[34,62,67] or were calculated either according to the correlations reported by Huyskens[58] or from the partial dispersive and polar Hansen's cohesion parameter values,[68] or were simply estimated on the analogy to similar solvents with known values of the modified nonspecific cohesion parameter. The molar volume and the modified nonspecific cohesion parameter of water are 18.1 cm^3 mol^{-1} and 20.5 MPa$^{1/2}$.

highly polar substituents in the ortho position of aromatic compounds whose experimental lipophilicity seems to increase anomalously. As can be seen from the results given in the lower part of Table 3, the largest errors between the experimental and predicted log *P* values are observed for solutes bearing multiple electronically conjugated functional groups and/or are able to form internal H-bonds. These deviations are particularly enhanced in partitioning systems whose coexisting solvent phases are very distinct from one another and behave differently with respect to the complexation of the solute. For instance, the observed vs predicted log *P* differences of hydroquinone progressively increases from 0.72, 0.64, 2.40, 2.70, and 3.70, to 4.08 log *P* units in the mutually saturated partitioning systems made of water and respectively 1-octanol, diethyl ether, chloroform, carbon tetrachloride, or *n*-hexane. Similar results, e.g., 2.29, 2.45, 2.86, 3.03, 3.95, and 3.77, are observed in the case of *o*-hydroxybenzoic acid. By enlarging the difference in the H-bond donor or acceptor capacity of the coexisting phases, the model predicts the internally H-bonded molecules and conjugated functional groups containing solutes to have an increasing lipophobic character, which does not reflect the reality at all. The reason is that, with water/saturated solvent 1-octanol, ether, and chloroform systems which exhibit H-bond acceptor and/or donor properties such as the aqueous phase and include relative amounts of water molecules, all overestimations of the polar and H-bonding interactions in the organic phase partly cancel the corresponding but larger effects occurring in the water phase. In this case, both coexisting phases behave similarly with respect to the solute solvation and the errors are accordingly reduced. In contrast, in water/inert solvent systems and water/alkanes in particular, all overestimations in estimating the specific interactions that occur in the water phase are never counterbalanced by some corresponding effects in the organic phase. This absence in partial cancellation of the overestimations gives rise to very large errors in the partition coefficient evaluation and leads one to attribute the solute a too-high lipophobic character. These particular sources of error (conjugaison and internal H-bonding) may partly explain the relative variation in the prediction accuracies of the model reported in Table 7 with respect to the partitioning solvent systems. The more alike the solvent phases, the smaller the error in the log *P* estimation arising from the specific solvation of conjugated and/or internally H-bonded substances.

Practically, the overall model prediction accuracy, as measured by the standard deviation of the residuals, substantially changes by retrieving five compounds, namely, the *o*- and *p*-hydroxybenzoic acids a well as the *o*- and *p*-methoxybenzoic acids and hydroquinone from the whole

Table 3. Predicted vs Experimental[69] Water/Organic Solvent log *P* Values at 25 °C

	for given organic solvent											
	octanol		diethyl ether		$CHCl_3$		benzene		CCl_4		hexane	
solute	expt	calc	expt	calc	expt	calc	expt	calc	expt	calc	expt	calc
acetone	−0.24	−0.24	−0.21	−0.13	0.24	−0.74	−0.05	−0.06	−0.30	−0.29	−0.91	−0.79
methyl acetate	0.18	−0.01	0.43	0.24	1.16	1.11	0.53	0.31	0.32	0.08	−0.26	−0.43
ethyl acetate	0.73	0.66	0.93	0.99	1.80	1.83	1.01	1.07	0.95	0.85	0.29	0.30
pyridine	0.65	0.57	0.08	0.70	1.43	1.53	0.41	0.77	0.23	0.58	−0.21	0.10
methanol	−0.77	−0.95	−1.15	−1.27	−1.26	−1.91	−1.89	−2.11	−2.10	−2.68	−2.80	−2.89
ethanol	−0.31	−0.32	−0.57	−0.58	−0.85	−1.22	−1.62	−1.42	−1.40	−1.96	−2.10	−1.16
1-propanol	0.25	0.24	−0.02	0.04	−0.40	−0.58	−0.70	−0.80	−0.82	−1.33	−1.52	−1.53
1-butanol	0.88	0.83	0.61	0.68	0.45	0.07	−0.12	−0.14	−0.40	−0.68	−0.70	−0.94
2-methyl-2-propanol	0.65	0.86	0.65	0.71	0.34	0.08	−0.11	−0.14	−0.32	−0.66	−0.60	−0.81
1-pentanol	1.56	1.41	1.20	1.31	1.05	0.70	0.62	0.48	0.40	−0.05	−0.40	−0.27
1-hexanol	2.03	1.98	1.80	1.94	1.69	1.34	1.30	1.10	0.95	0.58	0.46	0.38
1-heptanol	2.41	2.56	2.40	2.58	2.41	1.98	1.91	1.73	1.67	1.22	1.01	1.00
phenol	1.46	1.24	1.64	1.38	0.39	0.48	0.36	0.27	−0.36	−0.30	−0.70	−0.63
2-naphthol	2.70	2.66	1.77	2.94	1.74	2.06	1.74	1.83	0.99	1.26	0.30	0.87
ethylamine	−0.30	−0.46	−1.18	−1.15	−0.35	−0.33	−1.30	−0.92	−1.27	−0.94	−1.77	−1.14
propylamine	0.28	0.12	−0.54	−0.40	0.26	0.30	−0.52	−0.34	−0.59	−0.31	−1.00	−0.49
butylamine	0.74	0.68	0.11	0.13	0.99	0.90	−0.08	0.19	0.11	0.29	0.30	0.16
aniline	0.90	1.34	0.85	1.06	1.26	1.26	1.00	0.87	0.60	0.28	−0.15	−0.08
trimethylamine	0.27	−0.06	−0.26	−0.37	0.54	0.89	−0.29	−0.33	−0.09	−0.17	−0.48	−0.21
diethylamine	0.57	0.79	−0.07	0.17	0.81	0.79	−0.05	0.22	0.03	0.39	−0.48	0.34
acetic acid	−0.17	−0.14	−0.34	−0.58	−1.52	−1.50	−2.26	−1.89	−2.45	−2.25	−3.06	−2.47
propionic acid	0.33	0.38	0.27	0.01	−0.96	−0.92	−1.35	−1.32	−1.60	−1.66	−2.14	−1.87
butyric acid	0.79	0.88	0.61	0.56	−0.27	−0.35	−0.96	0.77	−0.97	−1.10	−1.76	−1.30
pentanoic acid	1.39	1.37	1.00	1.11	0.28	0.20	−0.10	0.23	−0.42	−0.55	−1.00	−0.76
hexanoic acid	1.92	1.85	1.95	1.65	1.15	0.74	0.30	0.31	0.57	−0.01	−0.46	−0.23
chloroacetic acid	0.22	0.20	0.37	−0.78	−1.35	−1.70	−1.60	−2.09	−2.56	−2.45	−3.14	−2.71
dichloroacetic acid	0.92	0.59	1.31	−0.34	−0.89	−1.25	−1.40	−1.64	−2.31	−2.03	−2.72	−2.33
trichloroacetic acid	1.33	1.14	1.21	0.27	−0.69	−0.62	−1.30	−1.03	−1.66	−1.39	−2.63	−1.71
benzoic acid	1.87	1.35	1.89	1.55	0.50	0.37	0.21	0.29	−0.22	−0.60	−0.72	−0.95
2-nitroaniline	1.85	1.18	1.95	0.97	2.13	1.19	1.78	0.79	1.08	0.19	0.25	−0.21
2-nitrophenol	1.79	0.87	2.18	1.06	0.60	0.16	0.48	−0.05	−0.64	−0.70	−1.40	−1.14
2-methoxyphenol	1.32	0.98	1.44	1.21	1.70	0.99	1.32	0.09	0.98	−0.44	0.36	−0.73
2-methoxybenzoic acid	1.59	0.94	0.78	1.24	2.53	0.74	2.68	−0.03	2.40	−0.88	2.08	−1.20
2-hydroxybenzoic acid	2.26	−0.03	2.37	−0.08	0.58	−2.28	0.50	−2.53	0.00	−3.95	−0.57	−4.34
2-aminobenzoic acid	1.21	0.24	1.43	−0.22	−1.15	−1.30	−0.40	−2.25	−1.10	−3.16	−2.12	−3.59
3-nitroaniline	1.37	1.30	1.71	0.97	1.61	1.19	1.31	0.79	0.45	0.19	−0.62	−0.21
3-nitrophenol	2.00	0.87	2.18	1.06	0.60	0.16	0.48	−0.05	−0.64	−0.70	−1.40	−1.14
3-nitrobenzoic acid	1.83	0.90	1.97	1.16	0.48	−0.01	0.21	−0.10	0.15	−1.05	−1.22	−1.52
4-nitroaniline	1.39	1.18	1.48	0.97	1.23	1.19	0.93	0.79	−1.14	0.19	−1.14	−0.21
4-nitrophenol	1.94	0.87	2.01	1.06	0.20	0.16	0.17	−0.05	−0.92	−0.70	−2.00	−1.14
4-methoxyphenol	1.34	0.98	1.47	1.21	0.23	0.98	0.27	0.09	−0.34	−0.44	−0.76	−0.73
hydroquinone	0.59	−0.13	0.38	−0.26	0.23	−2.17	0.15	−2.55	0.04	−3.66	0.05	−4.03
4-hydroxybenzaldehyde	1.35	0.20	1.10	0.35	−0.12	−0.55	−0.55	−0.76	−1.70	−1.33	−0.95	−1.67
4-hydroxybenzoic acid	1.58	−0.03	1.42	−0.08	−0.50	−2.28	−1.07	−2.53	−1.38	−3.95	−1.82	−4.34
4-aminobenzoic acid	0.83	0.24	0.88	−0.22	−1.52	−1.30	−1.46	−2.25	−2.48	−3.16	−3.74	−3.59

data set. In doing this, the value of the standard deviation is lowered from 0.55 to 0.48 log *P* units, and the best regressions between calculated and experimental values are improved:

$$\text{for the whole data set:}\quad \log P^{\text{calc}}\ 0.993(\pm 0.005)\ \log P^{\text{expt}}$$

$$n = 2297;\quad r^2 = 0.94;\quad S_{y,x} = 0.55 \qquad (13)$$

minus five compounds

$$\log P^{\text{calc}} = 0.997(\pm 0.004)\ \log P^{\text{expt}}$$

$$n = 2263;\quad r^2 = 0.96;\quad S_{y,x} = 0.48 \qquad (14)$$

Finally, another theoretical source of errors could originate from the uncertainties associated with the group increment method used for calculating the molar volume of the supercooled solutes. As a matter of fact, such a procedure neither differentiates between structural isomers nor accounts for the three-dimensional structures of the molecules. As a matter of fact, a conformational change of the solute when going from one phase to another may have an impact on its partition behavior.

From the experimental point of view, the reported partition coefficient values of a chemical in a given distribution system seem to vary largely according to the experimental measurement method used. Moreover, in most nontraditional partitioning systems, measurements arising from different laboratories often yield more disperse values and are far from being as self-consistent as those obtained in the traditional 1-octanol/water system (see for instance the tabulations of log *P* values reported by Hansch and Leo in ref 73).

In conclusion, the present results clearly demonstrate that the MOD theory-derived partition model enables one real quantitative a priori predictions of the partition coefficient of at least simple solutes in a large number of binary solvent systems. The order of magnitude of the log *P* values, which spans over a 15-fold log *P* range, is in most cases obtained theoretically. Nevertheless, due to the data limitation to

Table 4. Experimental[a] and Predicted Non-Aqueous-Phase Liquid (NAPL)/Water log *P* Values of Selected Solutes at 25 °C and the Free Energy Contributions ΔB, ΔF, ΔD, and $\Delta(O + OH)$[b]

NAPL	log P_{expt}	log P_{pred}	ΔB	ΔD	ΔF	$\Delta O + \Delta OH$	ref	NAPL	log P_{expt}	log P_{pred}	ΔB	ΔD	ΔF	$\Delta O + \Delta OH$	ref
n-Octane ($V_B = 163.5$ cm^3 mol^{-1}, $\delta'_B = 14.85$ MPa$^{1/2}$)															
n-hexadecane	5.79	6.30	−2.45	0.90	7.85		53	chloroform	6.01	6.47	−1.85	0.47	7.85		71
dibutyl ether	5.95	6.33	−2.24	0.72	7.85		70	1-octanol	5.15	6.02	−2.21	0.83	7.40		72
Cyclohexane ($V_B = 108.8$ cm^3 mol^{-1}, $\delta'_B = 14.82$ MPa$^{1/2}$)															
n-hexadecane	3.91	3.99	−1.83	0.60	5.22		53	chloroform	4.16	4.20	−1.34	0.32	5.22		71
cyclohexane	4.15	3.86	−1.48	0.11	5.22		53	1-octanol	3.44	3.85	−1.63	0.56	4.92		72
dibutyl ether	3.91	4.05	−1.65	0.48	5.22		70								
Benzene ($V_B = 89.4$ cm^3 mol^{-1}, $\delta'_B = 18.95$ MPa$^{1/2}$)															
n-hexane	2.33	1.91	−1.36	−0.30	4.29	−0.73	73	PGDP	2.36	1.74	−1.69	−0.13	4.29	−0.73	70
n-heptane	2.26	1.88	−1.40	−0.28	4.29	−0.73	73	triolein	2.25	1.55	−1.91	−0.09	4.29	−0.73	74
n-hexadecane	2.15	1.78	−1.61	−0.17	4.29	−0.73	53	chloroform	2.80	2.41	−1.16	0.01	4.29	−0.73	73
cyclohexane	2.01	2.01	−1.28	−0.26	4.29	−0.73	53	1-octanol	2.13	1.81	−1.42	−0.08	4.05	−0.73	72
Toluene ($V_B = 106.9$ cm^3 mol^{-1}, $\delta'_B = 18.10$ MPa$^{1/2}$)															
n-hexane	2.75	2.64	−1.54	−0.22	5.13	−0.73	73	PGDP	2.89	2.44	−1.89	−0.06	5.13	−0.73	70
n-heptane	2.85	2.61	−1.58	−0.20	5.13	−0.73	73	triolein	2.77	2.25	−2.12	−0.03	5.13	−0.73	74
n-hexadecane	2.68	2.49	−1.81	−0.10	5.13	−0.73	53	chloroform	3.41	3.09	−1.32	0.01	5.13	−0.73	73
cyclohexane	2.99	2.76	−1.46	−0.18	5.13	−0.73	53	1-octanol	2.73	2.47	−1.61	−0.02	4.84	−0.73	72
dibutyl ether	3.19	2.78	−1.63	0.01	5.13	−0.73	70								
2-Propanone ($V_B = 74.0$ cm^3 mol^{-1}, $\delta'_B = 21.91$ MPa$^{1/2}$)															
n-hexane	−0.92	−0.79	−1.20	−0.70	3.55	−2.44	73	tetrachloroethylene	−0.55	−0.09	−1.10	−0.10	3.55	−2.44	73
n-heptane	−0.91	−0.81	−1.23	−0.68	3.55	−2.44	75	carbon disulfide	−0.52	0.08	−0.88	−0.15	3.55	−2.44	73
n-hexadecane	−1.09	−0.85	−1.44	−0.51	3.55	−2.44	53	diethyl ether	−0.21	−0.13	−1.12	−0.13	3.55	−2.44	73
cyclohexane	−0.96	−0.67	−1.13	−0.65	3.55	−2.44	73	dibutyl ether	−0.60	−0.43	−1.28	−0.26	3.55	−2.44	70
CCl_4	−0.34	−0.29	−1.09	−0.31	3.55	−2.44	73	chloroform	0.24	0.74	−1.01	−0.03	3.55	−1.77	69
benzene	−0.04	−0.06	−1.05	−0.11	3.55	−2.44	73	1,1,2,2-tetrachloroethane	0.63	0.54	−1.12	−0.04	3.55	−1.86	73
toluene	−0.31	−0.20	−1.12	−0.19	3.55	−2.44	73	pentachloroethane	0.22	0.46	−1.17	−0.02	3.55	−1.90	73
trichloroethylene	0.05	−0.15	−1.06	−0.20	3.55	−2.44	73	1-octanol	−0.24	−0.21	−1.26	−0.18	3.35	−2.13	72
2-Pentanone ($V_B = 106.4$ cm^3 mol^{-1}, $\delta'_B = 20.13$ MPa$^{1/2}$)															
n-heptane	0.43	0.53	−1.57	−0.56	5.11	−2.44	75	cyclohexane	0.44	0.68	−1.45	−0.53	5.11	−2.44	53
n-hexadecane	0.18	0.48	−1.80	−0.38	5.11	−2.44	53	1-octanol	0.84	0.97	−1.60	−0.11	4.81	−2.13	72
2-Heptanone ($V_B = 140.8$ cm^3 mol^{-1}, $\delta'_B = 19.49$ MPa$^{1/2}$)															
n-hexadecane	1.53	1.75	−2.19	−0.37	6.77	−2.44	53	1-octanol	1.98	2.17	−1.97	−0.10	6.37	−2.13	72
cyclohexane	1.78	1.98	−1.80	−0.54	6.76	−2.44	53								
Acetophenone ($V_B = 116.9$ cm^3 mol^{-1}, $\delta'_B = 18.31$ MPa$^{1/2}$)															
n-hexane	1.15	1.46	−1.64	−0.29	5.61	−2.22	73	dibutyl ether	1.61	1.63	−1.74	−0.02	5.61	−2.22	70
n-heptane	1.08	1.43	−1.69	−0.27	5.61	−2.22	73	propylene glycol dipelargonate	1.63	1.28	−2.00	−0.11	5.61	−2.22	70
n-hexadecane	1.14	1.32	−1.92	−0.15	5.61	−2.22	53	triolein	1.61	1.08	−2.24	−0.07	5.61	−2.22	74
cyclohexane	1.25	1.58	−1.56	−0.25	5.61	−2.22	73	chloroform	2.79	2.65	−1.41	−0.00	5.61	−1.55	73
benzene	2.20	1.92	−1.46	−0.01	5.61	−2.22	73	1,2-dichloroethane	2.38	2.43	−1.54	−0.00	5.61	−1.64	73
diethyl ether	1.75	1.84	−1.54	−0.00	5.61	−2.22	73	1-octanol	1.58	1.64	−1.71	−0.03	5.29	−1.91	72
Ethyl Acetate ($V_B = 98.5$ cm^3 mol^{-1}, $\delta'_B = 20.79$ MPa$^{1/2}$)															
n-hexane	0.29	0.32	−1.45	−0.67	4.73	−2.29	69	benzene	1.01	1.09	−1.29	−0.06	4.73	−2.29	73
n-heptane	0.29	0.30	−1.49	−0.65	4.73	−2.29	75	diethyl ether	0.93	1.01	−1.36	−0.07	4.73	−2.29	73
n-hexadecane	0.15	0.26	−1.71	−0.46	4.73	−2.29	53	chloroform	1.80	1.86	−1.24	−0.02	4.73	−1.61	75
cyclohexane	0.34	0.45	−1.38	−0.62	4.73	−2.29	53	1,2-dichloroethane	1.34	1.89	−1.23	−0.00	4.73	−1.61	76
CCl_4	0.82	0.87	−1.33	−0.24	4.73	−2.29	73	2-methyl-2-propanol	0.86	0.84	−1.31	−0.17	4.27	−1.95	73
carbon disulfide	0.72	1.11	−1.09	−0.09	4.73	−2.29	73	1-octanol	0.73	0.70	−1.52	−0.18	4.46	−2.06	72
Trimethylamine ($V_B = 63.80$ cm^3 mol^{-1}, $\delta'_B = 14.10$ MPa$^{1/2}$)															
n-hexane	−0.48	−0.96	−0.94	−0.00	2.60	−2.62	69	diethyl ether	−0.26	−1.12	−0.86	−0.24	2.60	−2.62	69
n-hexadecane	−0.73	−1.21	−1.17	−0.02	2.60	−2.62	53	isopropyl ether	−0.36	−1.16	−0.96	−0.18	2.60	−2.62	73
cyclohexane	−0.44	−0.90	−0.88	−0.01	2.60	−2.62	73	dibutyl ether	−0.36	−1.16	−1.02	−0.12	2.60	−2.62	70
benzene	−0.29	−1.08	−0.81	−0.26	2.60	−2.62	69	chloroform	0.54	−0.11	−0.77	−0.03	2.60	−1.69	69
toluene	−0.22	−1.06	−0.87	−0.18	2.60	−2.62	73	2-methyl-2-propanol	0.49	−0.52	−0.82	−0.10	2.30	−1.99	73
CCl_4	−0.09	−0.95	−0.84	−0.10	2.60	−2.62	73	1-octanol	0.16	−0.75	−1.00	−0.02	2.43	−2.16	72
Triethylamine ($V_B = 63.80$ cm^3 mol^{-1}, $\delta'_B = 14.10$ MPa$^{1/2}$)															
n-hexadecane	1.45	1.16	−1.89	−0.01	5.67	−2.62	53	CCl_4	0.90	1.52	−1.44	−0.10	5.67	−2.62	73
cyclohexane	1.10	1.56	−1.49	−0.00	5.67	−2.62	73	2-methyl-2-propanol	1.32	1.61	−1.41	−0.01	5.02	−1.99	73
benzene	1.13	1.28	−1.39	−0.38	5.67	−2.62	73	*prim.* pentanols	1.42	1.56	−1.49	−0.02	5.11	−2.04	73
toluene	0.89	1.33	−1.49	−0.23	5.67	−2.62	73	1-octanol	1.45	1.45	−1.66	−0.02	5.29	−2.16	72
xylene	1.11	1.38	−1.55	−0.12	5.67	−2.62	73								
Pyridine ($V_B = 80.6$ cm^3 mol^{-1}, $\delta'_B = 20.94$ MPa$^{1/2}$)															
n-hexane	−0.21	0.10	−1.26	−0.57	3.87	−1.92	69	diethyl ether	0.08	0.70	−1.18	−0.07	3.87	−1.92	73
n-heptane	−0.31	0.08	−1.30	−0.56	3.87	−1.92	75	dibutyl ether	0.20	0.42	−1.35	−0.17	3.87	−1.92	75
n-octane	−0.21	0.08	−1.34	−0.52	3.87	−1.92	73	butyl acetate	0.45	0.65	−1.27	−0.02	3.87	−1.92	75
n-hexadecane	−0.31	0.03	−1.51	−0.40	3.87	−1.92	73	propylene glycol dipelargonate	0.08	0.01	−1.59	−0.34	3.87	−1.92	75
cyclohexane	−0.31	0.22	−1.20	−0.53	3.87	−1.92	73	chloroform	1.32	1.53	−1.07	−0.01	3.87	−1.25	75
benzene	0.45	0.77	−1.12	−0.06	3.87	−1.92	73	1,2-dichloroethane	0.72	1.56	−1.06	0.00	3.87	−1.24	75
toluene	0.22	0.64	−1.19	−0.11	3.87	−1.92	73	2-methyl-2-propanol	0.86	0.77	−1.13	−0.11	3.49	−1.47	73
xylene	0.31	0.51	−1.24	−0.20	3.87	−1.92	73	*tert*-pentanol	0.61	0.69	−1.20	−0.14	3.55	−1.52	73
CCl_4	0.32	0.58	−1.15	−0.21	3.87	−1.92	73	1-octanol	0.65	0.58	−1.33	−0.13	3.65	−1.61	72

Table 4 (Continued)

NAPL	log P_{expt}	log P_{pred}	ΔB	ΔD	ΔF	$\Delta O + \Delta OH$	ref	NAPL	log P_{expt}	log P_{pred}	ΔB	ΔD	ΔF	$\Delta O + \Delta OH$	ref
Phenol ($V_B = 89.0$ cm^3 mol^{-1}, $\delta'_B = 18.43$ MPa$^{1/2}$)															
n-pentane	−0.70	−0.63	−1.30	−0.28	3.40	−2.44	73	*m*-nitrotoluene	0.91	0.77	−1.31	−0.01	3.40	−1.31	73
n-hexane	−0.60	−0.62	−1.35	−0.23	3.40	−2.44	73	ethyl acetate	1.76	1.43	−1.24	−0.00	3.40	−0.73	73
n-heptane	−0.87	−0.65	−1.39	−0.22	3.40	−2.44	73	butyl acetate	1.66	1.19	−1.35	−0.00	3.40	−0.86	73
n-octane	−0.89	−0.67	−1.43	−0.20	3.40	−2.44	73	ispopentyl acetate	1.64	1.10	−1.39	−0.00	3.40	−0.90	73
isooctane	−1.02	−0.62	−1.43	−0.15	3.40	−2.44	73	*n*-hexyl acetate	1.60	1.02	−1.43	−0.00	3.40	−0.95	73
n-nonane	−0.75	−0.68	−1.56	−0.18	3.40	−2.44	73	*n*-heptyl acetate	1.54	0.95	−1.46	−0.00	3.40	−0.99	73
n-decane	−0.82	−0.70	−1.49	−0.17	3.40	−2.44	73	methyl decanoate	1.21	0.85	−1.51	−0.00	3.40	−1.04	73
n-dodecane	−0.70	−0.72	−1.53	−0.15	3.40	−2.44	73	propylene glycol dipelargonate	1.17	0.41	−1.68	−0.00	3.40	−1.30	70
n-hexadecane	−1.08	−0.77	−1.61	−0.12	3.40	−2.44	53	diethyl ether	1.71	1.38	−1.26	−0.00	3.40	−0.75	73
3-methylpentane	−0.96	−0.63	−1.35	−0.24	3.40	−2.44	73	diisopropyl ether	1.12	1.14	−1.38	−0.00	3.40	−0.88	73
cyclohexane	−0.82	−0.52	−1.28	−0.20	3.40	−2.44	73	dibutyl ether	1.01	1.00	−1.44	−0.00	3.40	−0.96	70
methylcyclohexane	−0.89	−0.57	−1.34	−0.18	3.40	−2.44	73	diethyl ketone	1.20	1.37	−1.27	−0.00	3.40	−0.76	73
decaline	−0.94	−0.46	−1.41	−0.00	3.40	−2.44	73	isobutyl methyl ketone	2.04	1.23	−1.33	−0.00	3.40	−0.83	73
CCl_4	−0.38	−0.30	−1.23	−0.03	3.40	−2.44	73	bromoform	0.19	0.41	−1.19	−0.01	3.40	−1.80	73
trichloroethylene	0.02	−0.25	−1.20	−0.00	3.40	−2.44	73	chloroform	0.32	0.48	−1.15	−0.00	3.40	−1.77	73
tetrachloroethylene	−0.37	−0.30	−1.25	−0.01	3.40	−2.44	73	dichloromethane	0.69	0.66	−1.04	−0.00	3.40	−1.69	73
carbon disulfide	−0.26	−0.05	−1.01	−0.00	3.40	−2.44	73	1,2-dichloroethane	0.60	0.67	−1.14	−0.00	3.40	−1.58	73
benzene	0.36	0.27	−1.20	−0.00	3.40	−1.93	73	1,1,2,2-tetrachloroethane	0.42	0.45	−1.27	−0.00	3.40	−1.68	73
toluene	0.21	0.14	−1.27	−0.00	3.40	−1.99	73	pentachloroethane	0.04	0.35	−1.32	−0.00	3.40	−1.73	73
ethylbenzene	0.15	0.05	−1.33	−0.00	3.40	−2.02	73	$CHCl(CH_2Cl)_2$	0.56	0.39	−1.30	−0.00	3.40	−1.71	73
n-butylbenzene	0.10	−0.11	−1.41	−0.01	3.40	−2.09	73	1-pentanol	1.43	1.43	−1.28	−0.00	3.48	−0.77	73
xylene	0.11	0.04	−1.33	−0.01	3.40	−2.02	73	1-hexanol	1.51	1.36	−1.33	−0.00	3.53	−0.83	73
mesitylene	0.13	−0.04	−1.37	−0.01	3.40	−2.06	73	1-heptanol	1.52	1.30	1.38	−0.00	3.56	−0.88	73
chlorobenzene	0.25	0.17	−1.25	−0.01	3.40	−1.97	73	1-octanol	1.46	1.26	−1.42	−0.00	3.59	−0.93	73
bromobenzene	0.18	0.11	−1.27	−0.04	3.40	−1.98	73	1-nonanol	1.46	1.19	−1.45	−0.00	3.61	−0.97	73
iodobenzene	0.10	0.09	−1.29	−0.03	3.40	−2.00	73	1-decanol	1.43	1.14	−1.48	−0.00	3.63	−1.01	73
nitrobenzene	0.91	0.89	−1.26	−0.01	3.40	−1.25	73	oleyl alcohol	1.19	0.86	−1.63	0.00	3.71	−1.22	73
o-nitrotoluene	0.86	0.78	−1.31	−0.01	3.40	−1.31	73								
Ethylamine ($V_B = 66.0$ cm^3 mol^{-1}, $\delta'_B = 17.61$ MPa$^{1/2}$)															
n-hexane	−1.77	−1.14	−1.11	−0.11	2.30	−2.22	69	ethylbenzene	−0.57	−0.60	−1.09	−0.00	2.30	−1.80	73
n-heptane	−0.85	−1.17	−1.15	−0.10	2.30	−2.22	73	xylene	−0.66	−0.60	−1.09	−0.00	2.30	−1.80	73
n-hexadecane	−1.62	−1.32	−1.35	−0.05	2.30	−2.22	53	chlorobenzene	−0.55	−0.49	−1.03	−0.01	2.30	−1.75	73
cyclohexane	−1.80	−1.06	−1.05	−0.09	2.30	−2.22	53	diethyl ether	−1.18	−0.98	−1.04	−0.02	2.30	−2.22	73
CCl_4	−1.27	−0.94	−1.01	−0.00	2.30	−2.22	69	chloroform	−0.35	−0.33	−0.94	−0.00	2.30	−1.68	69
benzene	−0.60	−0.39	−0.98	−0.00	2.30	−1.71	73	1-octanol	−0.30	−0.68	−1.17	−0.00	2.55	−2.05	72
toluene	−1.28	−0.51	−1.04	−0.00	2.30	−1.76	73								
n-Propylamine ($V_B = 82.4$ cm^3 mol^{-1}, $\delta'_B = 16.72$ MPa$^{1/2}$)															
n-hexane	−1.00	−0.49	−1.28	−0.07	3.09	−2.22	69	ethylbenzene	0.15	0.02	−1.26	−0.01	3.09	−1.80	73
n-heptane	−0.09	−0.52	−1.32	−0.06	3.09	−2.22	73	xylene	−0.36	0.02	−1.26	−0.00	3.09	−1.80	73
n-hexadecane	−1.08	−0.69	−1.53	−0.02	3.09	−2.22	53	chlorobenzene	0.15	0.11	−1.19	−0.04	3.09	−1.75	73
cyclohexane	−0.98	−0.40	−1.21	−0.05	3.09	−2.22	53	diethyl ether	−0.54	−0.40	−1.20	−0.06	3.09	−2.22	73
CCl_4	−0.59	−0.31	−1.17	−0.00	3.09	−2.22	69	chloroform	0.26	0.30	−1.09	−0.02	3.09	−1.68	69
benzene	0.18	0.22	−1.13	−0.02	3.09	−1.71	73	1-octanol	0.48	−0.10	−1.35	−0.00	3.29	−2.05	72
toluene	−0.65	0.11	−1.21	−0.01	3.09	−1.76	73								
n-Butylamine ($V_B = 98.6$ cm^3 mol^{-1}, $\delta'_B = 15.83$ MPa$^{1/2}$)															
n-hexane	0.30	0.16	−1.45	−0.03	3.86	−2.22	69	xylene	0.04	0.62	−1.43	−0.01	3.86	−1.80	73
n-heptane	0.30	0.13	−1.49	−0.02	3.86	−2.22	73	chlorobenzene	0.71	0.69	−1.35	−0.08	3.86	−1.75	73
n-hexadecane	−0.49	−0.07	−1.72	−0.00	3.86	−2.22	53	diethyl ether	0.11	0.13	−1.36	−0.15	3.86	−2.22	73
cyclohexane	−0.29	0.25	−1.38	−0.02	3.86	−2.22	53	diisopropyl ether	−0.04	0.07	−1.48	−0.09	3.86	−2.22	73
CCl_4	0.11	0.29	−1.33	−0.02	3.86	−2.22	73	chloroform	0.99	0.90	−1.24	−0.04	3.86	−1.68	73
benzene	0.65	0.81	−1.29	−0.05	3.86	−1.71	73	2-methyl-2-propanol	0.92	0.85	−1.31	−0.00	3.84	−1.68	73
toluene	0.30	0.70	−1.37	−0.03	3.86	−1.76	73	1-octanol	0.75	0.45	−1.52	−0.00	4.03	−2.05	72
ethylbenzene	0.68	0.61	−1.43	−0.03	3.86	−1.80	73								
Aniline ($V_B = 91.1$ cm^3 mol^{-1}, $\delta'_B = 18.77$ MPa$^{1/2}$)															
n-hexane	−0.07	−0.08	−1.37	−0.28	3.50	−1.92	73	diethyl ether	0.85	1.06	−1.29	−0.00	3.50	−1.16	73
n-heptane	0.03	−0.10	−1.41	−0.27	3.50	−1.92	73	dibutyl ether	0.71	0.71	−1.46	−0.01	3.50	−1.33	70
cyclohexane	0.03	0.03	−1.30	−0.25	3.50	−1.92	73	propylene glycol dipelargonate	0.95	0.18	−1.71	−0.05	3.50	−1.57	70
CCl_4	0.42	0.28	−1.25	−0.05	3.50	−1.92	73	ethyl acetate	1.40	1.09	−1.26	−0.01	3.50	−1.14	73
benzene	1.02	0.88	−1.22	−0.00	3.50	−1.41	73	butyl acetate	1.25	0.88	−1.38	−0.00	3.50	−1.24	73
toluene	0.83	0.74	−1.29	−0.00	3.50	−1.47	73	isopentyl acetate	1.20	0.80	−1.42	−0.00	3.50	−1.28	73
xylene	0.72	0.64	−1.35	−0.01	3.50	−1.50	73	chloroform	1.32	1.27	−1.17	−0.00	3.50	−1.07	73
chlorobenzene	0.90	0.77	−1.28	−0.00	3.50	−1.45	73	1,2-dichloroethane	1.45	1.27	−1.16	−0.01	3.50	−1.06	73
bromobenzene	0.86	0.72	−1.29	−0.03	3.50	−1.46	73	1-octanol	0.90	1.34	−1.44	−0.01	3.69	−0.90	72
o-Toluidine ($V_B = 107.3$ cm^3 mol^{-1}, $\delta'_B = 18.53$ MPa$^{1/2}$)															
n-heptane	0.51	0.46	−1.57	−0.28	4.23	−1.92	73	CCl_4	1.18	0.87	−1.40	−0.04	4.23	−1.92	73
n-octane	0.37	0.45	−1.61	−0.25	4.23	−1.92	73	benzene	1.33	1.46	−1.36	−0.00	4.23	−1.41	73
n-hexadecane	0.38	0.35	−1.80	−0.16	4.23	−1.92	73	chloroform	1.96	1.85	−1.31	−0.00	4.23	−1.07	75
cyclohexane	0.64	0.60	−1.45	−0.26	4.23	−1.92	73	1-octanol	1.43	1.87	−1.60	−0.01	4.37	−0.90	72

Table 4 (Continued)

NAPL	log P_{expt}	log P_{pred}	ΔB	ΔD	ΔF	ΔO + ΔOH	ref	NAPL	log P_{expt}	log P_{pred}	ΔB	ΔD	ΔF	ΔO + ΔOH	ref
Butyric Acid ($V_B = 92.0$ cm^3 mol^{-1}, $\delta'_B = 16.83$ MPa$^{1/2}$)															
n-hexane	−1.76	−1.30	−1.18	−0.08	2.88	−2.92	69	*o*-nitrotoluene	−0.44	−0.23	−1.14	−0.03	2.88	−1.94	73
n-heptane	−0.96	−1.33	−1.22	−0.08	2.88	−2.92	75	diethyl ether	0.61	0.56	−1.09	−0.00	2.88	−1.23	75
n-octane	−1.76	−1.36	−1.26	−0.06	2.88	−2.92	73	diisopropyl ether	0.36	0.32	−1.21	−0.00	2.88	−1.36	73
n-dodecane	−1.87	−1.44	−1.37	−0.04	2.88	−2.92	73	dibutyl ether	0.14	0.17	−1.27	−0.00	2.88	−1.43	70
n-hexadecane	−1.92	−1.50	−1.44	−0.02	2.88	−2.92	73	ethyl acetate	0.72	0.61	−1.07	−0.00	2.88	−1.21	73
cyclohexane	−1.76	−1.21	−1.11	−0.06	2.88	−2.92	53	butyl acetate	0.69	0.37	−1.18	−0.00	2.88	−1.33	75
CCl_4	−0.99	−1.10	−1.06	−0.00	2.88	−2.92	73	2-butanone	0.70	0.68	−1.03	−0.00	2.88	−1.17	73
benzene	−0.76	−0.77	−1.02	−0.03	2.88	−2.59	73	chloroform	−0.27	−0.69	−0.98	−0.03	2.88	−2.57	73
toluene	−0.87	−0.86	−1.10	−0.01	2.88	−2.63	73	dichloromethane	−0.19	−0.58	−0.87	−0.09	2.88	−2.51	70
ethylbenzene	−1.10	−0.95	−1.16	−0.01	2.88	−2.66	73	1,2-dichloroethane	−0.39	−0.77	−0.97	−0.12	2.88	−2.56	73
isopropyllbenzene	−1.05	−1.00	−1.20	−0.00	2.88	−2.68	73	*n*-butanol	0.95	1.14	−1.04	−0.00	2.88	−0.70	73
xylene	−0.79	−0.93	−1.16	−0.00	2.88	−2.66	73	2-methyl-2-propanol	0.95	1.14	−1.04	−0.00	2.89	−0.71	73
chlorobenzene	−1.22	−0.88	−1.08	−0.06	2.88	−2.62	73	*sec*-butanol	0.72	1.14	−1.04	−0.00	2.89	−0.71	73
o-dichlorobenzene	−1.52	−0.92	−1.12	−0.03	2.88	−2.64	73	*n*-pentanol	1.02	1.07	−1.11	−0.00	2.95	−0.78	73
bromobenzene	−1.40	−1.00	−1.10	−0.16	2.88	−2.63	73	2-ethylhexanol	0.86	0.89	−1.24	−0.00	3.06	−0.93	73
iodobenzene	−2.00	−1.00	−1.12	−0.13	2.88	−2.64	73	1-octanol	0.79	0.88	−1.25	−0.00	3.07	0.94	72
nitrobenzene	−0.38	−0.13	−1.09	−0.04	2.88	−1.89	73	oleyl alcohol	0.46	0.50	−1.46	−0.00	3.19	−1.23	73
Valeric Acid ($V_B = 108.8$ cm^3 mol^{-1}, $\delta'_B = 16.63$ MPa$^{1/2}$)															
n-hexane	−1.00	−0.76	−1.32	−0.08	3.57	−2.92	69	diisopropyl ether	1.05	0.86	−1.35	−0.00	3.57	−1.36	73
n-heptane	−0.85	−0.79	−1.37	−0.07	3.57	−2.92	73	dibutyl ether	0.77	0.71	−1.42	−0.00	3.57	−1.44	70
n-octane	−1.18	−0.82	−1.41	−0.06	3.57	−2.92	73	2-butanone	1.01	1.23	−1.16	−0.01	3.57	−1.17	73
n-dodecane	−1.25	−0.90	−1.52	−0.03	3.57	−2.92	73	chloroform	0.33	−0.14	−1.11	−0.04	3.57	−2.57	73
n-hexadecane	−1.14	−0.97	−1.60	−0.02	3.57	−2.92	53	1,2-dichloroethane	0.23	−0.24	−1.09	−0.16	3.57	−2.56	73
cyclohexane	−1.05	−0.66	−1.25	−0.06	3.57	−2.92	53	*n*-butanol	1.36	1.62	−1.17	−0.00	3.49	−0.70	73
CCl_4	−0.42	−0.55	−1.20	−0.00	3.57	−2.92	69	2-methyl-2-propanol	1.39	1.61	−1.18	−0.00	3.49	−0.71	73
benzene	−0.10	−0.23	−1.15	−0.05	3.57	−2.59	73	*sec*-butanol	1.06	1.61	−1.17	−0.00	3.49	−0.71	73
toluene	−0.20	−0.32	−1.24	−0.02	3.57	−2.63	73	*prim*-pentanols	1.48	1.55	−1.25	−0.00	3.57	−0.78	73
xylene	−0.33	−0.39	−1.30	−0.00	3.57	−2.66	73	*sec*-pentanols	1.44	1.55	−1.25	−0.00	3.57	−0.78	73
nitrobenzene	0.23	0.41	−1.22	−0.05	3.57	−1.89	73	2-ethylhexanol	1.36	1.38	−1.39	−0.00	3.70	−0.93	73
diethyl ether	1.26	1.11	−1.23	−0.00	3.57	−1.23	73	1-octanol	1.39	1.37	−1.40	−0.00	3.71	−0.94	72
n-Hexanoic Acid ($V_B = 108.8$ cm^3 mol^{-1}, $\delta'_B = 16.63$ MPa$^{1/2}$)															
n-hexane	−0.46	−0.20	−1.47	−0.06	4.24	−2.92	69	diethyl ether	1.93	1.64	−1.36	−0.00	4.24	−1.23	73
n-heptane	−0.24	−0.24	−1.51	−0.05	4.24	−2.92	75	diisopropyl ether	1.48	1.39	−1.50	−0.00	4.24	−1.36	73
n-octane	−0.52	−0.27	−1.55	−0.04	4.24	−2.92	73	2-butanone	1.36	1.78	−1.29	−0.01	4.24	−1.17	73
n-dodecane	−0.72	−0.37	−1.67	−0.02	4.24	−2.92	73	chloroform	0.95	0.38	−1.23	−0.06	4.24	−2.57	73
n-hexadecane	−0.64	−0.44	−1.76	−0.01	4.24	−2.92	53	1,2-dichloroethane	0.82	0.24	−1.22	−0.22	4.24	−2.57	73
decaline	−0.23	−0.37	−1.54	−0.16	4.24	−2.92	73	*n*-butanol	1.86	2.08	−1.30	−0.00	4.09	−0.70	73
iodomethane	0.81	0.24	−1.07	−0.01	4.24	−2.92	73	2-methyl-2-propanol	1.88	2.08	−1.30	−0.00	4.09	−0.71	73
CCl_4	0.57	−0.02	−1.33	−0.02	4.24	−2.92	73	*sec*-butanol	1.39	2.08	−1.30	−0.00	4.09	−0.71	73
benzene	0.57	0.29	−1.28	−0.08	4.24	−2.59	73	*prim*-pentanols	2.04	2.02	−1.38	−0.00	4.18	−0.78	73
toluene	0.56	0.20	−1.37	−0.04	4.24	−2.63	73	*sec*-pentanols	1.94	2.02	−1.38	−0.00	4.18	−0.78	73
xylene	0.34	0.13	−1.43	−0.01	4.24	−2.66	73	1-octanol	1.92	1.85	−1.54	−0.00	4.33	−0.94	72
nitrobenzene	0.77	0.94	−1.35	−0.06	4.24	−1.89	73	oleyl alcohol	1.65	1.49	−1.78	−0.00	4.51	−1.23	73
Benzoic Acid ($V_B = 108.0$ cm^3 mol^{-1}, $\delta'_B = 18.15$ MPa$^{1/2}$)															
n-hexane	−0.72	−0.94	−1.32	−0.24	3.54	−2.92	69	dibutyl ether	1.86	1.15	−1.41	−0.00	3.54	−0.97	70
n-heptane	−0.72	−0.98	−1.36	−0.23	3.54	−2.92	73	dipentyl ether	0.95	1.01	−1.48	−0.00	3.54	−1.05	73
CCl_4	−0.22	−0.59	−1.19	−0.02	3.54	−2.92	73	ethyl benzoate	1.50	1.29	−1.35	−0.00	3.54	−0.89	73
benzene	0.22	0.29	−1.15	−0.00	3.54	−2.10	73	propylene glycol dipelargonate	1.15	0.54	−1.67	−0.00	3.54	−1.32	70
toluene	0.42	0.14	−1.23	−0.00	3.54	−2.16	73	chloroform	0.56	0.37	−1.10	−0.00	3.54	−2.06	75
xylene	0.12	0.03	−1.29	−0.00	3.54	−2.21	73	2-methyl-2-propanol	1.69	1.59	−1.17	−0.00	3.47	−0.71	73
diethyl ether	1.84	1.55	−1.22	−0.00	3.54	−0.76	73	1-octanol	1.87	1.35	−1.39	−0.00	3.68	−0.94	72

[a] When issued from Hansch's table of ref 73, the experimental log *P* value is taken as the average of all reported values. [b] Δ(O+OH) is the sum of the terms $\Delta(O)$ and Δ(OH) given by the eqs 6 and 7.

essentially nonfunctional or monofunctional compounds, the MOD log *P* model in its present state of development should be regarded as being preliminary for more complex molecules. To pass from the fundamental theory to the practical predictions of the partition coefficient of all chemicals in any mutually saturated two-phase system, much work has to be done until the proposed model might deal with polyfunctional molecules and with conjugated or internally H-bonded structures in particular.

Influence of the Solute Structural Features on Its Water/Organic Solvent Partition Coefficient. Beyond its fairly good predictive capacity, the MOD log *P* model also provides better knowledge of the solute partitioning by both identifying the different physical phenomena enfolded in the distribution process and quantifying their contributions to the overall partition coefficient value. Depending on the functional groups present on the solute, the partition coefficient, as calculated in this work, may encode up to five contributions, namely, two entropic-related components, ΔB and ΔF, and three interaction-related components, one being relative to the nonspecific forces, ΔD, and two being associated with the H-bond interactions, ΔO and ΔOH or more simply Δ(O+OH). Whereas the three former contributions always exist and determine the log *P* dependence on the solute molar volume, the latter combined component is volume-independent and differs from zero only for functional substances able to interact specifically with at least one of the solvent phases. On this basis, all solutes can be separated

Table 7. Physical Properties of Selected Partitioning Systems and the MOD Model Capacity Prediction as Determined from the Goodness of Fit ($\log P^{pred} = a \log P^{expt}$) between Predicted and Experimental log *P* Values Assuming a Zero Intercept for Correct Scaling[a]

(solvent 1/solvent 2)	V_1	δ'_1	*a*	*n*	*r*	$S_{y,x}$
cyclohexane/water	108.8	14.82	1.030 ± 0.027	146	0.95	0.51
n-hexane/water	131.6	14.56	1.024 ± 0.020	138	0.97	0.66
n-heptane/water	147.5	14.66	0.959 ± 0.021	142	0.96	0.59
n-octane/water	163.5	14.85	0.449 ± 0.054	24	0.87	0.33
n-hexadecane/water	294.1	15.61	1.056 ± 0.009	334	0.99	0.44
CCl_4/water	97.1	17.04	0.899 ± 0.146	45	0.68	1.17
benzene/water	89.4	18.95	0.752 ± 0.121	45	0.69	0.89
1,2-dichloroethane/water	78.8	20.99	1.036 ± 0.039	41	0.97	0.52
chloroform/water	80.7	18.77	0.874 ± 0.045	123	0.96	0.58
diethyl ether/water	104.8	18.78	0.810 ± 0.054	68	0.87	0.65
dibutyl ether/water	170.3	17.40	0.911 ± 0.022	87	0.97	0.43
butyl acetate/water	132.5	19.66	0.709 ± 0.057	42	0.89	0.71
PGDP/water	390.1	16.00	0.832 ± 0.032	53	0.96	0.54
triolein/water	949.0	16.43	0.991 ± 0.026	28	0.99	0.54
1-octanol/water	124.2	16.60	0.986 ± 0.008	482	0.98	0.49
n-heptane/ethylene glycol	147.5	14.66	0.943 ± 0.037	56	0.96	0.46

[a] *a*, *n*, *r*, and $S_{y,x}$ are respectively the slope of the regression line (95% confidence intervals are given in parentheses), the number of compounds studied, the correlation coefficient, and the standard deviation of the residuals in log *P* units.

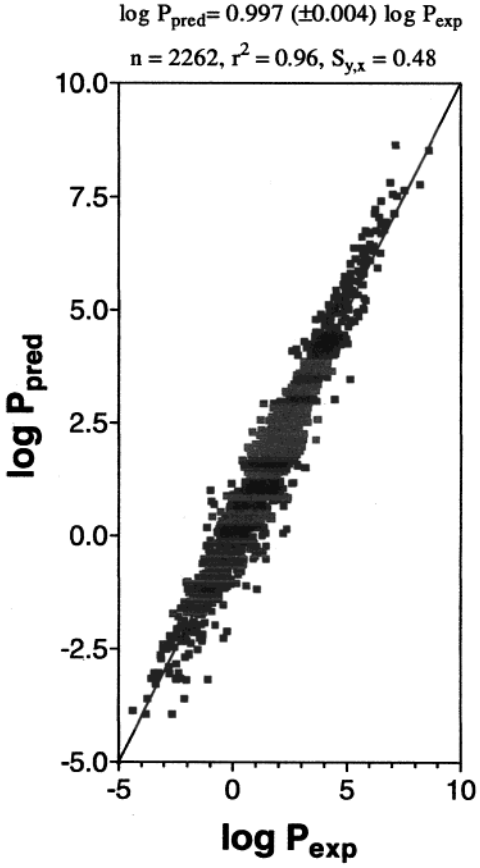

Figure 1. Scatterplot of 2262 predicted vs experimental partition coefficients of solutes (minus the *o*- and *p*-hydroxy- and -methoxybenzoic acids and hydroquinone) distributed in various immiscible two-phase systems. The linear equation (with a zero intercept required for a correct scaling) expresses the best relationship between experimental and predicted values.

into two groups: the inert (or lipophilic) and the complexing (or lipophobic) solutes. Such a difference in the partitioning behaviors is always present regardless of the chemical nature of the organic solvent coexisting with water. However, for convenience, the analysis of the influence of the solute physicochemical profile on its log *P* value has been limited to essentially four different partitioning systems composed of water and one of the nonaqueous phase liquids that constitute the critical "quartet" mentioned in the Introduction. The selected organic liquids are as follows: *n*-hexadecane as apolar aprotic (inert) solvent, dibutyl ether as proton-acceptor solvent, $CHCl_3$ as proton-donor solvent, and 1-octanol as amphiprotic solvent. These four liquids are believed to represent all types of solvents with the largest range of interaction and solubilizing capacity, whereas the four corresponding water/nonaqueous liquid partitioning systems are supposed to sufficiently differ from one another to model all possible effects that may modify the distribution process.

In each partitioning system, the log *P* value is related to the physicochemical profile of the solute in a complex way. It depends in particular on the molar size of the molecule, on its ability to H-bond with one or both phases, and on the relative strengths of these H-bonds. To unravel the respective influence of these factors appropriately, the partitioning of a series of structurally different compounds of comparable volume is first analyzed. The results, illustrated in Figure 2, reveal the following:

(a) Whatever the nature of the solute, the main contribution to the partition coefficient is the hydrophobic effect-related term, ΔF. By increasing strongly with the solute volume and decreasing slightly with the presence of amphiphilic groups, this term appears relatively constant for all the investigated chemicals of similar size, though being a little bit smaller with the amphiprotic solutes such as 1-pentanol, *n*-valeric acid, and *o*-toluidine. The effect of this contribution on the partitioning of the solute is to drive it out of the more polar solvent, e.g., water. Because this contribution is also the only important factor that favors the solute to be preferentially localized in the organic phase, the hydrophobic effect entirely answers for the lipophilicity of the solute and so fully justifies why hydrophobicity is such a good descriptor of lipophilicity.

(b) The nonspecific solvation (dipolarity/polarizability) effect given by the ΔD term remains negligible in most cases, and particularly when H-bonds are formed in at least one of the two solvent phases. Note that, for aliphatic hydrocarbons, this contribution favors the solute transfer into the organic phase, whereas it favors the transfer toward water for all other chemicals.

(c) The hydrophobic effect, ΔF, is partly counterbalanced by another entropic contribution, e.g., the exchange entropy-related term, ΔB. This term only depends on both the solute size and the relative molar volumes of the partitioning solvents. It remains roughly unchanged within a given chemical series, and contrary to the hydrophobic effect, it generally causes the solute to remain in the water phase. So, in the absence of any solute/solvent specific interactions, such as for cyclohexane, the partitioning of the solute essentially originates from two entropic effects acting in opposite directions with respect to the transfer of the solute toward one or the other phase. However, the combined result of these entropic contributions always yields the solute to migrate into the organic phase ($|\Delta F| \gg |\Delta B|$).

(d) What essentially differentiates the partitioning of nonpolar and polar chemicals is that, for the polar com-

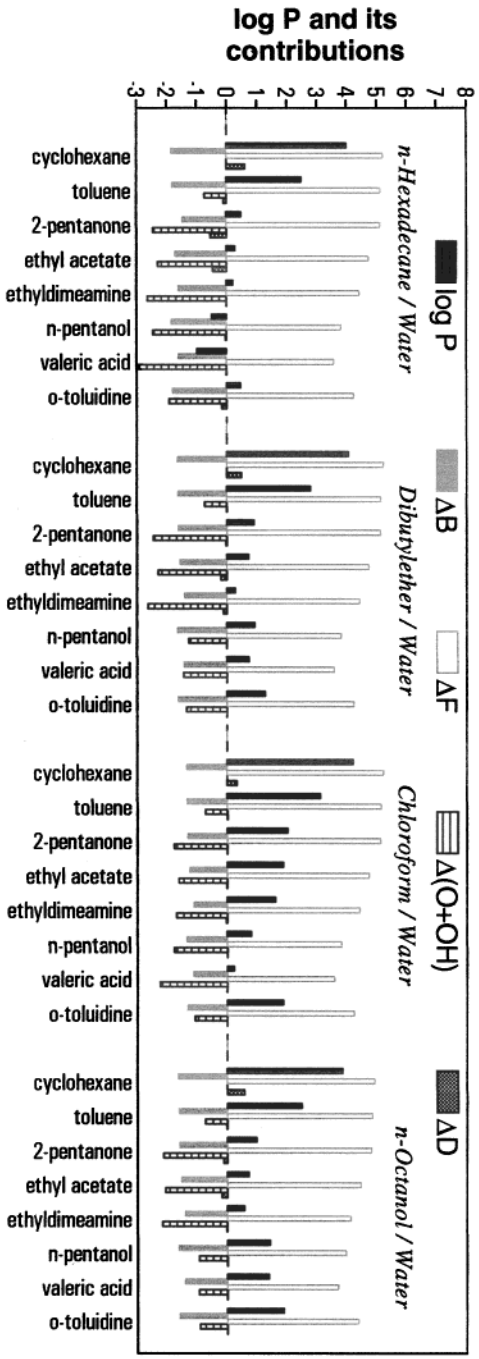

Figure 2. Partition coefficients (and its various contributions) of the same solutes partitioned in four different nonaqueous phase liquid/water systems.

pounds, the combined result of both the hydrophobic and mixing entropy effects is more or less counterbalanced by some solute/solvent functional group associations, i.e., the specific solvation accounted for by the exoergic interaction-related term, Δ(O+OH). As shown by eqs 6 and 7, this contribution only varies with the number and chemical nature of the interaction sites displayed by the solute: the greater the number of these sites and the stronger the interactions they form, the more the specific solvation will be able to counterbalance the hydrophobic contribution. Depending on the magnitude of the overall solvation effect, the lipophilicity of the chemical will then shift from very lipophilic to more or less lipophobic while its partition coefficient will change from a positive to a negative value. In the present treatment, each interaction site on the solute contributes to a decrease the log *P* by a constant value depending on the relative strength of the association formed by this site in each solvent phase. When the solute displays multiple functional groups, the overall Δ(O+OH) component is then determined by the sum of the partial contributions brought about by each proton-donor and -acceptor sites.

From the above observations, the partitioning behavior of chemicals of similar volume can easily be understood and rationalized. First of all, all solutes may be sorted into two classes depending on whether the solute is able to interact with at least one of the two phases. In the absence of H-bond interactions, the larger value of the hydrophobic effect with respect to that of the mixing entropy makes the compounds highly lipophilic, such as cyclohexane and toluene which are characterized by high log *P* values in all partitioning organic solvent/water systems. On the contrary, when solute/solvent H-bonds are formed, the corresponding additional contribution renders the solutes more lipophobic. Such substances are then characterized by clearly lower log *P* values. At this stage, the factors which reduce the log *P* values closer to zero or even negative depend (i) on the number and strength of the interactions formed between the solute and water molecules and (ii) on whether the aqueous interactions are partly canceled by weaker interactions in the organic phase. The ranking of the polar solutes by decreasing log *P* values thus appears as a complex function of the interacting properties of both the solute and the organic solvent phase.

We now analyze the dependence of log *P* on the solute molar volume. For this purpose, the variation of log *P* with its components is illustrated in Figure 3 for aliphatic ketones and alcohols distributed in various partitioning systems. This figure clearly evidences the following, irrespective of the distribution system.

(a) Increasing the size of the solute increases its log *P* value, hence its lipophilicity.

(b) The increase in log *P* roughly parallels the increase of the hydrophobic effect-related contribution, Δ*F*.

(c) The volume−log *P* dependence results more precisely from two opposite entropic effects, Δ*B* favoring the transfer toward water and Δ*F* favoring the transfer into the organic phase. A greater difference in the exchange entropy (Δ*B*) between the organic and aqueous phases tends to reduce the log *P* value, whereas a larger hydrophobic effect difference (Δ*F*) enhances lipophilicity. Although both contributions increase in absolute value with the increasing size of the partitioned chemical, the hydrophobic effect component always remains greater and grows far more rapidly than the mixing entropy contribution. As a result, the partition coefficient always increases when the size of the partitioned solute increases.

(d) The specific solvation measured by the Δ(O+OH) term is not affected by the size of the solute.

According to the MOD log P model, the extent of the change in the log *P* value by increasing the solute molar volume varies according to the relative molar volumes of the phases constituting the distribution system (see eqs 3−5). For practical uses, it can be demonstrated thermodynamically that, neglecting the Δ*D* contribution, any addition of a methylene group in a parent compound increases the log *P* value in water/organic solvent systems by an amount of

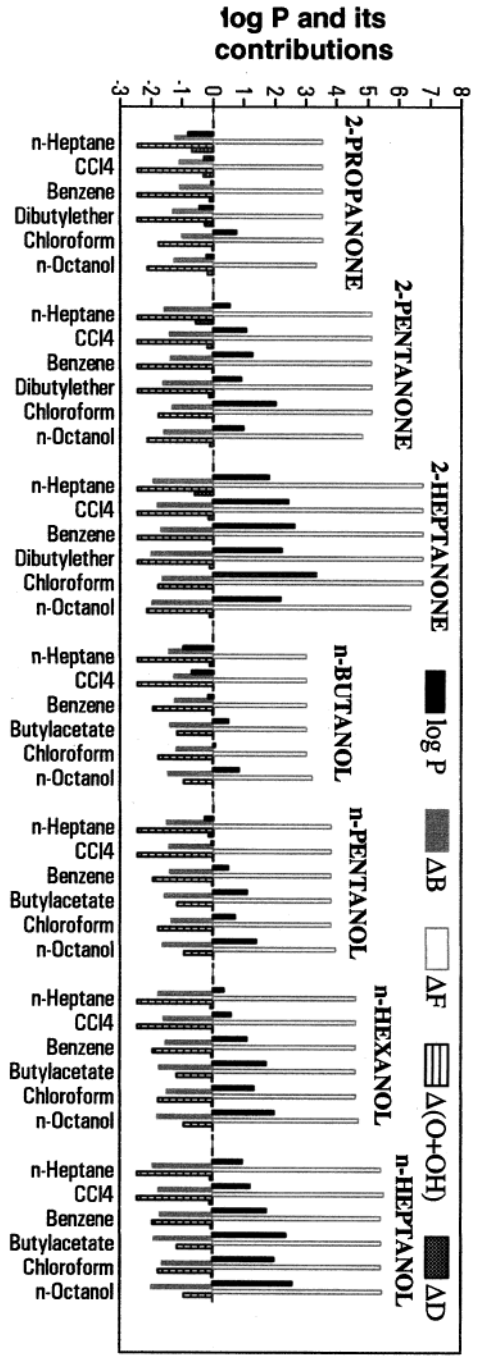

Figure 3. Influence of the molar volume of 2-alkyl ketones and *n*-alcohols on their partitioning in various organic solvent/water distribution systems.

0.50−0.65 log units. In this connection, Figure 4 reports the theoretical variation of the log *P* increment related to the hydrocarbon chain lengthening with respect to both the molar volume and the amphiprotic character (given by the value of the structuration factor r_1) of the organic phase coexisting with water.

Influence of the Water Coexisting Organic Ccsolvent on the Partition Coeffcient. The analysis of the relative magnitude of the contributions involved in the log *P* calculation provide very useful conclusions regarding how and to what extent any change in the physicochemical properties of the organic phase of a solvent/water distribution system affects the partition coeffcient of a given solute. For such purposes, all solvents used as a coexisting phase to

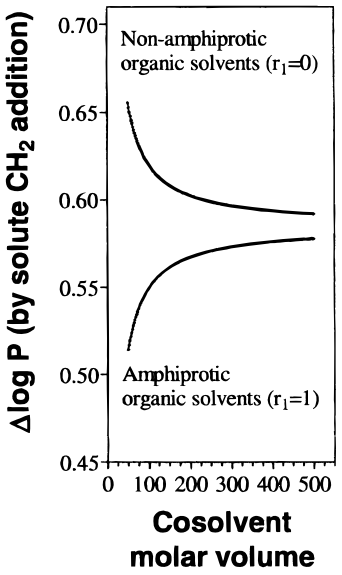

Figure 4. Dependence on the cosolvent molar volume of the organic solvent/water log *P* increment due to lengthening of the solute hydrocarbon chain by one CH_2 methylene group.

water in the partition calculation have been once more classified into four categories, retaining for the analysis the reference "critical quartet" of solvents composed of *n*-hexadecane (inert), *n*-dibutyl ether (proton-acceptor), chloroform (proton-donor), and 1-octanol (amphiprotic). Because the impact of the solvent nature on log *P* also depends on the chemical profile of the partitioned solute, various compounds of differing polarity and H-bonding capability have been selected with very similar molar volumes in order to limit the number of influencing variables. So, six substances, namely, cyclohexane, 2-pentanone, ethyldimethylamine, 1-pentanol, *n*-valeric acid, and *o*-toluidine with molar volumes close to 108 $cm^3\ mol^{-1}$ were retained to analyze the variation of their partition in the four distribution systems. These results [the analysis does not account for the mutual partitioning of the solvents within each other), presented in Figure 5 call for the following comments.

(a) The partition coefficient of a solute distributed between two immiscible liquids involving water is always governed by the hydrophobic effect-related term, ΔF. Given a solute, this effect always remains constant with respect to the physicochemical properties of the organic phase except when this solvent is amphiprotic like 1-octanol. In this case, the ΔF term may either decrease or increase according to whether the solute is itself nonprotic or protic. When the solute is nonprotic (cyclohexane, 2-pentanone, and ethyldimethylamine), the hydrophic effect occurring in water is partially compensated for that occurring in the 1-octanol phase and the ΔF term is then slightly lower than in nonamphiprotic organic phase/water systems where no mutual compensation of the hydrophobic effects may take place. In contrast, when the solute is amphiprotic (1-pentanol, *n*-valeric acid, and o-toluidine) and able to form a mixed H-bonded chain with both water and 1-octanol molecules, the hydrophobic effect is decreased in each phase, but the resulting difference ΔF appears slightly greater than that observed for partitioning systems involving nonprotic organic phases. Remember that this contribution which largely favors the solute transfer toward the organic phase is almost solely responsible for the lipophilicity of the solutes.

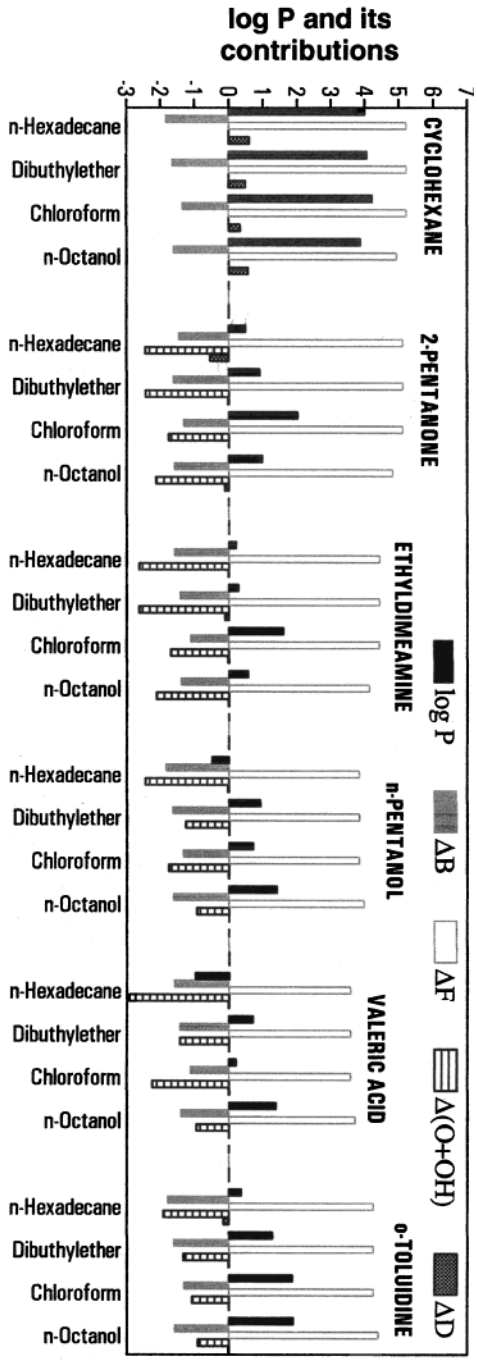

Figure 5. Partition coefficients (and its various contributions) of several solutes partitioned in four different nonaqueous phase liquid/water systems.

(b) The nonspecific solvation (dipolarity/polarizability) effect given by the ΔD term is completely negligible in all cases regardless of the chemical nature of both the solute and organic cosolvent. Small positive (lipophilic) contributions in all distribution systems are, however, observed for aliphatic hydrocarbon solutes such as cyclohexane. The positive character of that contribution arises from the fact that the modified nonspecific cohesion parameter of cyclohexane is lower than that of each solvent phase.

(c) The exchange entropy-related contribution, ΔB, is always negative (lipophobic) and opposes the hydrophobic effect, ΔF. Given a solute partitioned between water and an organic phase, the ΔB term only depends on the molar volume of the organic solvent irrespective of its chemical nature: the higher the molar volume of the organic solvent, the greater the mixing entropy effect and the more the solute will transfer toward water. On the basis of their molar volumes, the four organic phases considered can thus be ranked with respect to their capacity to counterbalance the hydrophobic effect as follows: *n*-hexadecane (294.1 $cm^3\ mol^{-1}$), *n*-dibutyl ether (170.3 $cm^3\ mol^{-1}$), 1-octanol (158.3 $cm^3\ mol^{-1}$), and chloroform (80.7 $cm^3\ mol^{-1}$). In the absence of particular specific interactions between the solute and any phase of the distribution system, the sorting out of the organic solvent phases by the decreasing order of their molar volumes approximately corresponds to the reverse ranking of the log *P* values of a given solute.

(d) Because lipophilicity always expresses the combined result of all effects taking place in each separate phase, the organic solvents can be divided into two classes according to their capacity to form H-bonds with the solute, whereas three behaviors of the solute may be observed concerning their lipophilicity. First, the solute does not interact in either phase. In this case, the solute is highly lipophilic since its log *P* value is essentially ruled by the hydrophobic contribution, ΔF. Second, the solute interacts in the water phase only. In this case, the formation of solute/water specific interactions transfers the solute toward the aqueous phase, leading to a decrease in its lipophilicity, and the corresponding log *P* values are rather small or negative. In practice, the log *P* reduction varies according to the number of H-bonds that the solute makes with water and to the values of the corresponding stability constants. Third, the organic solvent phase is able to H-bond with the solute. In this case, the solute interacts in both phases and the stabilization issued from the H-bonds formed in the organic phase partly cancel that occurring in water, and the log *P* values observed in such situations always turn out to be intermediate between the previous ones. As a result, a given solute always exhibits the greatest lipophobicity (the lowest log *P* value) in water/solvent systems in which it may interact in the aqueous phase only. The relative strengths of the solute/water and solute/solvent H-bond interactions then modulate the variation in the log *P* value.

It is therefore quite easy to understand why, among all solutes, the aliphatic hydrocarbons show the highest log *P* values whatever the distribution system of concern (no specific interaction in either phase). It also appears evident why, among all polar solutes considered in Figure 5, the amphiprotic *n*-valeric acid and 1-pentanol present the lowest log *P* values in the *n*-hexadecane/water distribution system (very strong interactions in the aqueous phase only combined with reduced hydrophobic effects due to the insertion of the molecules in the H-bonded chains of water). All other log *P* values are intermediate, resulting from the combination of all contributions accompanying the partitioning process.

It may finally be interesting, just as it was done with the solute, to study how the molar volume, V_1, of the organic solvent phase affects the organic solvent/water partition coefficient. Because this parameter is mainly implied in the ΔF and ΔB contributions, Figure 6 presents the variations of the sum of these contributions with respect to the organic solvent molar volume when the size, V_B, of the solute is fixed to either at 100, 200, or 300 $cm^3\ mol^{-1}$. Such variations would really correspond to the change in the log P of solutes which are unable to interact specifically in both phases and

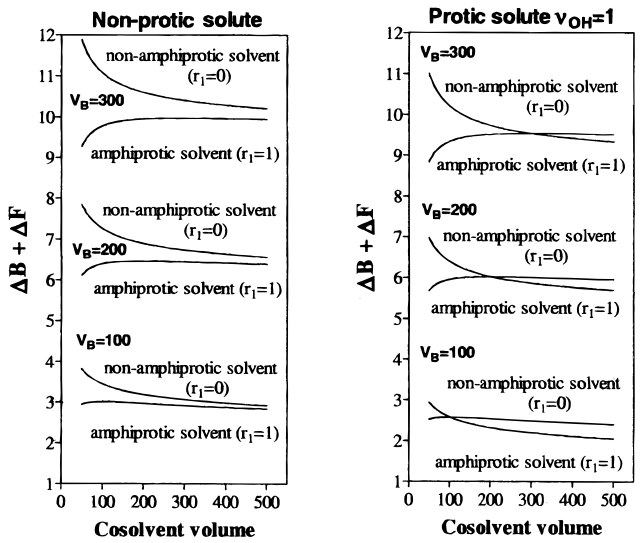

Figure 6. Dependence of the organic solvent/water log *P* via the ($\Delta B + \Delta F$) free energy contribution on the cosolvent molar volume. Different curves are obtained according to the protic or nonprotic nature of the solute and to its molar size.

for which the dipolarity/polarizability effects would be negligible. The results show that although it remains always positive (lipophilic), the combined result of the hydrophobic and mixing entropic effects decreases in most cases with the increasing size of the cosolvent. This means that, by increasing the size of the cosolvent in a homologous chemical series, the log *P* of a given protic or nonprotic solute will generally decrease. Note that the log *P*−cosolvent volume dependence is not exactly the same according to the amphiprotic and nonamphiprotic nature of the cosolvents considered. The observed decrease is generally more pronounced with nonamphiprotic cosolvents ($r_1 = 0$), and in that case, the greater the size of the solute the stronger the decrease. With amphiprotic cosolvents such as *n*-alcohols ($r_1 = 1$), the sum of ΔB and ΔF first begins to increase until the cosolvent molar volume equals that of the solute and then slowly decreases with the further increase of the cosolvent size. Note that, in most cases, the expected variations of the sum ΔB and ΔF are relatively small and remain often lower than the measurement errors so that they appear difficult to be observed experimentally.

Influence of the Polar Phase on log P: Water vs Ethylene Glycol. As shown in the previous sections, any solute partitioning is the result of a combination of entropic and enthalpic processes relevant to the formation of solvent/solvent and solute/solvent interactions. It has furthermore largely been demonstrated to what extent, in the case of water/solvent partitioning systems, the diffference in the hydrophobic effect exerted by each phase toward the solute constitutes the essential contribution to the partition coefficient value. For most substances studied in this work, the hydrophobic effect-related term, ΔF, predominates over the remaining contributions encoded in the overall partition coefficient. From a practical viewpoint, it is only in the case of small sized polar chemicals capable of numerous and/or very strong H-bonds in water that the overall specific solvation terms, Δ(O+OH), will offset the hydrophobic component, ΔF, whose value is essentially governed by the hydrophobic effect taking place in the aqueous phase. Indeed, due to both the very small size of the water molecule and its ability to form a tridimensional network of double H-bonded chains, the solvophobic (hydrophobic) effect will always be the greastest in water compared to that exhibited by any other amphiprotic solvent. Accordingly, all water/organic solvent partitioning systems will mainly emphasize differences in the hydrophobicity of the solutes at the expense of their hydrogen-bonding-donor or -acceptor capacity.

The question is then to know, what would be the partition of a solute and its governing process if water, traditionally chosen as the polar phase in most distribution systems, was replaced by another polar but less amphiprotic solvent?

To address that problem, we decided to analyze the origin of the partition coefficient of solutes in two comparable distribution systems made of a common apolar solvent, *n*-heptane, and a polar phase composed of either water or ethylene glycol. One the one hand, *n*-heptane as an inert phase is unable to cancel or even partly counterbalance either the hydrophobic effect or the specific interactions occurring between the solute and solvent molecules in the polar phase. On the other hand, water and ethylene glycol only differ by their molar volume since both kinds of molecules in their pure liquid state are assumed to be inserted in double H-bonded chains (their structuration factor $r_S = 2.0$).

The partition coefficients of 142 and 56 different solutes have been calculated respectively in the *n*-heptane/water and *n*-heptane/ethylene glycol systems. The results are compared to the experimental values in Table 5, and the parameters relevant to the model prediction accuracies obtained with both data sets are indicated in Table 7. The larger standard deviation of the residuals observed in *n*-heptane/water undoubtedly stems from the wider variety of functional chemicals studied in this partitioning system. Notwithstanding, the predictions in both solvent pairs are of sufficiently good quality to be used for the sake of comparison. Figure 7 reports the log *P* values and the various contributions of a series of 14 selected solutes (with different H-bond-donating or -accepting ability) distributed in both *n*-heptane/water and *n*-heptane/ethylene glycol two-phase systems. The analysis of the results leads to the following observations:

(a) The log *P* of most substances in *n*-heptane/ethylene glycol is lower than the corresponding value in *n*-heptane/water. The solutes are thus more lipophilic in the distribution system involving water. Nevertheless, the general trends observed in the evolution of the log *P* data vs the structural solute features are similar in both solvent systems.

(b) With respect to the values calculated in *n*-heptane/water, all lipophilic (positive) and lipophobic (negative) contributions involved in the log *P* estimation in *n*-heptane/ethylene glycol are lessened in absolute value. The magnitudes of the various physicochemical phenomena implied in this partitioning system are in a way leveled to a value closer to zero, which reduces the discriminating power of this two-phase system to differentiate the partition property of structurally related chemical solutes.

(c) Due to the closeness of the nonspecific cohesion parameter values of water (20.5 $MPa^{1/2}$) and ethylene glycol (19.9 $MPa^{1/2}$), the nonspecific solvation contribution, ΔD, remains quite unaffected by the change of the polar phase of the distribution system. However, if this contribution is often negligible in distribution systems including water, its role in the *n*-heptane/ethylene glycol system becomes much

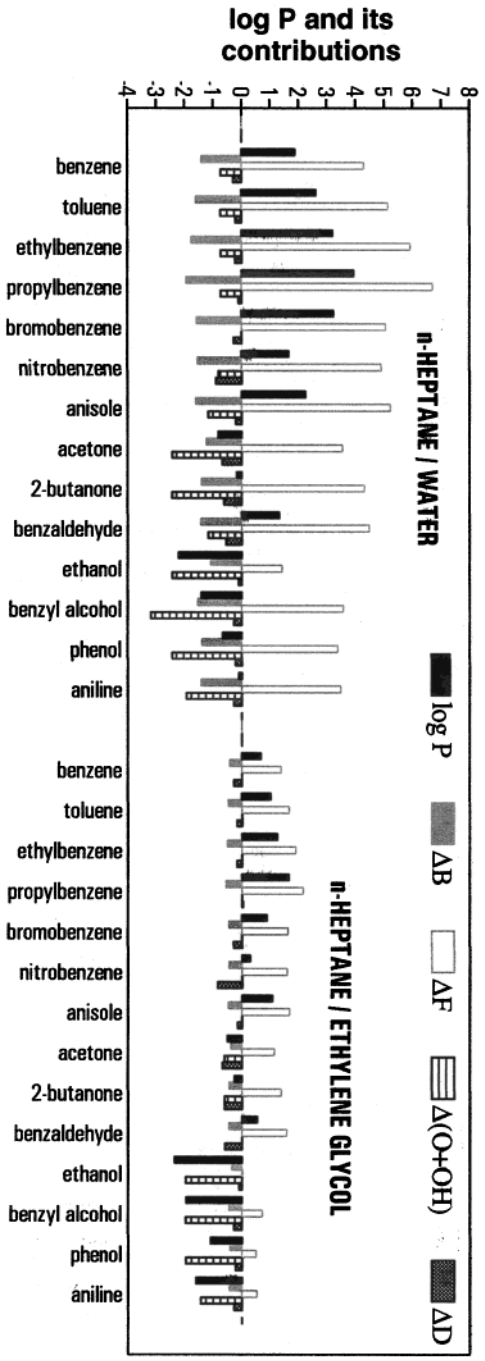

Figure 7. Partition coefficients (and its various contributions) of solutes partitioned respectively in *n*-heptane/water and *n*-heptane/ethylene glycol systems.

more important with respect to the other terms encoded in the log *P* values.

(d) The volume increase associated with the replacement of water (18.1 cm^3 mol^{-1}) by ethylene glycol (55.8 cm^3 mol^{-1}) significantly affects the mixing entropy (*B*) as well as the hydrophobic effect (*F*) contributions to the solution process occurring in the polar phase. Depending on the ratio between the solute and solvent molar volumes, both terms are simultaneously reduced in ethylene glycol with respect to water, and the corresponding ΔB and ΔF contributions to *n*-heptane/ethylene glycol log *P* are also diminished. Whereas the ΔB decrease favors the departure of the solute toward the nonpolar phase and increases lipophilicity, on the contrary, the ΔF decrease favors the localization of the solute in the polar phase and increases lipophobicity.

(e) With respect to the solute/solvent H-bond interactions occurring in water, the weaker interactions formed in ethylene glycol leads the solute to be less attracted by this polar phase, hence to be more evenly distributed between the polar and nonpolar phases. The lowering of Δ(O+OH) in *n*-heptane/ethylene glycol reinforces the lipophilicity of the solute and therefore superimposes the reduction of the mixing entropy-related effect dragging the solute molecule toward the nonpolar phase.

The effect of modifying the polar phase can be rationalized, and important conclusions may be derived. Any replacement of the small-sized water solvent, used as the polar phase of a distribution system, by another amphiprotic solvent of larger volume like alcohols results in a decrease in absolute value of all contributions encoded in the partition process. Because the lowering of some of these contributions, namely, ΔB and Δ(O+OH), increases lipophilicity, whereas the reduction of ΔF decreases it, the resulting log *P* value in the new distribution system (by comparison with the value in the system in which water is the polar phase) will depend on the balance and the mutual cancellation between both lipophilic and lipophobic effects. For instance, the much larger decrease of the lipophilic ΔF contribution with respect to the diminution of the sum of the lipophobic ΔB and Δ(O+OH) contributions explains why solutes are more lipophobic in the *n*-heptane/ethylene glycol system than in *n*-heptane/water partitioning system. As a matter of fact, the hydrophobic effect exerted by ethylene glycol tends to drive much less the solute molecules into the *n*-heptane phase than water does.

Finally, it is important to point out, in the particular case of protic solutes, that the replacement of water by another amphiprotic polar solvent in the distribution system provokes such a large decrease of the hydrophobic contribution that, although the interactions of the solute with the new polar phase are weaker and the corresponding specific solvation contribution is reduced, this latter contribution may become the governing term of the partition coefficient. This situation is observed in the *n*-heptane/ethylene glycol partitioning system in which hydrogen-bonding rather than volume effects predominate and control the partitioning of H-bond-donating solutes. As a result, such a distribution model could then be used as an appropriate alternative system to model drug or peptide biochemical phenomena, such as membrane transport, known to be essentially controlled by hydrogen-bonding effects.

CONCLUSION

The nonergodic thermodynamic treatment of the mobile order and disorder theory in H-bonded liquids is used to derive a universal model to predict partition coefficient. The great advantage of the present approach is the possibility of predicting the log *P* of solutes not only in the traditional 1-octanol/water reference, but also in all two-phase systems made of two largely immiscible solvents.

The predictive log *P* model is obtained on a strictly thermodynamic basis and may contain as many as five Gibbs free energy contributions, depending on the functional groups of the solute and/or the two phases between which the solute

partitions. These contributions account for all the physicochemical processes which may take place in the overall partitioning phenomenon: two strongly volume-dependent entropic-related terms, ΔB and ΔF, reflecting the difference between the two phases (a) in the entropy of mixing occurring between the solute and solvent molecules in each phase and (b) in the propensity of each phase to induce a hydrophobic effect toward the solute; two relatively volume-independent specific solvation-related terms, ΔO and ΔOH, describing the differences in the H-bonds taking place between the solute and solvent molecules in each phase; and one term, ΔD, describing the difference between the two phases in the changes of the nonspecific interactions upon mixing the solute and solvent molecules.

The model has been applied successfully to predict the partition coefficients of a large number of chemicals in a great variety of partitioning solvent pairs. Besides its good predictive ability, the model provides a comprehensive understanding of the partition phenomenon. As a matter of fact, the analysis of the relative importance of the free energy contributions encoded in the log *P* value, as well as the comparison of these contributions from one system to another, unravel (i) the origin of the partition coefficient of a solute in a given distribution system, (ii) the dependence of the partition coefficient on the structural features of the solute, such as its molar volume, and (iii) the variation of the partition coefficient of a given solute between two different partitioning systems. In the latter case, the results concerning the log *P* modifications relevant to a change of either the polar or nonpolar phase have been rationalized.

Clearly, the solute and solvent properties are important and interact in determining the magnitude of the partition coefficient. Regardless of the nature of the organic solvent phase, the distribution of substances incapable of interaction in both phases of any organic/aqueous biphasic system is essentially governed by the hydrophobic effect free energy contribution (ΔF): the larger the molar volume of the solute, the more it is so. Although this conclusion remains valid for all polar and complexing chemicals, the hydrophobic contribution is in this case partly counterbalanced by the net specific solvation effect related to the exoergic free energy contributions (ΔO and ΔOH). These contributions do not vary extensively with the volume of the solute but essentially depend on the number and the strength of the H-bonds that the solute is able to form with the solvent molecules in each phase, given that the interactions in water are always stronger than those formed in the organic phase. The stronger and larger the number of these interactions, the more lipophobic the substance and the lower its log *P* value. As a matter of fact, the MOD thermodynamics provides a clear demonstration that hydrophobicity, quantified by the hydrophobic effect-related term, (i) represents the driving force for typical distribution processes occurring in aqueous environments, and (ii) constitutes, as its mere contribution, a useful measure of lipophilicity when this parameter is conventionally expressed by the distribution coefficient between water and 1-octanol or any immiscible nonpolar solvent.

The replacement of the aqueous polar phase by another amphiprotic solvent substantially reduces all the contributions involved in the partitioning process, and the hydrophobic contribution in particular. Such two-phase systems mainly differ from those involving water by the fact that the distribution process of complexing solutes is ruled rather by their hydrogen-bonding capabilities than by their hydrophobicities.

From a phenomenological point of view, partitioning incorporates two major factors, namely, a "bulk or volume" entropic component ($\Delta B + \Delta F$) favoring lipophilicity and a "solvation" component ($\Delta D + \Delta O + \Delta$OH) opposing lipophilicity. In this sense, the MOD model does not differ fundamentally from the traditional descriptions of log *P*, and from the linear free energy relationship (LSER) based on the so-called solvatochromic parameters in particular. Although, at first glance, both the MOD and solvatochromic models closely resemble each other owing to the factorization of the partition coefficient, they, however, completely differ in the way the factors are obtained as well as in the physical meaning of some of these factors.

Concerning the obtention of the predictive log *P* expressions, the factorization of the partition coefficient of neutral solutes proposed by the solvatochromic approach originates from the method of multiple linear regression analysis (MLRA) between a training set of experimental log *P* data and four physicochemical parameters (V_W, π^*, α, β) used as the solute structural descriptors. Even if the fitting coefficients may contain some chemical information reflecting the difference in the properties of the liquid phases composing the distribution system, they are only constants and remain valid only for the partitioning system under investigation. Such an approach must therefore be qualified as an extrathermodynamic "a posteriori" predictive method. The MOD log *P* model on the contrary is derived on the basis of the general thermodynamic treatment of all phenomena taking place in each phase during the distribution process. By doing so, it does not contain any regression coefficient and can therefore be used to predict the partition coefficient "a priori", in all mutually saturated two-phase systems made up of two largely immiscible solvents.

As for the physical interpretation of the factors involved in the respective log *P* factorizations, both models essentially differ in the meaning given to the volume-related factor. On the one hand, the volume-based term of the solvatochromic approach mainly relies on the endoergic free energy process associated with the cavity work, i.e., the creation of solute-sized cavities within each phase to accommodate the solute molecules. This process is believed to be due to a combination of breaking solvent/solvent interactions and a loss of entropy resulting from some restricted spatial distribution of the solvent molecules in the vicinity of the solute. The energy requiremement is thus quite linearly dependent on the molar volume of the solute. On the other hand, the log *P* dependence on the solute molar volume in the MOD model essentially results from the balance between two opposite entropic processes, or more precisely between the differences of these processes occurring in each phase upon introduction and partition of the solute: the hydrophobic effect and the mixing entropy. According to the quantitative thermodynamic treatment of these processes, these contributions (eqs 3 and 5) and their sum are approximately proportional to the solute molar volume.

In conclusion, owing to both its "*universal*" and strictly "*thermodynamic*" character, the MOD log *P* model can be considered as the fundamental theoretical background which could serve as the rational explanatory basis for all empirical

and semiempirical "extrathermodynamic" log *P* models using a varying number of solute descriptors to discuss the partitioning process in terms of hydrophobicity and polarity.

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Supporting Information Available: Tables showing log *P* values for binary immscible solvent systems and organic solvent/water systems. This material is available, free of charge, on the Internet via http://pubs.acs.org.

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