Empirical Method for the Quantification and Localization of Molecular Hydrophobicity

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An empirical method for the localization, the quantification, and the analysis of relative hydrophobicity of a molecule or a molecular fragment is presented. The approach is based on two concepts: (i) that the overall hydrophobicity of a molecule (measured, for example, by the logarithm of the partition coefficient in an octanol/water system $\log(P) = \Delta G_{transfer}/-2.303RT$ with the transfer free energy $\Delta G_{transfer}$ for one mole substance from one solvent to the other) can be obtained as a superposition of fragmental contributions and (ii) that this free energy can be represented as a surface integral over the solvent accessible surface of the molecule on the basis of a local surface density ϱ. This surface density function is represented in terms of a three-dimensional scalar field which is composed as a sum of atomic increment functions describing lipophilicity in the molecular environment. For these atomic increment functions a nonlinear distance law is postulated between the atomic coordinates and any point in space. This law guarantees that only those atomic fragments contribute significantly to the surface values, which are in close neighborhood of the surface point. Free parameters for the distance function and for characteristic increment contribution to the surface density are determined on the basis of experimental log P values for the 1-octanol/water system. It is demonstrated with a few examples that the procedure not only works for the prediction of unknown partition coefficients but also for the localization and quantification of the contribution of arbitrary fragments to this quantity. The formalism can be used also for an estimation of the hydrophobicity index, a hypothetical log P value which depends on the actual molecular conformation.

I. INTRODUCTION

The interaction of a nonpolar molecule with an aqueous solvent or the quasi-attractive interaction of organic compounds or nonpolar groups in the water phase is known as the *hydrophobic effect* or *hydrophobic interaction*, respectively.[1−4] Both are strongly related, although this relationship is not a simple one.[1,2,5−8] In the present paper we will not contribute to the discussion about this relationship, but simply accept the statement that hydrophobic molecules or molecular fragments are attracted by other hydrophobic molecules in aqueous solution. Medicinal chemists have believed for at least five decades that hydrophobic interaction is one of the most important forces that arise from the interaction of nonpolar regions of drugs with their receptor. Usually, hydrophobic interaction weakens with decreasing temperature.[3] From the thermodynamical point of view, the hydrophobic effect can be quantified using the solvation free energy of a molecular compound ΔG or the Gibbs free energy change $\Delta\Delta G = \Delta G_{transfer}$ of transfer of the compound between an aqueous and an apolar liquid phase. $\Delta G_{transfer}$ can be considered as one of the key quantities to describe the hydrophobic effect, but this statement is not very helpful for an understanding of this effect within a model scenario since there is no simple way to estimate $\Delta G_{transfer}$.[1] Up to now, there is still no simple physical model available for hydrophobicity. However, there are several attempts to define relative hydrophobicity values on the basis of empirical findings. Such values can be obtained, for example, from the partition coefficients P[9−15] or the hydrophobic index log P[24,25] of the sample in polar−apolar heterogeneous reference systems. Fujita et al.[9] could prove within a comprehensive study the additive-constitutive nature of the partition coefficient. Based on their results hydrophobicity values can be established for any molecule as well as for arbitrary molecular fragments. The so defined hydrophobicity of a molecule—measured, for example, by its hydrophobicity index (log P)—can be regarded as the sum of increments related to the hydrophobicities of its fragments, f_i

$$\log P = \sum_i f_i \qquad (1)$$

Rekker et al.[10,11] gave some fragmental values for partition coefficients in the octanol/water system, followed by more detailed studies by Hansch and Leo.[12] Although other systems have also been used for hydrophobicity studies, the vast majority of measurements was carried out in the octanol/water system, leading to tables of lipophilicity values for a large number of molecular fragments.

One problem with the Hansch−Leo approach arises from the fact that correction factors for the f_i values are required to cover the mutual influence of neighboring fragments. An alternative approach of Broto et al.[13] could avoid such correction factors by diminishing the fragments, but this method still does not include the explicit treatment of

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H-atoms. The last step toward an empirical quantification of lipophilicity contributions of individual atoms has been accomplished by Ghose and Crippen.[14] In their treatment the atomic contributions were defined by using a classification of each atomic fragment according to the number and nature of their next (and second next) connected neighbors. Up to now roughly 120 constitutive atom types are listed, describing the atoms in their individual structural environment,[14-16] and this list is still in progress.

Very successful methods for the estimation of log P for octanol/water partitioning have been based on the fragment method of Hansch and Leo[12] and extended to proteins by Abraham and Leo.[17] The hydrophobic atom constants a_i used in the HINT program of Abraham[18-20,4] are derived from the hydrophobic fragment constants f_i of Leo by using a formalism to retain the empirical information content of the solvent partitioning data. Partitioning between atoms within a fragment invokes the assumption that frontier or mantle atoms of a fragment have a more significant role in hydrophobic interaction than shielded interior atoms. Thus, they are generally maintained at near-atomic values within fragments, while the interior atom hydrophobic constants are adjusted to reflect the cumulative bonding effects on hydrophobicity within the fragments, i.e., $\sum c_i = f_i$. In addition, all Leo system fragments (e.g. bond, chain, branching, polar proximity, etc.) are applied in the HINT strategy to the involved atoms and divided equally between the atoms in the case of bond-type factors.

Abraham and co-workers[21,22] as well as Zavslavsky[23] also used thermodynamic arguments for the empirical study of solvent solvophobic effects. Abraham[21,22] calculated the transfer free energy $\Delta G_{\text{transfer}}$ from water to another solvent by an equation of the type $\Delta G_{\text{transfer}} = MR_T + D$, where R_T is a solute parameter and M and D characterize the solvent. The M values in this equation are then used to define a solvent solvophobic effect (measured by a quantity Sp) so that Sp values are scaled from unity (water) to zero (hexadecane). The Sp values obtained were shown to be quantitatively related to HPLC capacity factors.

In the investigations mentioned above, the possible change of the molecular conformation while changing the solvent or the occurrence of different conformations of one molecule are not explicitly considered.

Kantola et al.[24] and Alkorta and Villar[25] presented a method for computation of a hydrophobic index that depends on molecular conformation based on atomic contributions. The main descriptors used in their method are the molecular surfaces and the atomic charges, both of which depend on the conformation adopted by the system as well as a set of parameters that depend only on the atomic number. The adjustable parameters were determined by linear regression using experimental values of the octanol/water partition coefficient for rigid molecules. Alkorta and Villar[25] extended this work by including a parameter that would be related to the ability of an atom to form a hydrogen bond with the solvent. They included terms in the log P expression which are proportional to the molecular dipole moment and a lone pair index.[26]

Roseman observed that the hydrophobicity of polar amino acid side chains is remarkably reduced by flanking peptide bonds.[27] This study verifies the need to consider specific structural features that cause deviation from the additivity of increments in composing the log P value. Richards and co-workers[28,29] presented an algorithm for computing the water/1-octanol partition coefficient of conformationally flexible molecules, based on an expression wherein experimental free energies in both solvents were expressed as functions of the solvent-accessible surface of the fragments. In their approach the effects of population of accessible conformation minima in both phases are explicitly considered.

In this paper we follow the argumentation of Richards[28,29] and co-workers, i.e., we start from the assumption that the transfer free energy $\Delta G_{\text{transfer}}$ for one mole substance from one solvent to the other can be composed of additive contributions which are related to the solvent accessible surface of the molecule. In the present approach the $\Delta G_{\text{transfer}}$ value does not occur as a sum but as a surface integral over a free energy surface density ϱ.

The paper is organized as follows: In section II a phenomenological treatment of the localization of hydrophobicity is presented, and the basis for the numerical studies is outlined. In section III the computational basis for a quantitative treatment of local hydrophobicity on the basis of experimental data is formulated, while in section IV it is demonstrated with a set of molecules that the method indeed leads to excellent predictions. Section V deals with some consequences of the formalism with respect to the conformation of the molecules, while in the final section some conclusion are drawn.

II. THE LOCALIZATION OF HYDROPHOBICITY

The empirical methods described above are of great importance for the estimation of octanol/water partition coefficients of molecules which have not been studied experimentally, i.e., a molecule which has not been synthesized up to now can be checked with respect to an expected overall hydrophobicity. However, the formalisms do only give a vague impression on a local measure of hydrophobicity. The manifestation of local hydrophobicity can be of great importance for the generation of approximative models for the geometrical and energetical topography of a receptor site. This has recently been demonstrated by Lichtenthaler et al.[30,31] who studied the sweetness receptor. In this particular case it seems to be generally accepted that the receptor should contain a proton acceptor function, a proton donor function, and a hydrophobic functionality, all three arranged in a triangle ("the sweetness triangle"). While proton donor and acceptor functions can be easily identified in a molecular structure, this is not obviously possible for the hydrophobic interaction site. Such questions require the localization of hydrophobic (or hydrophilic) interaction at least in a qualitative way.

The subdivision of molecular lipophilicity into fragmental contributions seems to be a prerequisite for the manifestation of local hydrophobicity and a surface map of this quantity. It seems to be reasonable to postulate a distance-dependent rule for the influence of different fragments on the lipophilicity at a certain surface point. One possible function for this rule has been proposed by Audry et al.[32] They introduced the name "molecular lipophilicity potential" (MLP) and postulated (in analogy to the electrostatic potential function) a functional form

$$V_{hydophobic} = \sum_i f_i/(1 + d_i) \qquad (2.1)$$

where f_i is the partial lipophilicity of the ith fragment of a molecule and d_i is the distance of the measured point in 3D-space from the center of fragment i. The long range distance dependence of this function is that of a Coulomb potential, i.e., a large number of atoms contributing to an MLP value at a certain point of the molecular surface may be dominantly determined by a large number of contributions which are far away from this point. Despite the lack of any physical basis for this type of distance dependency of the MLP, useful results could be obtained from the application of this function for visualization of molecular lipophilicity[33,34] for sufficiently small molecules (where the number of contributions is small). Cohen et al.[33] were able to display MLP profiles on the van der Waals surface of the 20 proteinogenic amino acids using Crippen's single atom fragment lipophilicities. Their results are in agreement with the concept of a "hydrophobic dipole moment" introduced by Eisenberg and McLachlan.[35,36]

Fauchère et al.[37] proposed another form for the MLP. They defined an exponential distance dependence for fragmental contribution: MLP $\sim \exp(-d)$. This potential function was designed on the basis of the proximity effects observed by Rekker[10,11] and Hansch and Leo[12] and was used for the examination of a drug-receptor system.

Both methods mentioned above have been successfully applied to small molecular systems. Brasseur could extend the approach to helical peptides, calculating isopotential contours of hydrophobicity[38] by projecting the atomic partial values on the van der Waals surface, starting from there with an exponential decrease to any point in space.

Despite of the success of the MLP approach for small molecules there is no physical reason for the use of one or the other distance dependencies in this "potential" and at the same time using the partial log P values of Crippen and co-workers as "partial charges" located at the positions of the atoms in a molecule. As mentioned above, the long range parts of the individual potential contributions may lead to an overcompensation of local effects as has been demonstrated by Heiden et al.[39]

Since the incrementation of the log P values is based on strictly local contributions, an overcompensation of these local effects as a consequence of accumulation of many long range contributions would be in contradiction with the method of the determination of the f_i values by statistical procedures.

In a recent paper[39] some of the present authors proposed a molecular hydrophobicity mapping (MHM) approach which was particularly designed for projecting atomic increment values of Crippen and others[14-16] on the molecular surface (a solvent accessible surface or contact surface[40] of a molecule. [Here and in the following text we will use the term "molecular surface" in a sense of Connolly,[40] i.e., a contact surface of a "spherical" water probe (radius $r = 1.4$ Å) with a CPK-model of a molecule of given conformation is taken as a reference.] Following the above-mentioned authors, a MHM mapping function (instead of the MLP function) was introduced as a superposition

$$V_{MHM} = \sum_i f_i g^*(d_i) \qquad (2.2)$$

with some function $g^*(d_i)$ which is dependent on the distance d_i. d_i is the difference between a vector to a surface point $\mathbf{r}_s$ and a vector $\mathbf{r}_i$ from the center of an atomic increment i of the molecule. The g^* function was chosen such that it is equal to unity for $d < d_{lower}$ and approaches zero for $d > d_{upper}$ with a smooth transition between both values in the range $d_{lower} \le d \le d_{upper}$ where d_{lower} and d_{upper} are empirical parameters which control the proximity effect, i.e., the contribution of different atomic fragments as a function of their distance to the surface point.

The MHM approach of Heiden et al.[39] is well suited for a qualitative discussion of local hydrophobicity on the basis of incremental contributions because the formalism induces a weighted projection of the incremental f_i values of Crippen and co-workers[14,15] onto the molecular surface and so allows an easy visualization of this quantity. However, there is no way up to now to compute quantitative data like $\Delta G_{transfer}$ or the partition coefficient P from molecular hydrophobicity maps.

In this work we extend the MHM approach toward such a quantification. The concept is based on the idea that the overall hydrophobicity index is related to the solvent accessible surface[41,28,29] and a quantity which measures to what extent a certain surface element contributes to the $\Delta G_{transfer}$ value per unit surface.

We restrict our considerations here to rigid molecules, i.e., it is postulated

(i) that the molecular conformation of a given solute is the same in both solvents (in water and octanol, for example).

Moreover it is assumed

(ii) that the molecular surface (i.e., the surface which separates the cavity in which the solute molecule is located and the continuous space area of the solvent) is identical for the solvents considered here.

The central model assumption is

(iii) that the total free energy $\Delta G_{transfer}$ for the transfer of one mol solute from solvent I (water) to solvent II (octanol) can be represented as a surface extensive property (a surface integral)

$$\Delta G_{transfer} = \oint_0 \varrho(\mathbf{r}) dO \qquad (2.3)$$

with the local function $\varrho(\mathbf{r})$ which may be defined as a function in the whole space but has a physical meaning only on the molecular surface ($\mathbf{r}_s$). Here it represents the transfer free energy per unit surface which will be termed in the following as free energy surface density (FESD).

Since it is generally accepted that $\Delta G_{transfer}$ can be phenomenologically described as a superposition of local contributions, this should be a reasonable model assumption also for the FESD, i.e.

(iv) the free energy surface density can be represented as a superposition of local contributions

$$\varrho(\boldsymbol{r}_S) = \sum_i \varrho_i(\boldsymbol{r}_S) \tag{2.4}$$

where the summation is taken over atomic or molecular increments i.

It is obvious, that the global hydrophobicity index log P can be decomposed on the basis of the representation of the FESD (eq 2.4) into incremental contributiohns

$$\Delta G_{\text{transfer}} = -2.303RT \log P = \sum_i \Delta G_i \tag{2.5}$$

with

$$\Delta G_i = \oint_0 \varrho_i(\boldsymbol{r}) dO \tag{2.6}$$

where the identification with an empirical increment value f_i (see eq 1.1) is straightforward

$$f_i = \Delta G_i / -2.303RT \tag{2.7}$$

However, the f_i values are not necessarily those found by other authors because the incrementation is by no means unique. The formulation 2.4 is much more general than a simple incrementation of the log P value. Even if one assumes that the ϱ functions are independent of the molecular conformation, the total FESD will be definitely not in general. Consequently, there is a straighforward possibility to predict the conformational dependence of the hydrophobicity index when the incremental contributions are known (in opposite to an expression of the type eq 1.1, where such a prediction is not possible).

"Local" hydrophobicity can now be calculated on the basis of thermodynamic arguments as a surface integral of the type

$$(\log P)_i = \frac{1}{-2.303RT} \oint_{O_i} \varrho(\boldsymbol{r}) dO \tag{2.8}$$

where now O_i is a surface element which may be associated to a certain molecular increment i and some neighbor increments by a physical argumentation or by phenomenological reasons.

In the next section an analytical expression for an empirical representation of the local densities ϱ_i is developed on the basis of experimental log P values for the octanol/water system.

III. COMPUTATIONAL STRATEGY

Following the general concept outlined in the last section the FESD is represented here as a superposition of incremental contributions ϱ_i ($\boldsymbol{r}_S$) which are chosen in a similar way as the mapping functions of Heiden et al.,[39] i.e., we consider only atomic increments and assume that ϱ_i can be adequately modeled by

$$\varrho_i(\boldsymbol{r}_S) = F_i g_i^*(d_i) \tag{3.1}$$

with an increment specific constant F_i and a "mapping function"

$$g_i^*(d_i) = N g(|\boldsymbol{r}_i - \boldsymbol{r}_S|; c_i, \delta_i) \tag{3.2}$$

where for the distance function $g(d)$ with $d = |r_S - r_i|$ an expression of Fermi type[39] was chosen (see Figure 1)

$$g(d;c,\delta) = \frac{\exp(-2c/\delta) + 1}{\exp(2(d-c)/\delta) + 1} \tag{3.3}$$

and N is a "normalization" function

$$N^{-1} = \sum_i g(|\boldsymbol{r}_i - \boldsymbol{r}_S|; c_i, \delta_i) \tag{3.4}$$

while c_i and δ_i are characteristic parameters (termed proximity parameters in the following text) which determine in what way an increment i influences the FESD values at a certain surface point.

The distance function $g(d)$ has a priori no physical meaning. It only fulfills two conditions:

(i) It is smooth and has finite values for $d < c$ where c is a cutoff value which is termed the *proximity distance* of an increment. The value of the parameter c should be larger than any van der Waals radius of the increment in the molecule under consideration.

(ii) For distances $d > c$ the function values of $g(d)$ rapidly tend toward zero, i.e., the corresponding increment does not significantly contribute to the overall value of the FESD.

The explicative expression for the free energy surface density ϱ, eq 2.4 with eq 3.1, is not based on a rigorous physical concept. The function represents a weighted average of all the F_i values of atomic increments i for which $d_i < c_i$ is fulfilled, where d_i is the distance from a surface point to the center of the ith increment. All atoms which are farther away from the surface point do not contribute significantly. This can be demonstrated by a few simple examples (see Figure 2).

(i) For an atomic solute particle **1** the molecular surface has spherical symmetry and from eqs 3.1−3.4 it follows

$$\varrho(\boldsymbol{r}_S) = \varrho_1(\boldsymbol{r}_S) = F_1 = \text{const} \tag{3.5}$$

and consequently

$$\Delta G_{\text{transfer}} = \oint_{O_i} F_1 dO = F_1 O_1 \tag{3.6}$$

i.e., the choice of the parameter F_i depends on the definition of the surface as expected.

(ii) If there is more than one increment contributing to the solute particle but only one atomic center 1 is located within a proximity distance c_1 (see Figure 2a) from a surface point $\mathbf{r}_S$, only this atom contributes significantly to the FESD value at this point, i.e.

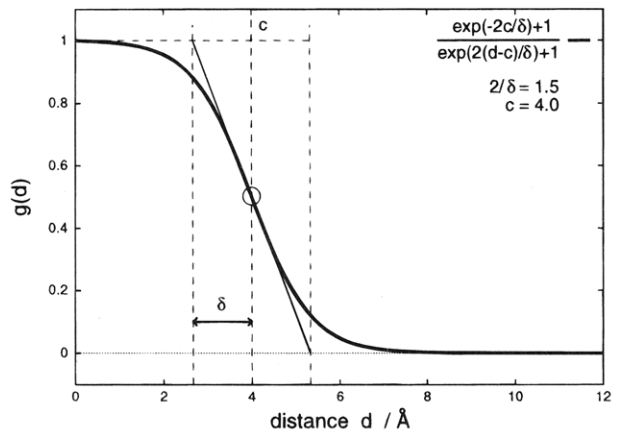
$$\sum_i F_i g(d_i) \cong F_1 g(d_1) \tag{3.7}$$

and

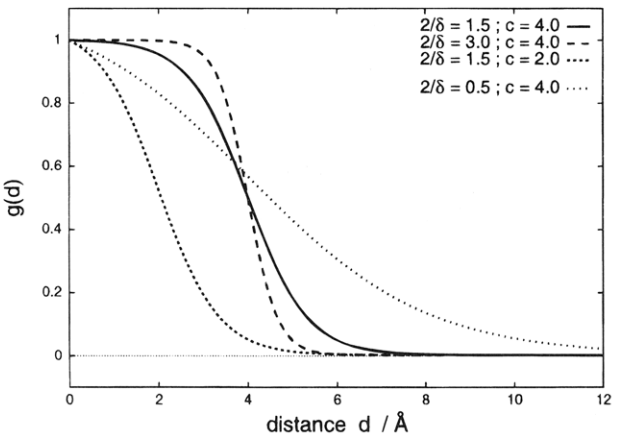
$$N^{-1} = \sum_i g(d_i) \cong g(d_1) \tag{3.8}$$

and consequently

$$\varrho(\boldsymbol{r}_S) = F_1 \tag{3.9}$$



(a)



(b)

Figure 1. Distance function $g(\boldsymbol{d};c,\delta)$ used for the local representation of the FESD: (a) definition of the proximity parameters c and δ and (b) influence of different values of c and δ on $g(\boldsymbol{d})$.

as in case (a), i.e., the increment FESD value F_1 is mapped on the surface point $\mathbf{r}_S$.

(iii) If two increment centers 1 and 2 with identical proximity parameters are located within the proximity distances c_1 and c_2, respectively and a surface point is chosen in such a way that $d_1 = d_2$ (see Figure 2b), only these two will contribute significantly to the FESD value at $\mathbf{r}_S$, i.e.

$$\sum_i F_i g(d_i) \cong F_1 g(d_1) + F_2 g(d_2) = (F_1 + F_2) g(d_1) \quad (3.10)$$

and

$$N^{-1} = 2g(d_1) \quad (3.11)$$

and consequently

$$\varrho(\boldsymbol{r}_S) = (F_1 + F_2)/2 \quad (3.12)$$

The FESD value becomes equal to the arithmetic average of the two increment values F_3 and F_4.

(iv) For the case where, as in (c), only two contributions are relevant but the distances d_3 and d_4 are different (see Figure 2c), one obtains analogously

$$\varrho(\boldsymbol{r}_S) = \frac{F_1 g(d_1;c_1,\delta_1) + F_2 g(d_2;c_2,\delta_2)}{g(d_1;c_1,\delta_1) + g(d_2;c_2,\delta_2)} \quad (3.13)$$

i.e., the FESD values are weighted averages of F_1 and F_2

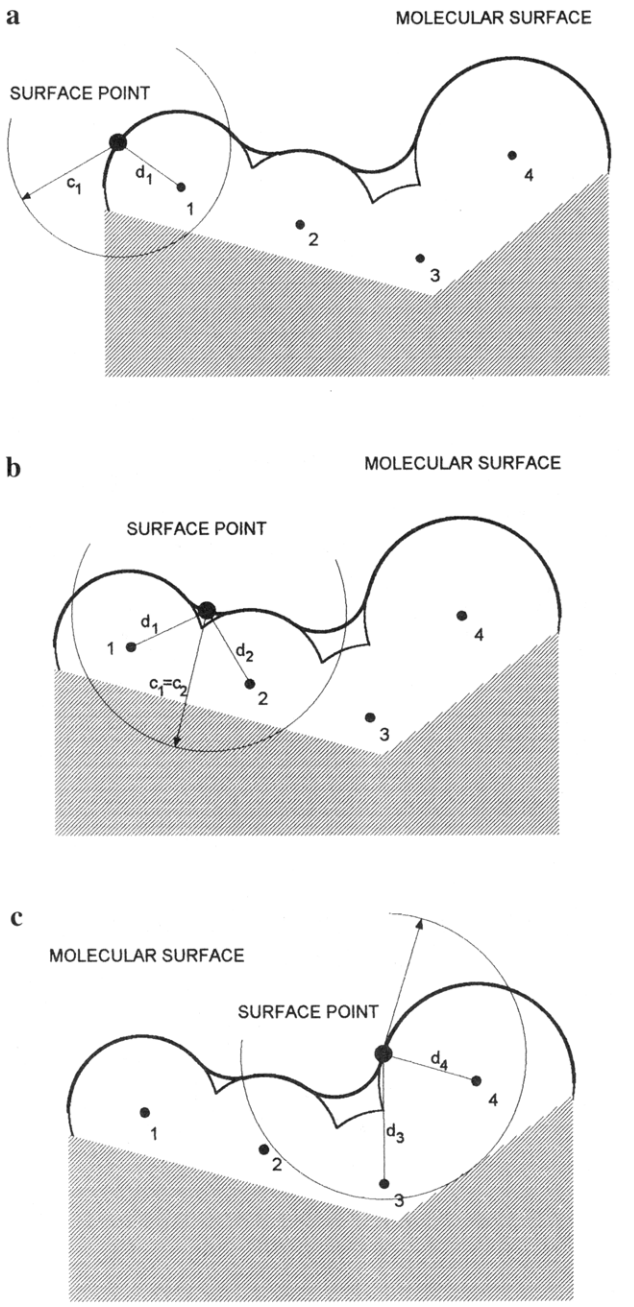


Figure 2. Influence of the proximity function $g^*(\boldsymbol{d})$ on the FESD value (schematically): (a) The F_i value is mapped onto the surface if only one fragment center is located within the proximity distance c_i. (b) The arithmetic mean of two FESD values is mapped on the molecular surface if the two increment centers which contribute dominantly to the surface point have the same distance and the distance functions $g_i(\boldsymbol{d})$ have identical proximity parameters c_i and δ_i. (c) A weighted average of two incremental values is projected as a surface FESD value if there are two centers of different distances (and possibly different proximity parameters) from the surface point.

with the weighting factors

$$p_1 = \frac{g(d_1;c_1,\delta_1)}{g(d_1;c_1,\delta_1) + g(d_2,c_2,\delta_2)};$$

$$p_2 = \frac{g(d_2;c_2,\delta_2)}{g(d_1;c_1,\delta_1) + g(d_2;c_2,\delta_2)} \quad (3.14)$$

which now depend on the explicative form of the g functions and the corresponding proximity parameters c_i and δ_i.

The examples demonstrate that the model approach generates weighted averages of the F_i data. The quantities

$$p_i = g_i^*(d_i) = \frac{g(d_i;c_i,\delta_i)}{\sum_j g(d_j;c_j,\delta_j)} \tag{3.15}$$

with $\sum_i p_i = 1$ can be interpreted as probabilities or weighting factors for the contributions of individual atomic free energy surface densities F_i to the local FESD value

$$\varrho(\mathbf{r}_S) = \sum_i p_i F_i \tag{3.16}$$

The discussion of these simple expressions is based on the assumption that the proximity parameters c_i and δ_i for all atomic increment types are known and that the increments' FESD value are well established. This establishment can only be done within an empirical statistical scheme where a large number of experimental data is incorporated. From eqs 2.5 and 2.6 one obtains with the explicative form of $\varrho_i(\mathbf{r})$ eq 3.1

$$\Delta G_i = F_i O_i \tag{3.17}$$

with

$$O_i = \int_O g_i^*(d_i) dO \tag{3.18}$$

The expression 3.18 represents the contribution of the increment i to the total molecular surface O, and one simply has

$$O = \sum_i O_i \tag{3.19}$$

One should note here that although the total surface is given as a sum of increment surfaces, O_i, the latter are not strictly local properties, i.e., a given surface point can only be associated to an increment with a certain probability. There is no sharp borderline between the individual O_i areas in contrast to the treatment of Richards and co-workers.[28,29]

The surface increments O_i are in this representation not only dependent on properties of the increment but on the relative position of all the other increments of the molecule relative to the increment i, i.e., O_i is explicitly dependent on the molecular conformation. The same atomic increment i will, in general, contribute to the total $\Delta G_{\text{transfer}}$ value in a different way, even if the F_i value of the increment is the same. This is demonstrated in Figure 3. This fact opens the possibility to include the conformation of a given compound in an empirical parametrization strategy. Comparing expression 1.1 and 2.5 with 3.17 one should expect that the f_i values of Ghose and Crippen should fulfil the equation

$$f_i = F_i O_i \tag{3.20}$$

However, this identity holds true only as a very rough estimate as can be seen from Table 1 where the O_i data were calculated with the c_i and δ_i values listed in Table 3.

Although the structure data of the molecules are similar, the F_i values show relatively large fluctuations. The F_i values have to be reparametrized on the basis of experimental log P values or on the basis of other thermodynamic data.

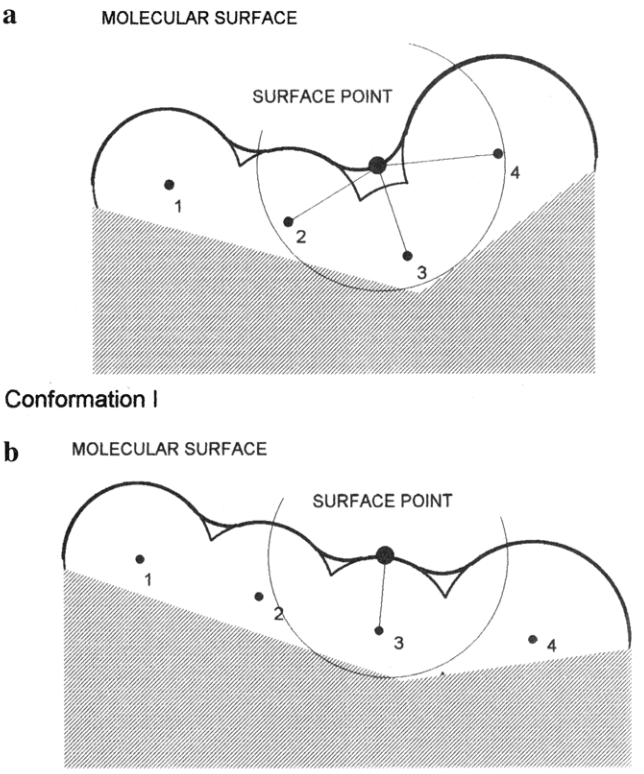


Figure 3. Influence of the molecular conformation on the FESD value (schematically): (a) The local FESD value is the sum of three weighted contributions. (b) A conformational change leads to a FESD value where now only one increment contributes significantly.

Table 1. Surface Integrals and Increments of Some Sample Substances for Crippen Type 89 (Cl)

substance	integral, Å^2	increment O_iF_i
m-chlorotoluene	10.54	−0.616
o-chlorotoluene	9.44	−0.552
2,4,5-trichlorophenol	11.55	−0.676
4-chloro-3-methylphenol	9.51	−0.556
m-chloroaniline	10.49	−0.614
m-dichlorobenzene	10.56	−0.618
p-chlorophenol	10.46	−0.612
	average	−0.606 ± 0.039

In the next section the parametrization strategies are described, and it is demonstrated that the strategy indeed leads to a self-consistent set of data.

IV. PARAMETRIZATION OF SUBSTITUTED BENZENES

This paper is the first within a series concerning the parametrization of transfer free energy surface density (FESD) values for a variety of organic compounds. The data as well as the computational strategy are part of the program system MOLFESD which is still under development in the group of the authors. At the present status the parametrization is based on structural data and experimental log P values for *rigid* molecules in the water/*n*-octanol solvent system with T = 300 K, i.e., only those molecules are used for a parametrization for which the main skeleton is rigid, guaranteeing that the molecular conformations in both solvents are (roughly) identical. We have made the following model assumptions:

Table 2. Log *P* Values for Those Substances Used for the Parametrization of Substituted Benzenes[a]

substance	log *P* (exp)	log *P* (calc)	log P^{15}	substance	log *P* (exp)	log *P* (calc)	log P^{15}
aniline	0.9	1.18	1.26	*m*-iodophenol	3	2.96	3.02
anisole	2.08	1.78	1.79	*m*-methoxyaniline	0.93	1.11	1.01
benzene	2.13	2.03	2.05	*m*-methoxyphenol	1.58	1.49	1.51
benzoic acid	1.87	1.91	1.75	*m*-methylphenol	1.96	2.03	2.23
benzyl alcohol	1.1	1.07	1.51	*m*-nitroaniline	1.37	1.17	1.22
benzylamine	1.09	1.09	1.16	*m*-nitrobenzoic acid	1.83	1.8	1.70
bromobenzene	2.99	2.99	2.84	*m*-toluidine	1.4	1.38	1.73
chlorobenzene	2.46	2.77	2.56	*m*-trifluoromethylphenol	2.95	2.95	2.65
hexachlorobenzene	4.13	4.15	5.15	*o*-aminobenzoic acid	1.21	1.35	0.96
hexafluorobenzene	2.22	2.2	2.88	*o*-aminophenol	0.62	0.82	0.98
2-chloronitrobenzene	2.24	2.13	2.52	*o*-bromoaniline	2.29	2.23	2.06
2,3-dichloroaniline	2.78	2.5	2.30	*o*-bromophenol	2.35	2.23	2.55
2,4-dichlorophenol	3.3	3.24	2.80	*o*-chlorobenzoic acid	1.98	1.94	2.26
2,4-dihydroxybenzoic acid	2.06	1.77	1.18	*o*-chlorophenol	2.15	2.05	2.28
2,4-dinitrophenol	1.51	1.62	1.67	*o*-chlorotoluene	3.42	3.46	3.03
2,4,5-trichlorophenol	3.72	3.71	3.32	*o*-dibromobenzene	3.64	3.53	3.63
2,4,6-tribromophenol	4.23	4.23	4.14	*o*-dichlorobenzene	3.38	3.27	3.08
2,5-dihydroxybenzoic acid	1.74	1.74	1.18	*o*-dinitrobenzene	1.58	1.53	1.95
2,6-dihydroxybenzoic acid	2.2	2.22	1.18	*o*-fluoroaniline	1.26	1.22	1.40
2,6-dinitrophenol	1.25	1.49	1.67	*o*-fluorophenol	1.71	1.67	1.90
3-bromonitrobenzene	2.64	2.58	2.79	*o*-hydroxybenzaldehyde	1.62	1.62	1.44
3-chloronitrobenzene	2.46	2.4	2.52	*o*-hydroxybenzyl alcohol	0.73	0.71	1.23
3-iodonitrobenzene	2.94	2.83	3.26	*o*-iodobenzoic acid	2.4	2.4	3.00
3,4-dichloroaniline	2.69	2.42	2.30	*o*-iodophenol	2.65	2.5	3.02
4-chloronitrobenzene	2.39	2.53	2.52	*o*-methoxyaniline	0.95	1.11	1.01
4-chloro-3-methylphenol	3.1	3.06	2.75	*o*-methoxyphenol	1.33	1.34	1.51
5-bromosalicylic acid	2.87	3	2.25	*o*-nitroaniline	1.44	1.25	1.22
N-methylaniline	1.66	1.66	1.62	*o*-nitrophenol	1.77	1.79	1.72
nitrobenzene	1.85	1.93	2.00	*o*-toluidine	1.4	1.41	1.73
pentachlorophenol	3.81	3.95	4.35	*p*-bromoaniline	2.26	2.17	2.06
phenol	1.48	1.68	1.76	*p*-bromobenzoic acid	2.86	2.94	2.54
toluene	2.73	2.45	2.51	*p*-bromophenol	2.59	2.65	2.55
trifluoromethoxybenzene	3.17	3.17	3.54	*p*-chloroaniline	1.83	1.94	1.78
trifluoromethylbenzene	2.79	2.79	2.93	*p*-chlorobenzoic acid	2.65	2.73	2.26
α-bromotoluene	2.92	2.92	2.72	*p*-chlorobenzyl alcohol	1.96	1.89	2.03
α-chlorotoluene	2.3	2.3	2.66	*p*-chlorophenol	2.39	2.42	2.28
m-bromoaniline	2.1	2.13	2.06	*p*-dichlorobenzene	3.39	3.48	3.08
m-bromobenzoic acid	2.87	2.87	2.54	*p*-dinitrobenzene	1.46	1.81	1.95
m-chloroaniline	1.88	1.89	1.78	*p*-fluoroaniline	1.15	1.35	1.40
m-chlorobenzyl alcohol	1.94	1.85	2.03	*p*-fluorobenzoic acid	2.07	2.13	1.88
m-chlorophenol	2.5	2.39	2.28	*p*-fluorophenol	1.81	1.84	1.90
m-chlorotoluene	3.28	3.35	3.03	*p*-hydroxybenzoic acid	1.58	1.58	1.46
m-dibromobenzene	3.75	3.88	3.63	*p*-iodobenzoic acid	3.02	3.2	3.00
m-dichlorobenzene	3.38	3.44	3.08	*p*-iodophenol	2.91	3	3.02
m-fluoroaniline	1.3	1.34	1.40	*p*-methoxyaniline	0.95	0.95	1.01
m-fluorobenzoic acid	2.15	2.01	1.88	*p*-methoxyphenol	1.34	1.39	1.51
m-hydroxybenzaldehyde	1.38	1.38	1.44	*p*-methylphenol	1.94	2.13	2.23
m-hydroxybenzoic acid	1.5	1.44	1.46	*p*-nitroaniline	1.39	1.19	1.22
m-hydroxybenzyl alcohol	0.49	0.69	1.23	*p*-nitrobenzoic acid	1.89	1.7	1.70
m-iodobenzoic acid	3.13	3.14	3.00	*p*-nitrophenol	1.91	1.62	1.72

[a] The values in the second column are those calculated with the optimized parameters F_i, c_i, and δ_i; those in the third column are Ghose and Crippen values.

(i) The equilibrium conformations of the molecules are identical in water and *n*-octanol.

(ii) The molecular contact surface is identical for both solvents. This surface is calculated via the MS algorithm of Connolly[40] with a water molecule as a probe (probe radius r = 1.4 Å).

(iii) There is no dimerization in the solvents, and water molecules which may be bound to the molecules by hydrogen bonds are explicitly excluded.

It is clear that, in particular, assumption (iii) may not hold very strongly if there are strong proton donor and proton acceptor functionalities in the molecules considered here, but we just like to demonstrate that the procedure works, rather than to present final data for the parametrization.

A set of 100 molecules (see Table 2) containing a central phenyl ring as a building block have been taken to parametrize the atomic increments F_i as well as the proximity parameters c_i and δ_i. The 3D structural data of the molecules have been generated using standard building tools provided by the SYBYL package[42] and MO calculations by MOPAC/AM1.[44] It turned out that for the set of molecules considered here, the standard geometries did not significantly differ from the MO values. The classification of the increments are those of Ghose and Crippen.[14] The increments are listed in Table 3 together with the f_i values of these authors and the parameters of this work.

The parametrization was performed according to the following procedure:

(a) In the first step the calculations were performed with the uniform proximity values c_i = 4 Å and δ_i = 1.33 Å of Heiden et al.[39] for all atomic increments.

Table 3. Increments and Increment Values According to the Classification of Ghose and Crippen[16] [a]

atom type		no.	f_i	F_i, Å^{-2}	c_i, Å	δ_i, Å
C in	CH_3R	1	−0.6771	1.17	3.1	0.57
	CH_3X	5	−1.0824	3.76	2.25	0.41
	CH_2RX	6	−0.8370	−0.19	2.25	0.41
	CRX_3	13	0.2263	−33.65	2.4	0.44
	CX_4	14	0.8282	−30.91	2.4	0.44
	Ar CH	24	−0.0068	0.24	3.1	0.57
	Ar CR	25	0.1600	0.9	2.4	0.44
	Ar CX	26	−0.1033	0.09	2.8	0.51
	Ph−CH=X	37	0.3568	−4.89	3	0.55
	R−C(=X)−X	40	0.0709	−1.62	2.45	0.45
H at	$CO(sp_3)$	46	0.4418	−1.08	2.3	0.42
	$CO(sp_2)$	47	0.3343	−0.44	2.3	0.42
	$C_3(sp_3)$, $C_2(sp_2)$	49	−0.1488	6.12	2.4	0.44
	heteroatom	50	−0.3260	0.33	2.85	0.52
	alkohol	56	0.1402	−0.43	2.4	0.44
	phenol, enol	57	0.4860	−0.51	2.4	0.44
	=O	58	−0.3514	0.98	2.75	0.5
	Al−O−Ar, Ar−O−Ar	60	0.2712	−3.05	2.3	0.42
	−O	61	1.5810	−0.02	2	0.37
N in	$Al-NH_2$	66	0.1187	−0.82	2.4	0.44
	Al_2-NH	69	0.3132	−0.84	2.55	0.47
	Ar−NH−Al	70	0.4238	−2.94	2.4	0.44
	$Ar-NO_2$	76	−2.7640	−0.02	5.4	0.99
F at	$C_3(sp_3)$	83	0.2798	15.43	2.2	0.4
	$C_1(sp_2)$	84	0.5839	−0.12	2.2	0.4
Cl at	$C_1(sp_2)$	86	0.9609	0.08	2.4	0.44
	$C_1(sp_2)$	89	0.9624	−0.06	2.2	0.4
Br at	$C_1(sp_3)$	91	1.0242	0.09	2.8	0.51
	$C_1(sp_2)$	94	1.2362	−0.03	2.65	0.49
I at	$C_1(sp_2)$	99	1.7018	−0.01	2.95	0.53

[a] f_i are the increment values reported by these authors. F_i, c_i, and δ_i are the increment parameters determined in this work.

(b) On the basis of the c_i and δ_i values the surface contributions O_i of the ith increment to the jth molecule were calculated using the Connolly[40] surface as a uniform reference

$$O_{ij} = \sum_{\alpha} O_{ij}^{(\alpha)} \tag{4.1}$$

where the summation is taken over all surface elements related to the increment type i in the molecule j.

(c) A least squares fit was performed with fixed proximity parameters c_i and δ_i, i.e., the linear matrix equation[43]

$$\boldsymbol{O}^T\boldsymbol{O}x = O^T p \tag{4.2}$$

with $\boldsymbol{O} = (O_{ij})$, $\boldsymbol{O}^T = (O_{ji})$, was solved for the unknown increment values

$$x_i = F_i/-2.303RT \qquad (i = 1 - n_I) \tag{4.3}$$

where n_I is the number of different increment types used for the parametrization. The column vector $\boldsymbol{p}$ contains the experimental log P values of the molecules listed in Table 2.

(d) The theoretical log P values can then be calculated according to

$$(\log P)_j = \sum_{i=1}^{n_I} x_i O_{ij} \tag{4.4}$$

(e) The correlation coefficient r is calculated as

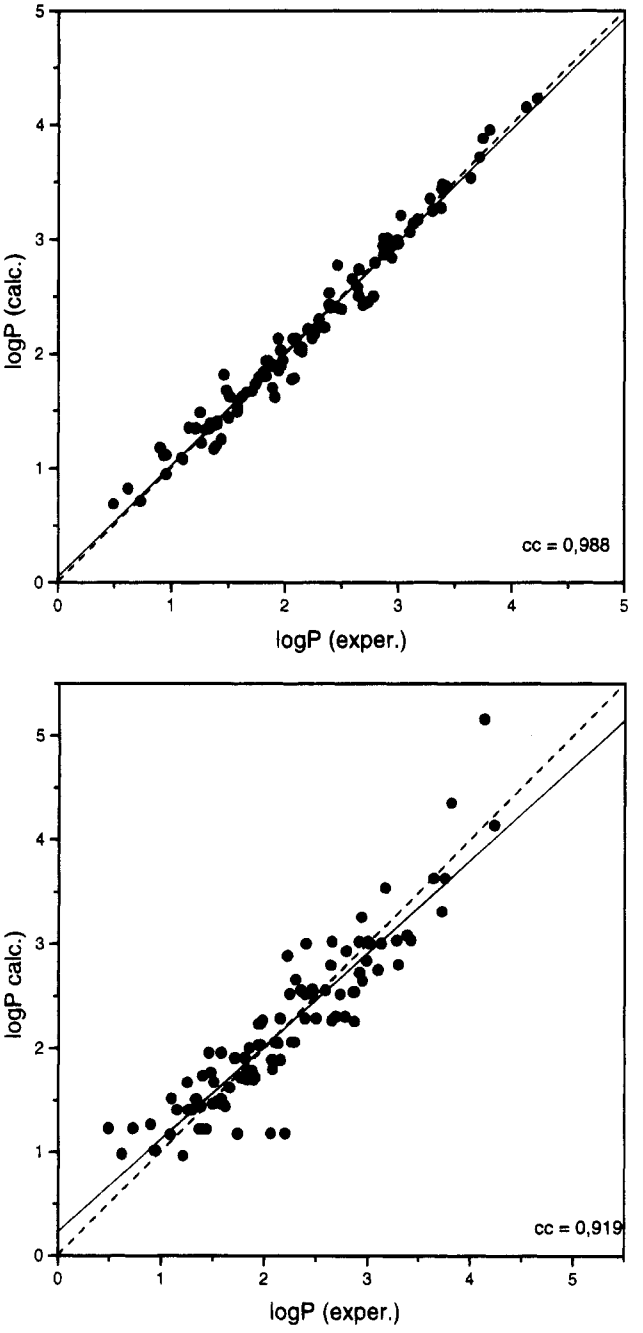


Figure 4. Calculated vs experimental log P values of the 100 substances used for parametrization (see Table 2): (a) FESD method (eq 4.4) and (b) atomic increment method of Ghose and Crippen.[15]

$$r = \frac{\langle \alpha_j \beta_j \rangle - \langle \alpha_j \rangle \langle \beta_j \rangle}{[\langle (\alpha_j - \langle \alpha_j \rangle)^2 \rangle \langle (\beta_j - \langle \beta_j \rangle)^2 \rangle]^{1/2}} \tag{4.5}$$

where α_j and β_j are the experimental and theoretical log P values (see eq 4.4), respectively.

(f) Finally, the nonlinear proximity parameters c_i and δ_i of one increment type i were changed systematically, and the procedure was continued with step (b) until the correlation became maximal.

The results of the parametrization basing on 100 substituted benzenes are listed in Table 2. Table 3 contains the log P values of these molecules as calculated on the basis of these parameters together with the experimental values and those based on the incrementation of Ghose and Crippen.[15]

Table 4. Experimental and Calculated Log P Values of 20 Sample Substances

substance	log P (exp)	log P (calc)	no.
benzaldehyde	1.48	1.62	1
fluorobenzene	2.27	2.18	2
iodobenzene	3.25	3.42	3
1,3,5-trinitrobenzene	1.18	1.33	4
2,4-dibromophenol	3.48	3.7	5
2,4,6-trichlorophenol	3.69	3.52	6
2,5-dinitrophenol	1.75	1.75	7
4-bromonitrobenzene	2.55	2.74	8
4-chloro-2-methylphenol	2.78	2.8	9
salicylic acid	2.24	2.05	10
m-bromophenol	2.63	2.62	11
m-chlorobenzoic acid	2.68	2.6	12
m-dinitrobenzene	1.49	1.65	13
m-fluorophenol	1.93	1.82	14
o-chloroaniline	1.9	1.95	15
o-iodoaniline	2.32	2.75	16
o-methylphenol	1.97	1.89	17
p-chlorotoluene	3.33	3.36	18
p-hydroxybenzaldehyde	1.35	1.3	19
p-toluidine	1.39	1.53	20

One can see that in most cases the tendencies of the Crippen values and that from the present parametrization quantitatively agree, while in some cases this is not the case. These qualitative differences are probably related to the fact that the parameters partly depend or are nearly dependent on each other which leads then to a plateau type scoring function near the minimum value. In future development these parameter dependencies will be removed by additional constraints. For log P predictions the parameter dependency, however, is of no relevance. In Figure 4a the theoretical log P values are plotted against the experimental ones for the set of molecules used in the parametrization while Figure 4b shows the log P values calculated with the Ghose and Crippen scheme. There is indeed a much better correlation ($r = 0.988$) for our values than for that of the authors cited above ($r = 0.919$). This is, however, not surprising, because our parameters were chosen in order to give a maximal correlation coefficient. For a validation of our parameters the log P values of a set of 20 additional substituted benzenes (see Table 4) were theoretically determined and compared to experimental data. Figure 5a shows now that the parametrization works very well indeed. The predicted values nicely correlate with the experimental data ($r = 0.979$), while the correlation coefficient for the incrementation of Ghose and Crippen[16] (Figure 5b) is much smaller ($r = 0.898$). We did not include molecules with high flexibility in the backbone because such molecules may not have the same structure in both solvents under consideration. Richards and co-workers have already pointed out[28,29] that the occurrence of different conformers may influence the log P results quite dramatically. One should expect that a similar effect may occur when the molecular structures are systematically changed. This is investigated with an example in the next section.

V. CONFORMATIONAL DEPENDENCE OF HYPOTHETICAL LOG P VALUES FOR 2-HYDROXYBIPHENYL

In order to study the influence of molecular conformational changes on the predicted log P value some test calculations were performed with 2-hydroxybiphenyl (I) wherein the dihedral angle φ of the central bond was systematically varied.

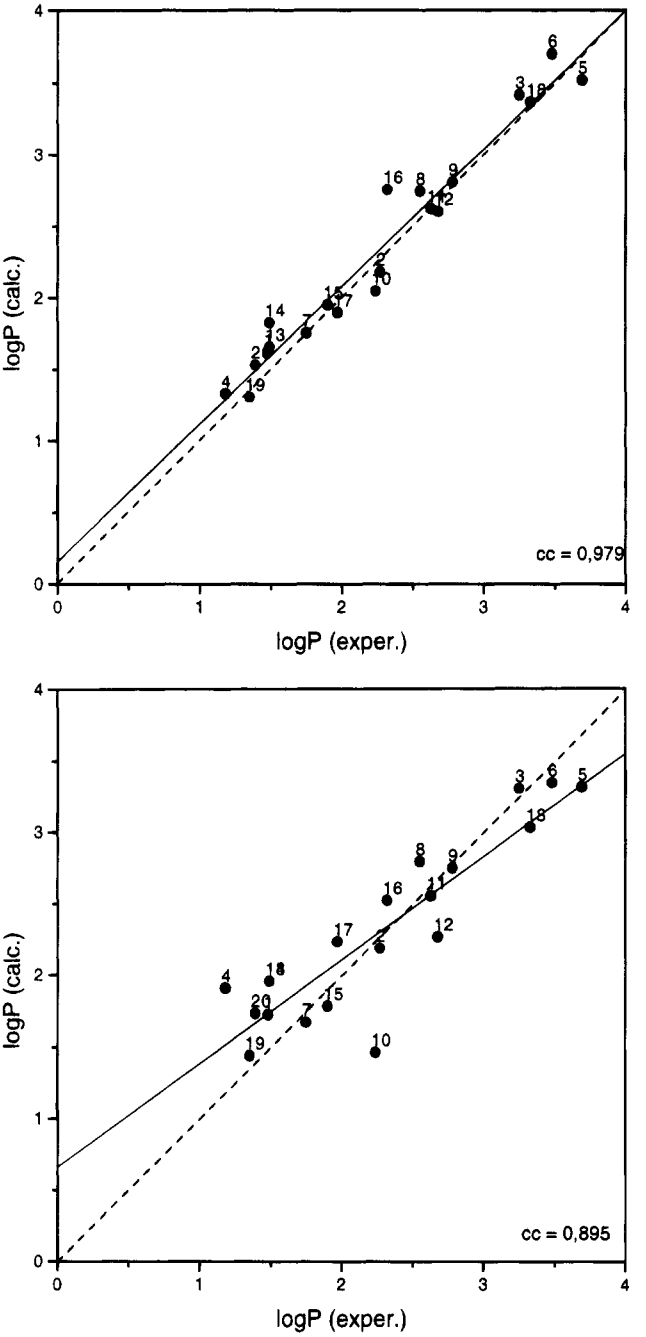
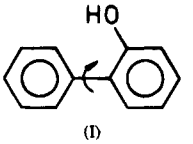


Figure 5. Calculated vs experimental log P values of 20 substances not included in parametrization (see Table 4): (a) FESD method (eq 4.4) and (b) atomic increment method of Ghose and Crippen.[15]



(I)

The intramolecular energy in this demonstration case was simply calculated within the program package MOPAC[44] where both parts of the molecule are kept rigid, i.e., no structural relaxation was included here. The intramolecular rotational barrier was $\Delta E = 14.2$ kcal/mol, a value which is probably, by a factor of two, too high because of a systematic overestimation of the AM1 method[44] and because of missing structural relaxation. The energy profile is shown in Figure 6 together with hypothetical ΔG values as calculated on the basis of the present model approach as a function of φ. These latter values are not really observable quantities; they have

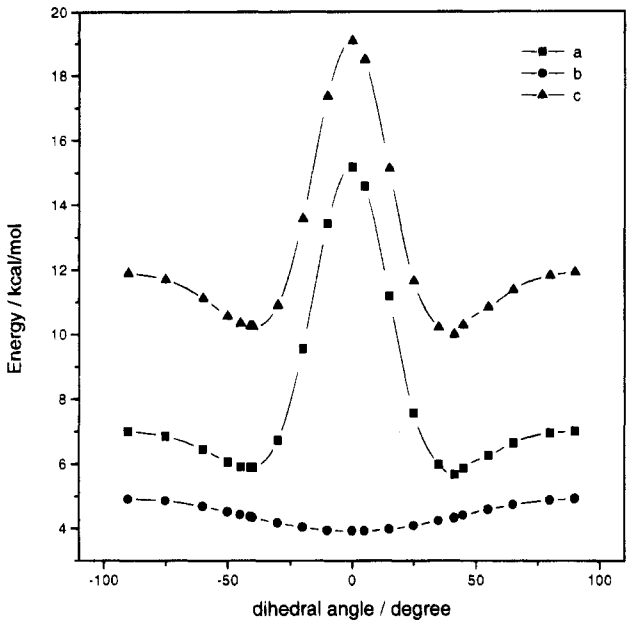


Figure 6. Energy profiles as functions of the central dihedral angle: (a) internal energy without structural relaxation (AM1[44]), (b) free energy of hypothetical transfer, and (c) sum of (a) and (b).

just been calculated in order to demonstrate the possible effect of the change of the molecular structure. In this case, it turns out that the contribution of the different solvents to the total barrier is to be expected in the order of a few kcal/mol. It is remarkable in this context that the solvent effect contributes to a decrease of the barrier in this case.

VI. CONCLUSIONS AND OUTLOOK

We have demonstrated in this work that the transfer free energy for bringing a molecule from one solvent (*n*-octanol) to another (water) can be well represented as a surface integral over the molecular contact surface with the solvent. A free energy surface density (FESD) concept has been formulated on the basis of atomic increment contributions. It was shown that the concept of the FESD function can be very well used for an empirical fit of parameters in such a way that the surface integral can be linearly related (with a proportionality factor of $(RT)^{-1}$) to the experimentally determined log *P* values in the case of *n*-octanol/water solvents. In addition, the formalism allows to study the influence of conformational changes on hypothetical log *P* values. This opens up a variety of applications.

The FESD approach, however, not only is very useful for the prediction of unknown log *P* values, but also can form the basis of an understanding and quantitative treatment of local hydrophobic interaction. In the integral representation of the log *P* value there are, in general, surface areas which contribute positively, and there are such which contribute negatively. Areas of the first type are those which would prefer to be surrounded by water, while those of the second type preferably would tend to be surrounded by the less polar solvent. When we call the first type hydrophilic and the second one hydrophobic, the molecular surface can be subdivided into these two classes. Moreover the FESD approach allows us to take the surface integral over each of these areas in order to establish local contributions to the total $\Delta G_{transfer}$. These local contributions may be used as correlation parameters in QSAR studies. Works along these lines are in progress.

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