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Modeling lipophilicity from the distribution of electrostatic potential on a molecular surface

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Summary

Molecular lipophilicity L is represented as a function of four surface electrostatic potential descriptors: $L = f(B_F^+, B_F^-, B_R^+, B_R^-)$. Each B descriptor is computed from the products of elements of molecular surface area, Δs_i, and the molecular electrostatic potential (MEP), $V(\mathbf{r}_i)$, at the center of an area element: $B = \sum_i \Delta s_i V(\mathbf{r}_i)$. Octanol–water partition coefficients (P_{ow}) are correlated with these four surface–MEP descriptors: $\log P_{ow} = c_0 + c_1 B_F^+ + c_2 B_F^- + c_3 B_R^+ + c_4 B_R^-$. Good correlations are obtained for homologous series of aliphatic alcohols, amines and acids, as well as for a set of aromatic compounds with various functional groups. Within this approach, we find that the molecular fragment contributions of surface–MEP descriptors to log P are approximately additive. We have computed the values for the following fragments: $-CH_2-$, $-CH_3$, -COOH, -OH and $-NH_2$. These contributions can be used to estimate the molecular lipophilicity and partition coefficients of new compounds, without additional quantum-mechanical calculations. The proposed approach provides a reasonably accurate tool that can be useful in quantitative structure–activity relations for computer-aided rational drug design. More importantly, the correlation model is conceptually simpler than previous work in the literature and can be improved systematically.

Introduction

Hydrophobicity (or lipophilicity) is an important property of biomolecules. Biological activity of many drugs, bioaccumulation of organic pollutants, and soil adsorption of environmental contaminants have all been attributed, to some degree, to the hydrophobic character of molecules. In drug action, the hydrophobicity of a solute controls its distribution among body fluids, liquid-rich phases, and tissue proteins. For this reason, a quantitative assessment of hydrophobicity is of great importance in quantitative structure–activity relationship (QSAR) studies with applications in numerous disciplines, including medicinal chemistry (drug design), pharmacology, and environmental monitoring.

Hydrophobicity constitutes one of the three main interactions responsible for molecular bioactivity, together with hydrogen bonding and electrostatic interactions. The nature and magnitude of hydrogen bonding are well characterized, and the molecular electrostatic interaction has a clear physical nature and can be calculated accurately in quantum chemistry. On the other hand, hydrophobicity is a difficult property to estimate theoretically from first principles. Unlike the other two 'forces', the hydrophobic 'force' has no simple physical definition, and cannot be attributed to a single physical entity or potential [1–5].

The so-called 'lipophilicity force' is a phenomenological interaction resulting from averaging the dynamics of electrostatic interactions in large solute–solvent clusters. Its precise contribution to the stabilization energy of ligand–macromolecule complexes or hydrated proteins is difficult to assess. Nevertheless, there is ample evidence that hydrophobicity significantly contributes to the energy and plays an important role in the processes described above. One of the tasks of theoretical chemistry is to produce models, either semiempirical or based on first principles, which provide a satisfactory link between experimental measures of hydrophobicity and microscopic struc-

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tural information on the molecule. In this work, we deal with modeling the logarithm of the partition coefficient (log P) from a small number of specially chosen, fundamental structural parameters. Partition coefficients play a key role in drug design as a good measure of hydrophobicity and drug transport across the cell membrane. Moreover, it is a simple physicochemical property related to the free energy change that accompanies the interaction between a drug and a receptor, which in most cases includes a dehydration process.

A satisfactory modeling of solvation phenomena and hydrophobicity should take into account electrostatic as well as entropic effects related to the change in the organization of solvent molecules around a solute. However, modeling solvation from first principles or by computer simulation of solvent–solute clusters is difficult. For this reason, semiempirical approaches are still valuable. In this work, we discuss a new empirical correlation model based on a simple physical analysis. The model satisfies fragmental additivity to hydrophobicity.

The goal of empirical correlation formulas is to correlate the experimental partition coefficients log P with various molecular properties, such as molecular surface area, volume, mass, atomic charges, electrostatic potential, and dipole moment [6–22]. Other molecular properties have been used in linear and nonlinear correlations for log P. The literature on these types of approaches is vast. Other significant contributions are reported in Refs. 23–28. Here, we will focus mostly on correlations with structural parameters derived from two-dimensional molecular electrostatic properties. The behavior of the molecular electrostatic potential (MEP) can be readily related to chemical reactivity [29,30].

The parameters used in correlations can be classified into two categories: experimental observables and theoretical structure-based properties. For the purpose of chemical design, the structure-based theoretical parameters are more popular, because they do not require complex experiments (moreover, a detailed experimental characterization often may not be feasible for new compounds). The empirical formulas used by Brinck et al. [16–18] and Murray et al. [19–22] belong to this class, and involve molecular surface and electrostatic potential properties. Using these approaches, the best correlations obtained with three- or four-parameter formulas for a large family of diverse chemical compounds have correlation coefficients (r) between 0.936 and 0.961 [16–22]. Empirical formulas used by Taft and co-workers [12,31] yield better correlations, but the latter involve parameters such as polarizability, a 'polarizability correction', and hydrogen bond donor–acceptor tendencies, which are either difficult to estimate or defined with arbitrary criteria. It is desirable to have models that use simpler molecular parameters, yet lead to comparable correlations for compounds with a variety of functional groups.

Another common empirical approach considers the log P as an additive contribution of properly chosen submolecular fragments. Usually, atoms are considered as the fragments. A number of definitions for 'optimal atomic fragments' have been given in the literature. (Regarding the values of fragmental contributions, see e.g. Refs. 32–39.) This approach is more convenient than the correlations discussed before, because the estimation of log P for a new compound requires a simple search in a database of atomic fragments.

The 'hydrophobicity index' of Kantola et al. [15] is appealing since it has the advantages of both correlation and fragmental-addition approaches. Their structural parameters are derived from standard quantum-mechanical computations, and the output is a data set of atomic contributions for predicting the hydrophobicity of new compounds. Here, we propose a new approach to predict hydrophobicity (e.g., the partition coefficients) that also combines these two features: a structure-based theoretical correlation model with parameters that exhibit fragmental additivity. Our methodology to study lipophilicity uses two properties with a clear physical meaning: molecular surface area and electrostatic potential. We do not seek to produce merely numerical formulas to estimate log P for generic compounds. Several excellent schemes described in the literature can be used to this effect. Rather, we want to test whether it is possible to derive an acceptable representation of log P by using simple criteria derived from two-dimensional electrostatic properties. We are concerned mostly with conceptual issues. Our goal is to gain an understanding of the structural parameters with a clear physical meaning that can be used to obtain acceptable correlations.

The work is organized as follows. In the next section, we discuss the characterization of the distribution of MEP on molecular surfaces, and its previous application to model partition coefficients. The discussion sets the background for our proposed surface–MEP descriptors, which are subsequently introduced together with their main properties and computational details. In the following section, we present several correlation models to represent log P and discuss their performance. Next, the fragmental contributions to the surface–MEP descriptors are evaluated and finally some further comments and conclusions are given.

Descriptors based on molecular surface and electrostatic potential

In almost all empirical correlation models, molecular surface area is one of the most important parameters used [7,8]. For organic compounds, the surface area accounts in part for the entropic contribution associated with the organization of the solvent around a solute molecule. However, molecular surface area contains no information

on specific features of the solute–solvent interaction. To this effect, one should study the electrostatic potential about the solute, in addition to its surface area. On the other hand, the electrostatic potential alone (without taking into account surface properties) is not sufficient to account for all local lipophilicity features [40].

Recent results indicate that log P correlates with some features of the MEP distribution on a molecular surface [16–22]. Various descriptors have been used in empirical correlations, including:

$$\Pi = \frac{1}{m}\sum_{i=1}^{m}\left|V(\mathbf{r}_i) - \overline{V}\right| \tag{1}$$

$$\sigma_+^2 = \frac{1}{m_+}\sum_{i=1}^{m_+}\left[V^+(\mathbf{r}_i) - \overline{V}^+\right]^2, \quad V^+(\mathbf{r}_i) \geq 0 \tag{2}$$

$$\sigma_-^2 = \frac{1}{m_-}\sum_{i=1}^{m_-}\left[V^-(\mathbf{r}_i) - \overline{V}^-\right]^2, \quad V^-(\mathbf{r}_i) < 0 \tag{3}$$

$$\sigma_t^2 = \sigma_+^2 + \sigma_-^2 \tag{4}$$

where $V(\mathbf{r}_i)$ is the quantum-mechanical MEP at point $\mathbf{r}_i$. The parameter $\overline{V}$ is the mean MEP over the complete molecular surface, whereas $\overline{V}^+$ and $\overline{V}^-$ are the averages restricted to the regions on the surface where the MEP takes only positive (or zero) and negative values, respectively:

$$\overline{V} = \frac{1}{m}\sum_{i=1}^{m} V(\mathbf{r}_i) \tag{5}$$

$$\overline{V}^+ = \frac{1}{m_+}\sum_{i=1}^{m_+} V^+(\mathbf{r}_i), \quad V^+(\mathbf{r}_i) \geq 0 \tag{6}$$

$$\overline{V}^- = \frac{1}{m_-}\sum_{i=1}^{m_-} V^-(\mathbf{r}_i), \quad V^-(\mathbf{r}_i) < 0 \tag{7}$$

In Eqs. 1–7 the molecular surface is represented by a discrete grid of m points (usually calculated at the STO-5G ab initio level on molecular surfaces defined by the 0.001 $e^-/bohr^3$ contour of electron density) [16]. The potential $V(\mathbf{r}_i)$ takes negative values over m_- points, whereas the MEP is positive (or zero) over m_+ points ($m = m_+ + m_-$). The parameter Π (Eq. 1) is the average absolute deviation from the mean of the surface electrostatic potential. It can be interpreted as a measure of local polarity or charge separation [16]. The total variance, σ_t^2 (Eq. 4), is a measure of the spread (or dispersion) of the surface potential.

Murray et al. [21] analyzed correlations of *n*-octanol–water partition coefficients (P_{ow}) for benzene, toluene, and nine nitroaromatic compounds. Their best correlation scheme (with a correlation coefficient r = 0.980) takes the form: $\log P_{ow} = c_0 + c_1 s + c_2 s\Pi$, where s is the molecular surface area. The results indicate that an increase in solute size favors partitioning into the organic phase (*n*-octanol). In contrast, an increase in Π favors partitioning into water. A study of water–octanol partition coefficients by Brinck et al. [18] included 70 organic molecules of various types and sizes. A number of ad hoc correlation schemes were explored. The best results obtained correspond to the formulas:

$$\log P_{ow} = c_0 + c_1 s + c_2\sigma_t^2 + c_3 s\Pi \tag{8}$$

$$\log P_{ow} = c_0 + c_1 s + c_2\sigma_-^2 + c_3 s\Pi \tag{9}$$

with correlation coefficients of 0.950 and 0.961, respectively. Even though the approach leads to good results for several families of compounds, it also leaves space for improvement at the quantitative as well as conceptual level. Two basic criticisms can be made to the scheme above.

(i) The terms included in the correlation models above (Eqs. 8 and 9) have different units. From a conceptual viewpoint, this is a drawback: Do we expect log P to be linear with area, area × potential, or the square of potential? Can we justify using only these terms and no others? Note that each term relates to rather different effects and phenomena. It is therefore difficult to interpret the physical meaning of a good correlation.

(ii) The parameters in Eqs. 8 and 9 are global properties of the entire molecular surface. For example, the parameter $s\Pi$ does not reflect the details of the local interrelations between the molecular shape and electrostatic potential. Depending on the local curvature, a small change in surface area elements may be accompanied by a large change in MEP or vice versa. These features may be crucial in determining a log P value.

In the next section, we propose a new set of parameters that address these drawbacks. The key idea is to represent log P as proportional to structural parameters satisfying two criteria: (i) they describe the interrelation of molecular surfaces and MEP at the local level; and (ii) they can be qualitatively related to entropic and enthalpic contributions to lipophilicity. To ensure a simple physical interpretation of the parameters in terms of energetics, we shall require that they all have the same units. Our goal is to investigate the performance of a simple representation of log P based on the above criteria.

A comment on the computation of the electrostatic potential is in order here. In principle, the MEP could be evaluated from a semiempirical distribution of charges, like those used in standard molecular mechanics methods. However, it has been well established that local charges produce artificial local MEP features on a molecular surface. For this reason, we shall use here only the quan-

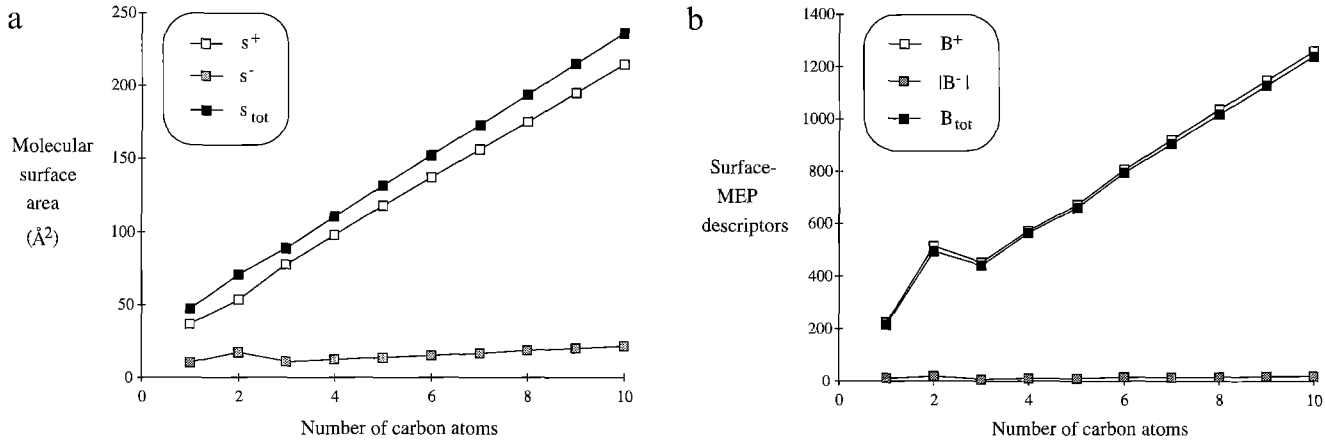

Fig. 1. Molecular surface area (a) and surface–MEP (b) of *n*-alkanes as a function of the number of carbon atoms in the chain. The MEP is calculated at the ab initio RHF/6-31G level, using the STO-5G-optimized all-trans conformation [46]. The surface area is calculated with a density of 25 points/Å². B descriptors are given in kcal Å²/mol. The parameter B_{tot} is given by $B^- + B^+$.

tum-mechanical MEP, computed by integrating the Hartree–Fock electron density [29,30].

Surface–MEP descriptors

Our present analysis of lipophilicity is restricted to compounds with a (hydrophobic) hydrocarbon skeleton and a number of hydrophilic functional groups. The selection has been made to ensure some variety, but it is by no means representative of all organic compounds. A thorough study of functional groups is not the goal of this section.

When designing correlations with experimental $\log P_{ow}$ data, one should have in mind that functional groups and hydrocarbon moieties may have different hydrophobic behavior. In order to account for this fact, we propose to use four structural descriptors evaluated from the differential distribution of positive and negative MEP over a molecular surface whose shape changes locally.

The definition of these parameters is simple. Consider a molecular envelope (e.g., a van der Waals surface). Let us label the part of the exposed surface contributed by the atoms in the functional group with 'F' and the part corresponding to the hydrocarbon moiety with 'R'. The surface can be represented, as usual, as a finite array of points $\{\mathbf{r}_i\}$ [41–43]. Let Δs_i be the local area contribution of an element of surface centered about point $\mathbf{r}_i$. (Such a contribution can be evaluated by triangulation and it is provided in standard molecular surface programs [43,44].) On a van der Waals surface, Δs_i is determined by the atomic radii and the molecular geometry. At a point $\mathbf{r}_i$, the MEP takes a value $V(\mathbf{r}_i)$. For positive MEP, we shall use the notation $V^+(\mathbf{r}_i)$ and Δs_i^+ for the MEP and local area contributions, respectively. The notation for negative MEP will be $V^-(\mathbf{r}_i)$ and Δs_i^-. We now introduce the structural descriptors B_F^+, B_F^-, B_R^+, and B_R^-, defined as follows:

$$B_F^+ = \left[\sum_i \Delta s_i^+ V^+(\mathbf{r}_i)\right]_F \tag{10}$$

$$B_F^- = \left[\sum_i \Delta s_i^- V^-(\mathbf{r}_i)\right]_F \tag{11}$$

$$B_R^+ = \left[\sum_i \Delta s_i^+ V^+(\mathbf{r}_i)\right]_R \tag{12}$$

$$B_R^- = \left[\sum_i \Delta s_i^- V^-(\mathbf{r}_i)\right]_R \tag{13}$$

In Eqs. 10–13, the subscript 'F' indicates that the sum is restricted to the points $\mathbf{r}_i$ lying on the exposed molecular surface of the functional group. On the other hand, the subscript 'R' indicates a computation carried out on the hydrocarbon moiety. The superscripts '+' and '–' stand for the positive and negative MEP, respectively. From now on, we refer to the parameters in Eqs. 10–13 as 'surface–MEP descriptors'. (If there were two or more distinct functional groups in a molecule, a series of descriptors for each group could be used. As mentioned before, we deal presently with examples where R, the hydrocarbon lipophilic moiety, and F, the hydrophilic functional groups, are unequivocally defined without a bias. However, in many cases a distinction between 'R' and 'F' might not be obvious. A different definition of surface–MEP descriptors may be needed in these cases.)

The surface–MEP descriptors given above have units of area × energy (e.g., kcal Å²/mol). Since most functional groups will have a small surface area, B_F^+ and B_F^- should be dominated by the behavior of the MEP. The dependence of B_F^- on both negative MEP and area should provide a measure of the group's hydrogen-bonding character as acceptor or donor. In contrast, since hydrocarbon residues have a large surface area and small (positive) MEP values, we can expect B_R^+ to be dominated mostly by the value of the molecular surface area. In general cases, where the MEP is distributed in a complicated manner, the descriptors B will properly describe the

changes of MEP over the surface. Our hypothesis is that the detailed information on MEP and surface area contained in these descriptors will be useful in a quantitative analysis of hydrophobicity.

We have computed the molecular surface–MEP descriptors for a series of 48 molecules, including linear hydrocarbons (*n*-alkanes) and aliphatic carboxylic acids, amines, and alcohols, as well as some aromatic compounds. The computations are restricted to one conformation per compound. In keeping with other calculations in the literature, we always considered minimum energy conformations with all-trans hydrocarbon chains. The nuclear geometry of the all-trans structures is determined by optimization at the ab initio RHF/STO-5G level. (This rather unusual basis set is used here only for the sake of comparison. It is the basis set employed by Politzer et al. [45] and Murray et al. [19–21] for evaluating statistical descriptors on isodensity contours of various molecules.) The MEP is computed at the RHF/6-31G level using the GAUSSIAN 92 package [46]. Van der Waals surface area

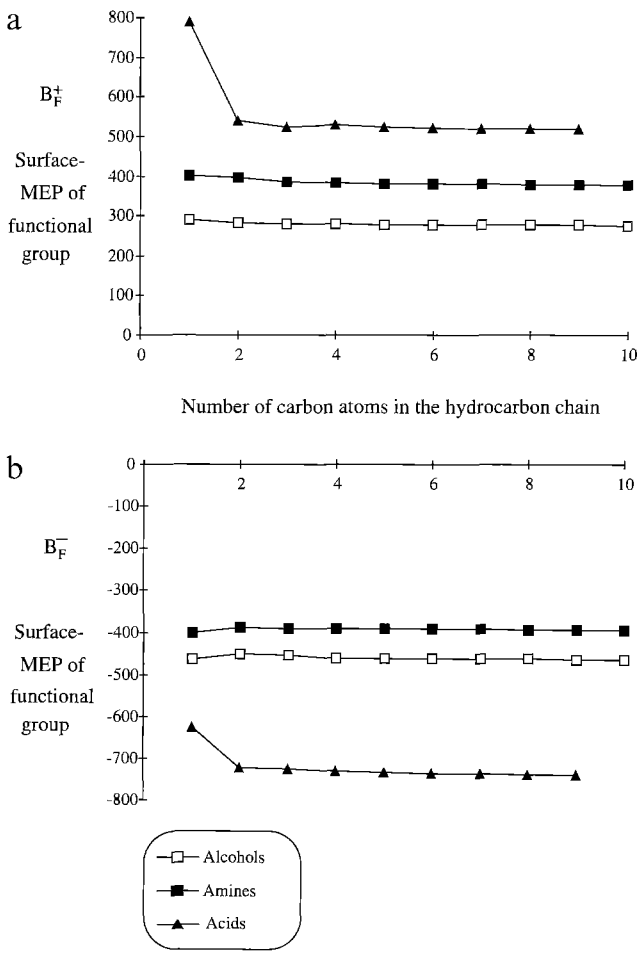

Fig. 2. Positive surface–MEP (B_F^+) (a) and negative surface–MEP (B_F^-) (b) for the functional groups of aliphatic alcohols, primary amines, and carboxylic acids as a function of the number of carbon atoms in the hydrocarbon chain. Units of B are kcal Å²/mol. The MEP and surface area are calculated as in Fig. 1.

elements $\{\Delta s_i^+, \Delta s_i^-\}$ are calculated with the MS program [41–43], with a surface density of 25 points/Å². The surfaces are built using those atomic radii that lead to the molecular van der Waals surface with the lowest average negative electrostatic potential, $\overline{V}^-$ [47]. The corresponding values of atomic radii (ρ) for the present compounds are (in Å): $\rho(C(sp^3)) = 2.00$, $\rho(C(\text{aromatic})) = 1.77$, $\rho(C(sp^2)) = 1.70$, $\rho(N) = 1.46$, $\rho(O) = 1.39$, $\rho(F) = 1.26$, $\rho(Cl) = 1.97$, and $\rho(H) = 1.17$. These values are not far from those associated with standard molecular volumes or crystallographic distances [48].

The dependence of surface area and electrostatic potential on molecular size can be illustrated with the results for 10 linear alkanes: methane, ethane and the series of compounds CH_3-$(CH_2)_n$-CH_3 with $1 \le n \le 8$. Figures 1a and b compare their surface area and surface–MEP descriptors B^+ and B^-, respectively, as a function of the total number of carbon atoms. In addition, we have also computed the individual (average) contributions to the surface area associated with one methyl group -CH_3 (Fig. 1a) and one methylene group -CH_2- (Fig. 1b). From these results, we can draw the following observations:

(i) The MEP of a linear hydrocarbon is basically positive everywhere on the molecular surface and depends linearly on the number of carbon atoms. The negative surface–MEP descriptor is very small and increases slightly with molecular size.

(ii) For alkanes with more than two carbon atoms, the area contributions s^+ and s^- associated with the groups -CH_3 and -CH_2- remain essentially constant. Therefore, they are transferable properties for these compounds.

(iii) Positive surface–MEP descriptors for the groups -CH_3 and -CH_2- present the same behavior as the surface areas in (ii), and therefore are also transferable. The contributions of negative MEP for both fragments are very small in absolute value.

Figures 2 and 3 present the results for the four surface–MEP descriptors of 10 aliphatic alcohols, 10 amines, and 9 carboxylic acids with linear hydrocarbon chains. All the compounds follow the formula CH_3-$(CH_2)_n$-Z, with Z the functional group and $n \ge 0$.

Figure 2a displays the descriptor B_F^+ for the functional groups in alcohols, amines and acids. For compounds with more than two carbon atoms in the chain ($n > 1$), the parameter B_F^+ remains almost constant within a particular functional group. A similar behavior is found in the negative surface–MEP descriptor B_F^- (see Fig. 2b). Note that the two descriptors B_F^+ and B_F^- take rather large absolute values. Consequently, the functional groups must exhibit regions susceptible to electrophilic and nucleophilic attacks. In other words, large values for both B_F^+ and B_F^- suggest that the functional groups may act as hydrogen-bonding donors and acceptors. Figure 2 shows that this 'hydrophilic character' varies with the nature of the functional group.

Figure 3 shows the two surface–MEP descriptors associated with the hydrocarbon chain 'R'. Figure 3a shows the positive surface–MEP descriptor B_R^+ for the alcohols, amines and acids. For chains with $n > 1$, B_R^+ increases with the number of carbon atoms. As suggested by Fig. 1, it is clear that this behavior is mostly related to an increase in the molecular surface area s^+, since the positive MEP takes only small values. Note, however, that the relation between s^+ and B_R^+ is not a trivial multiplication factor. Whereas s^+ for the hydrocarbon residue increases linearly with n (see Fig. 1), the increase in descriptor B_R^+ is slower than linear and it changes with the functional group (only hydrocarbons and alcohols show a quasi-linear behavior B_R^+ versus n). That is, s^+ and B_R^+ are distinct parameters and we should not expect them to provide necessarily the same description of molecular lipophilicity.

Figure 3b shows the negative surface–MEP descriptor B_R^-. This parameter takes small absolute values and changes little with the length of the chain. In conclusion, the B_R^+ parameter is the main source of information about

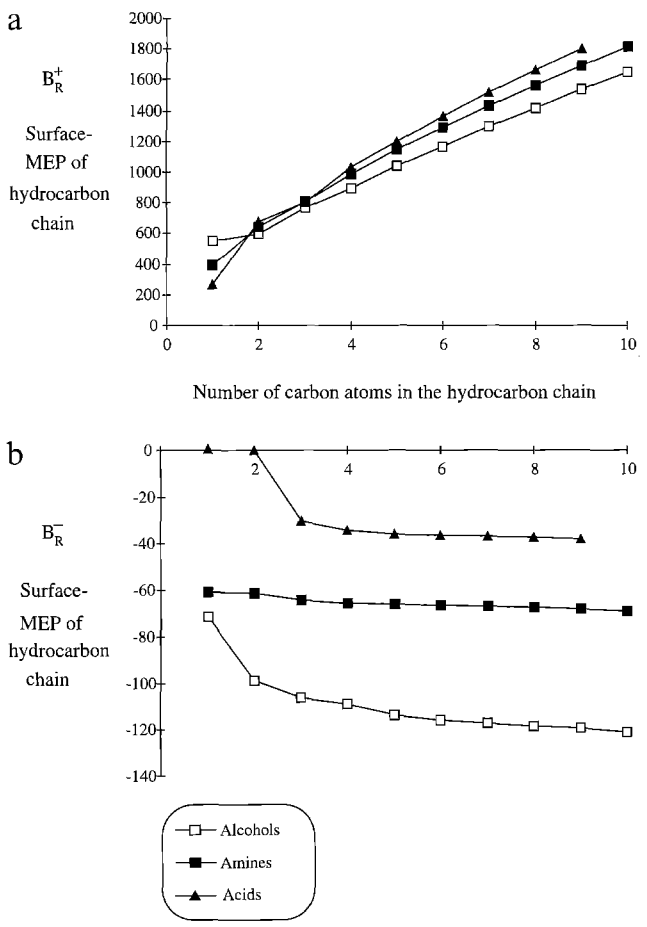

Fig. 3. Positive surface–MEP (B_R^+) (a) and negative surface–MEP (B_R^-) (b) on the hydrocarbon substituent of aliphatic alcohols, carboxylic acids, and amines as a function of the number of carbon atoms in the chain. Units of B are kcal Å^2/mol. The MEP and surface area are calculated as in Fig. 1.

group R. The behavior of this parameter appears to correlate with the lipophilic character of the hydrocarbon chain.

As suggested by these results, the four surface–MEP descriptors B_F^+, B_F^-, B_R^+ and B_R^- can be used to characterize the lipophilic and hydrophilic nature of molecular fragments. Below we briefly discuss an interpretation of the distinct contribution of the various parameters.

The surface–MEP descriptors of a functional group (B_F^+ and B_F^-) contain information on solute–solvent electrostatic interactions. These parameters can describe the hydrogen-bonding ability of the solute. If a hydrogen atom is included in the functional group, then B_F^+ indicates the ability of the group to act as a hydrogen-bonding donor. Similarly, the negative surface–MEP parameter (B_F^-) characterizes the functional group as a hydrogen-bonding acceptor.

The surface–MEP descriptors of the hydrocarbon chain (B_R^+ and B_R^-) could be interpreted differently in terms of lipophilicity effects. The parameter B_R^+ is associated with a region of the molecular surface exhibiting a large area but small $V^+(\mathbf{r}_i)$ values ('neutral MEP'). This region should experience the strongest 'hydrophobic effect', the one responsible for a large spatial reorganization in solute–water clusters. Accordingly, we believe that B_R^+ can be related to the 'entropic' (configurational) component of the solute–solvent interaction. The argument is as follows. As shown in Fig. 1, linear alkanes (which are hydrophobic) have a large surface area with a small positive MEP (s^+) and a small area with negative MEP. (The negative MEP centers around the $-CH_3$.) Now, the hydrocarbons are insoluble in water despite a favorable exothermic $\Delta H°$ of solution [49]. The hydrocarbon–water phase separation is mostly an entropic effect on the free energy of solution: the configurational reorganization of water molecules into compact clusters about the solute creates a very negative $\Delta S°$. The result is a positive $\Delta G°$ for the transfer of the hydrocarbon to the water phase, i.e., little affinity to water and a rather large partition coefficient P_{ow}. Within the microscopic description, this implies that the uniformly positive MEP on a large hydrocarbon surface will drive most water molecules away, despite a negative enthalpy change. This entropic contribution is thus directly linked to the B_R^+ descriptor.

Note that the negative surface–MEP descriptor B_R^- is small (in absolute value) for alkanes (Fig. 1), but it is larger in alcohols, amines, and acids (Fig. 3). The results indicate that the main contribution to B_R^- comes from the two methylene groups closer to the functional groups. Moreover, the surface area included in B_R^- is immediately adjacent to the area elements contributing to B_F^+. Therefore, this descriptor should be somewhat relevant to electrostatic interactions between solute and solvent molecules. In other words, B_R^- plays a different role than B_R^+ with regard to describing hydrophobic interactions.

TABLE 1
SURFACE–MEP DESCRIPTORS AND CALCULATED LOG P VALUES FOR ALIPHATIC ALCOHOLS, PRIMARY AMINES, AND CARBOXYLIC ACIDS

Substance	B_F^+	B_F^-	B_R^+	B_R^-	log P_{ow}		Residual error
					Experimental[a]	Estimated[b]	
Alcohol							
CH_3OH	288.67	−463.32	549.84	−71.273	−0.82	−0.817	0.003
C_2H_5OH	283.03	−451.77	595.01	−98.946	−0.32	−0.315	0.005
C_3H_7OH	279.00	−454.32	767.13	−106.48	0.34	0.342	0.002
C_4H_9OH	277.84	−459.99	896.15	−108.96	0.88	0.817	−0.063
$C_5H_{11}OH$	276.71	−461.00	1041.8	−113.69	1.40	1.457	0.057
$C_6H_{13}OH$	275.61	−461.57	1167.2	−116.07	2.03	1.982	−0.048
$C_7H_{15}OH$	275.35	−461.95	1296.5	−117.03	2.41	2.542	0.132
$C_8H_{17}OH$	275.20	−462.20	1413.9	−118.48	3.15	3.062	−0.088
Amine							
CH_3NH_2	401.87	−401.99	392.79	−60.902	−0.57	−0.564	0.006
$C_2H_5NH_2$	395.48	−389.58	639.69	−61.324	−0.27	−0.253	0.017
$C_3H_7NH_2$	385.35	−390.98	805.33	−64.342	0.15	0.010	0.140
$C_4H_9NH_2$	382.69	−390.79	989.89	−65.541	0.68	0.779	0.099
$C_5H_{11}NH_2$	380.80	−391.57	1143.94	−65.950	1.05	1.080	0.030
$C_6H_{13}NH_2$	379.71	−392.07	1289.74	−66.351	1.52	1.526	0.006
$C_7H_{15}NH_2$	378.99	−392.43	1428.70	−66.999	2.09	2.183	0.093
$C_8H_{17}NH_2$	378.52	−392.69	1561.86	−67.508	2.90	2.789	−0.111
Acid							
H_3COOH	788.13	−626.51	262.35	0.000	−0.54	−0.539	0.001
CH_3COOH	539.81	−723.46	677.35	0.000	−0.31	−0.310	0.000
C_2H_5COOH	523.96	−725.89	803.98	−30.111	0.25	0.253	0.003
C_3H_7COOH	528.78	−729.26	1032.7	−34.340	0.79	0.766	−0.024
C_4H_9COOH	522.90	−732.23	1196.9	−35.835	1.45	1.411	−0.039
$C_5H_{11}COOH$	520.30	−734.77	1365.2	−36.474	1.88	2.017	0.137
$C_6H_{13}COOH$	518.98	−735.98	1516.4	−36.838	2.72	2.642	−0.078

B values are in kcal Å²/mol. Molecular surfaces were built with the program MS [43] with a density of 25 points/Å². The surface MEP is calculated at the RHF/6-31G level.

[a] See Ref. 50.

[b] Results obtained with the correlation model, Eq. 15, restricted to compounds with the same functional group.

Based on the analysis given above, the molecular lipophilicity could be described as a function of the four surface–MEP descriptors:

$$L = f(B_F^+, B_F^-, B_R^+, B_R^-) \quad (14)$$

All important interactions between solute and solvent molecules can be related, in principle, to the B parameters. In the next section, we test the reliability of the representation (Eq. 14) by studying correlations between experimental partition coefficients and surface–MEP descriptors.

Correlations of log P with surface–MEP descriptors

As an equilibrium constant, log P_{ow} is proportional to the free energy of transfer of a solute from the water to the octanol phase: $\log P_{ow} = -\Delta\bar{G}_{tr}^{\circ} / (2.303\ RT)$. In turn, the free energy is the sum of enthalpic and entropic terms, $\Delta\bar{H}_{tr}^{\circ}$ and $-T\Delta\bar{S}_{tr}^{\circ}$, respectively. As discussed above, we can expect the entropic contribution to be related to the B_R^+ descriptor, which characterizes a quasi-uniform distribution of low positive MEP over a large surface area. On the other hand, the enthalpic contribution should relate to the descriptors accounting for specific solute–solvent interactions over small areas, namely B_F^+, B_F^- and B_R^-. Consequently, the simplest model of log P correlation can take the following multilinear form:

$$\log P = c_0 + c_1 B_F^+ + c_2 B_F^- + c_3 B_R^+ + c_4 B_R^- \quad (15)$$

where the linear coefficients are determined by least-squares fitting to experimental log P data. (Additional descriptors should be included in the presence of more than one functional group.)

Table 1 lists the surface–MEP descriptors for 30 aliphatic alcohols, amines, and carboxylic acids and compares the experimental partition coefficients [50] with the results of a multilinear regression using Eq. 15. A similar computational strategy was used to evaluate the surface–

MEP descriptors of aromatic compounds of the form C_6H_5-Z, where 'Z' stands for various functional groups. The conformer used was the lowest energy structure optimized at the RHF/STO-5G level. In this case, the liphophilic fragment R is taken as the phenyl moiety, -C_6H_5.

We show below the correlations restricted to families of compounds. The results include the correlation coefficient (r), the standard error (σ), the number of compounds in the fitting (n), and the standard errors in the linear coefficients for the compounds in Table 1.

(i) Aliphatic alcohols:

$$\log P_{ow} = (-10 \pm 48) + (0.04 \pm 0.11)\, B_F^+ + (0.01 \pm 0.03)\, B_F^- + (4.3 \pm 0.5) \times 10^{-3}\, B_R^+ - (0.01 \pm 0.03)\, B_R^- \quad (16)$$

$(n = 8,\ r = 0.999,\ \sigma = 0.107)$

The statistical errors in Eq. 16 indicate that the main contribution to a positive log P of aliphatic alcohols is associated with the positive MEP on the hydrocarbon chain (B_R^+). The same behavior is found in *n*-alkanes.

(ii) Aliphatic amines:

$$\log P_{ow} = (-100 \pm 37) + (0.199 \pm 0.085)\, B_F^+ + (0.047 \pm 0.043) B_F^- + (3.0 \pm 0.6) \times 10^{-3}\, B_R^+ - (0.61 \pm 0.32)\, B_R^- \quad (17)$$

$(n = 8,\ r = 0.997,\ \sigma = 0.131)$

Note that, in contrast to alcohols, the positive MEP on the functional group (B_F^+) is a more important factor in modeling the partition coefficients of amines (i.e., its corresponding coefficient c_1 takes a significative value). However, the two dominant terms of positive MEP (B_F^+ and B_R^+) have a distinct behavior. The separation of the surface–MEP descriptors into 'R' and 'F' contributions gives the necessary flexibility to mimic the behavior of log P.

(iii) Aliphatic carboxylic acids:

$$\log P_{ow} = (91 \pm 45) - (0.034 \pm 0.018)\, B_F^+ + (0.105 \pm 0.049)\, B_F^- + (4.7 \pm 0.6) \times 10^{-3}\, B_R^+ + (0.011 \pm 0.008)\, B_R^- \quad (18)$$

$(n = 7,\ r = 0.998,\ \sigma = 0.116)$

All terms appear to be important in the case of acids. Note that, as one moves from alcohols to amines and to acids, the compounds become more hydrophilic. Consistently with this empirical observation, Eqs. 16–18 indicate an increasing contribution of the MEP on the molecular surface for the functional group on going from -OH to -COOH. However, the contributions of the terms with B_F^+, B_F^- and B_R^- are almost constant within a family of compounds and their signs vary from one family to another. In contrast, the B_R^+ term is consistently positive for all compounds. This term provides the largest contribution to lipophilicity.

For the complete set of 23 compounds above, the correlation is still satisfactory, thus indicating that these compounds share a similar partitioning behavior:

$$\log P_{ow} = (-5.63 \pm 0.66) + (5.3 \pm 1.1) \times 10^{-3}\, B_F^+ - (1 \pm 5) \times 10^{-4}\, B_F^- + (3.0 \pm 0.1) \times 10^{-3}\, B_R^+ - (0.022 \pm 0.004)\, B_R^- \quad (19)$$

$(n = 23,\ r = 0.984,\ \sigma = 0.239)$

The results above compare with the best correlation schemes in the literature, derived by using a number of ad hoc structural parameters. Note, however, that differences between compound families are clearly noticeable (Eqs. 16–19). These differences are large in the case of hydrocarbons, whose log P values do not exhibit any contribution of B_F^+ and B_F^- (here, the choice of 'F' is ambiguous; it could be taken as either -CH_3 or -H). Similar systematic deviations have also been observed within functional groups for other hydrophobicity models and fragmental-additivity formulas [35].

For a set of nine benzene derivatives (C_6H_6, $C_6H_5CH_3$, C_6H_5OH, $C_6H_5NH_2$, C_6H_5COOH, $C_6H_5OCH_3$, $C_6H_5NO_2$, C_6H_5F and C_6H_5Cl), we find a correlation of similar quality:

$$\log P_{ow} = (3.70 \pm 0.35) - (2.9 \pm 0.4) \times 10^{-3}\, B_F^+ - (1.3 \pm 0.5) \times 10^{-3}\, B_F^- - (1.4 \pm 0.4) \times 10^{-3}\, B_R^+ + (7 \pm 3) \times 10^{-4}\, B_R^- \quad (20)$$

$(n = 9,\ r = 0.976,\ \sigma = 0.162)$

The different behavior obtained (cf. Eq. 19) correlates with the distinct hydrophobic character of the aromatic (phenyl) 'R' moiety with respect to that of an aliphatic chain. (Note that the coefficient accompanying B_R^+ is negative in the aromatic compounds, whereas it is positive for aliphatics.)

The fitting in Eqs. 16–20 spans over four orders of magnitude in P_{ow} values. Of course, the compounds considered do not represent an exhaustive list and the good agreement may not represent a general behavior for all functional groups. However, note that our approach provides good results even for small molecules, such as methanol, formic acid and methyl amine, whereas correlation models based on surface area fail to adequately describe these molecules [8].

The above correlations improve also on the results obtained by Brinck et al. [18], using surface area and MEP descriptors. As an example, we have used the data in Ref.

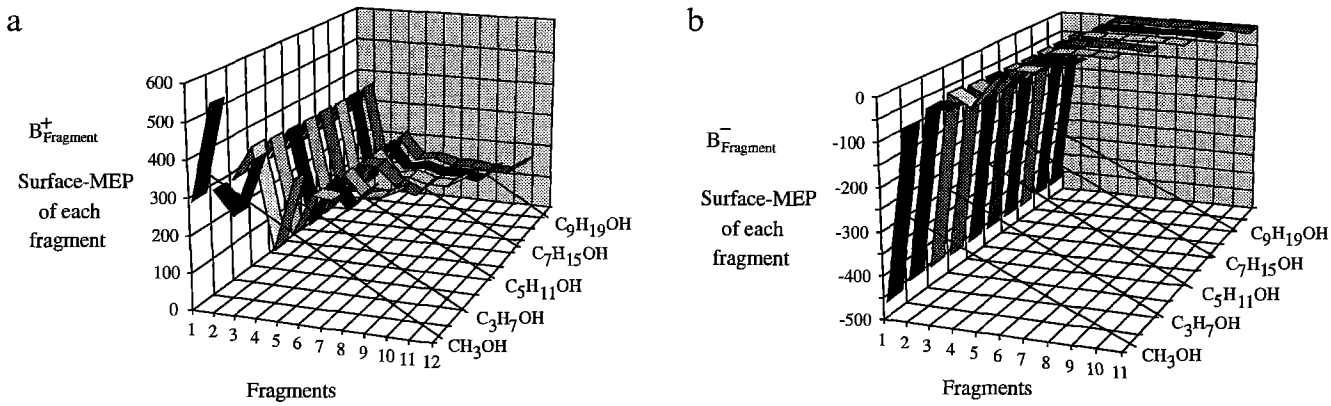

Fig. 4. Surface–MEP descriptors $B^{+}_{Fragment}$ (a) and $B^{-}_{Fragment}$ (b) (in kcal Å^2/mol) of molecular fragments in aliphatic alcohols. The fragments are ordered according to a walk along the chain: first -OH, followed by each -CH_2- group, and finally -CH_3 (x-axis or 'Fragment-axis'). The y-axis lists the 10 alcohols studied: CH_3-$(CH_2)_n$-OH, with $0 \le n \le 9$. For clarity, only the compounds with an odd number of carbons are listed.

18 for the nine benzene derivatives in Eq. 20 and tested the three-parameter correlation models expressed in Eqs. 8 and 9. The results show a poorer agreement: (i) $r = 0.906$ and $\sigma = 0.288$ when using Eq. 8; and (ii) $r = 0.878$ and $\sigma = 0.325$ when using Eq. 9.

In some cases, some of the surface–MEP descriptors may be correlated, thus allowing one to use a simpler model. For example, B^{+}_{F} decreases while the absolute value of B^{-}_{F} increases with the number of carbon atoms (see Table 1). Therefore, only one of the two descriptors may be needed. As noticed before, only B^{+}_{F} may be needed in the analysis of aliphatic amines. In this case, we obtain a result similar in quality to Eq. 16:

$$\log P_{ow} = (-64 \pm 18) + (0.112 \pm 0.028)\, B^{+}_{F} + (3.4 \pm 0.4) \times 10^{-3}\, B^{+}_{R} + (-0.29 \pm 0.13)\, B^{-}_{R} \quad (21)$$

$(n = 8,\ r = 0.996,\ \sigma = 0.132)$

In some particular cases, we can further simplify the log P correlations by absorbing the surface–MEP for the functional group into a constant (see Fig. 2). As shown in Eq. 16, the case of aliphatic alcohols provides an example of this behavior. Using only B^{+}_{R} and B^{-}_{R}, we obtain:

$$\log P_{ow} = (3.6 \pm 0.3) + (4.0 \pm 0.2) \times 10^{-3}\, B^{+}_{R} - (8 \pm 4) \times 10^{-3}\, B^{-}_{R} \quad (22)$$

$(n = 8,\ r = 0.998,\ \sigma = 0.100)$

In fact, only one parameter (B^{+}_{R}) would be sufficient to describe accurately the partition coefficients of alcohols [50]. However, alcohols are not a particularly challenging example, since a good single-parameter fitting can also be obtained by using only the surface area (s_{tot} or s^{+}). The reason is simple: for hydrocarbons and alcohols, the surface area and the B^{+}_{R} descriptor are almost linearly dependent on the number of chain atoms (cf. Figs. 1 and 3). However, this simplification is not generally valid: B^{+}_{R} and s^{+} are not strictly proportional to each other for other alkylic derivatives. In any case, the surface area s^{+} may be a better shape parameter than s_{tot} for these molecules. For other molecules, however, the surface area cannot be used for modeling partition coefficients. This situation is found in the aromatic compounds discussed before, whose log P values show no correlation whatsoever with s_{tot} or s^{+} (e.g., a linear fitting leads to $r = 0.047$). A similar lack of clear trends has already been pointed out in the literature [52], when correlating various properties with the partial surface areas associated with aromatic and saturated hydrocarbon moieties.

Summarizing, the results in this section suggest that a number of surface–MEP descriptors can be used in a simple molecular model of hydrophobicity. All four B descriptors should be used in order to obtain good results for a series of compounds with variable sizes and functional groups.

Fragmental additivities of B descriptors

The additivity of molecular lipophilicity in terms of fragments constituting the molecule has been used by many authors [15,34–36,53]. Ghose and Crippen [34] have evaluated the contributions to hydrophobicity of 90 'atom types', derived from the octanol–water partition coefficients of 494 molecules. A second data set given by Viswanadhan et al. [36] uses 893 compounds to derive the 120 atom-type contributions. These contributions can then be used to compute log P values for new compounds or empirical lipophilicity potentials. In this section, we discuss the additivity of molecular lipophilicity based on surface–MEP descriptors.

Figures 4a and b show the surface–MEP descriptors $B^{+}_{Fragment}$ and $B^{-}_{Fragment}$, respectively, for the molecular fragments of the aliphatic alcohols. The fragments are presented according to their occurrence along the molecular

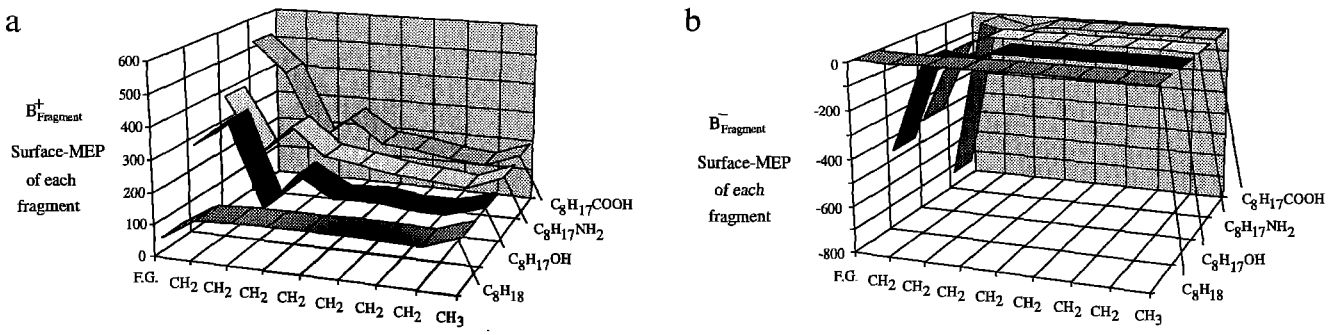

Fig. 5. Surface–MEP descriptors $B^+_{Fragment}$ (a) and $B^-_{Fragment}$ (b) (in kcal Å²/mol) for molecular fragments of octane derivatives: C_8H_{18}, $C_8H_{17}OH$, $C_8H_{17}NH_2$, and $C_8H_{17}COOH$. The first fragment is the functional group ('F.G.'), followed by the -CH_2- groups, and -CH_3. For a fair comparison of the hydrocarbon chains, the **'functional group'** of C_8H_{18} is taken as an H atom.

chain, starting at the functional group -OH, followed by the -CH_2- groups and the -CH_3 terminus. The figure reveals the following facts: (i) the surface–MEP descriptors for the functional group, B^+_{OH} and B^-_{OH}, appear to be transferable since they are practically constant; and (ii) the descriptors for the methylene and methyl fragments show changes depending on their position relative to the functional group. Oscillations are especially visible in $B^+_{CH_2}$ and $B^+_{CH_3}$, whenever these groups are close to the -OH fragment. In chains with more than three carbon atoms, these latter descriptors appear to reach 'limit' values.

A similar analysis for the molecular fragments in homologous aliphatic amines and carboxylic acids supports these observations. The effect of the functional group on the transferability of the hydrocarbon moiety can be seen in Fig. 5, where the fragmental descriptors $B^+_{Fragment}$ and $B^-_{Fragment}$ are compared for a series of compounds with the same hydrocarbon chain: C_8H_{18}, $C_8H_{17}OH$, $C_8H_{17}NH_2$ and $C_8H_{17}COOH$. The results indicate that the chain fragment descriptors are transferable starting from position '4' (the fourth carbon atom away from the functional group). Also, the results show that the functional group has a large effect in modulating the contributions of methylenic groups to the positive MEP on the molecular surface.

This behavior is not found in the aromatic derivatives. For these compounds, we find that the parameters $B^+_{C_6H_5}$ and $B^-_{C_6H_5}$ change enormously with the substituent group. In other words, the fragments in aromatic systems are strongly coupled electrostatically, and therefore it is not possible to assign a transferable value to the -C_6H_5 moiety.

Summarizing our conclusions for the transferability of fragmental contributions to the surface–MEP descriptors, we observe that:

(i) Functional groups have almost constant B^+_F and B^-_F values within a family of homologous, alkylic compounds.

(ii) In compounds with saturated linear hydrocarbon chains, the $B^+_{Fragment}$ and $B^-_{Fragment}$ descriptors for the -CH_3 and -CH_2- fragments depend on the functional group, the length of the chain, and the position of the fragment with respect to the functional group.

(iii) For hydrocarbon fragments in position '3' or higher, the $B^+_{CH_3}$ and $B^+_{CH_2}$ remain almost constant, whereas $B^-_{CH_3}$ and $B^-_{CH_2}$ make a negligible contribution.

(iv) For aromatic derivatives, there is no reasonable transferability of surface–MEP descriptors.

Table 2 lists the results obtained for the surface–MEP descriptors of the various molecular fragments studied in

TABLE 2
SURFACE–MEP DESCRIPTORS FOR MOLECULAR FRAGMENTS OF *n*-ALKANES, ALIPHATIC ALCOHOLS, AMINES AND CARBOXYLIC ACIDS[a]

	Functional group	CH_2 (1)	CH_2 (2)	CH_2 (3)	CH_2 (>3)	CH_3
$B^+_{Fragment}$						
n-Alkane					120.01	157.56
Alcohol	275.20	362.87	90.93	213.11	143.78	171.89
Amine	378.52	193.80	293.73	207.67	168.11	194.21
Acid	517.45	419.88	188.90	272.99	179.69	203.06
$B^-_{Fragment}$						
n-Alkane					−0.99	−5.59
Alcohol	−462.20	−46.42	−68.00	0.0	0.0	−3.36
Amine	−392.69	−66.63	0.0	0.0	0.0	−0.88
Acid	−737.46	0.0	−37.25	0.0	0.0	−0.55

[a] In units of kcal Å²/mol.

this work. By performing simple additions, these fragmental contributions can be used to produce rough estimates of the complete surface–MEP descriptors for some monofunctional aliphatic molecules (alcohols, amines and carboxylic acids) containing more than three carbon atoms. These values, together with Eq. 20, should allow one to derive reasonable log P_{ow} values for new compounds belonging to this selected group of molecules.

Further comments and Conclusions

In this work, we have used a number of surface–MEP descriptors to characterize the general distribution of electrostatic potential on molecular surfaces. They are derived from local contributions to the surface area and the potential. Qualitatively, the descriptors B_R^-, B_F^+ and B_F^- relate to enthalpic terms (solute–solvent electrostatic interactions, including hydrogen bonding). Similarly, the descriptor B_R^+ would appear to represent the entropic contribution to the interaction between nonpolar solutes and water molecules. Consequently, an assessment of molecular lipophilicity L can be based on these four parameters: $L = f(B_F^+, B_F^-, B_R^+, B_R^-)$. The methodology presented is simple and involves a single class of structural parameters. We believe it provides a good conceptual framework for interpretation and systematic improvements.

From a quantitative viewpoint, log P_{ow} is evaluated by a multilinear regression model using the above descriptors. In addition, the thermodynamic properties of hydration could be estimated by regressions of the form:

$$\Delta H_h^\circ = c_F^+ B_F^+ + c_F^- B_F^- + c_R^- B_R^- + \text{const} \quad (23)$$

$$\Delta S_h^\circ = c_R^+ B_R^+ + \text{const} \quad (24)$$

where ΔH_h° and ΔS_h° are the solvation enthalpy and entropy changes, respectively. This approach constitutes an extension over methods that use the molecular surface area and/or the global MEP as the only fitting parameters [54–56]. Similar correlations with surface–MEP descriptors could also be used to evaluate other physicochemical properties depending primarily on weak nonbonded interactions between molecules. Note that the linear correlations are the simplest representation of the functional dependence of lipophilicity (Eq. 14). In general, nonlinear (Taylor) expansions of all hydrophobicity-related properties in power series of the B descriptors would provide a systematic improvement of the correlation model.

Within some limitations, we have found that the surface–MEP descriptors are fragmentally additive. The contributions of a number of simple fragments (namely, $-CH_2-$, $-CH_3$, -OH, $-NH_2$ and -COOH) have been estimated. They can be used to predict the hydrophobicity of some compounds without additional quantum-chemical calculations. Unlike other methods based on fragments, the present approach involves only theoretical parameters that can be obtained by simple computations, once a molecular geometry is provided. The method can be extended to compounds containing several functional groups.

All computations in this work have been restricted to using a single conformation for each molecule. In this regard, the present approach uses the same approximation employed in the literature for empirical log P correlations at constant temperature. Such a scheme, however, is not appropriate to study the temperature dependence of the experimental partition coefficients. As the temperature changes, the conformational population will be affected. Some of these conformers may have rather different three-dimensional structure, leading to different surface areas and electrostatic potentials. The correct approach should take into account this fact, and compute surface–MEP descriptors averaged over configurational space. A similar approach was studied in Ref. 52 to compute averaged solvent-accessible surface areas. We have not attempted this here since it is computationally very demanding.

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