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Universal model for the calculation of all organic solvent–water partition coefficients

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Abstract

We present the basis for building a universal organic solvation model to calculate solubility in any organic solvent and in water, as well as the organic solvent–water partition coefficient (P). Log P values are of the same order of magnitude as reference calculations but for a few cases which are discussed. Normalized log P contributions are sensitive to the rest of the atoms. When comparing porphin with phthalocyanine, the latter results in an amphipathic molecule. For C_{70}, the contribution of a–e carbons to log P correlates with the distances from the nearest pentagon. The method has been also applied to benzobisthiazole oligomers and phenyl alcohols.

Keywords: Partition coefficients; Solvation parameter model

1. Introduction

The interaction of a solute molecule with the surrounding solvent or the transfer of a solute from one solvent to another can dramatically change the solute properties, including free energy, reaction rates, reaction paths, and even the identity of the solute molecule itself [1]. Thus the modelling of solute–solvent interactions in a range of solvents is a critical area for the development of predictive techniques in theoretical chemistry. While much work has been done by many groups in developing models for water, as reviewed elsewhere [2–6], much less effort has been devoted to developing models for non-aqueous solvents [7–14]. For some non-aqueous solvents, this is due to a lack of experimental data. However, a large body of data is available for 1-octanol [15] and *n*-hexadecane [16,17]. A significant amount is also available for other alkanes, cyclohexane, benzene, toluene, xylenes, diethyl ether, chloroform, carbon tetrachloride, and chlorobenzene [18]. The sparseness of data for other common solvents, however, is a serious impediment to solvent-by-solvent approaches for developing and validating solvation models for most individual solvents. But, if one takes data from all organic solvents, a very large number of data is available. In this paper we show that it is possible to analyze these data as a whole and develop a model that encompasses a large number of solvents in a single framework. This approach eliminates the need for extensive amounts of data measured in one solvent, and it allows us to predict solvation energies in solvents for which little or no experimental data exist [19–22].

The present model is an extension of the solvent-dependent conformational analysis (SCAP) 1-octanol–water model [23,24] to organic solvents. We have calculated the organic solvent–water partition coefficients in 1-octanol, cyclohexane and chloroform for: (1) porphyrins and phthalocyanines (2) benzothiazole (A)-benzobisthiazole (B) oligomers till $A–B_{13}–A$; (3) fullerene-60, -70, -82, C_{60} Van der

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Waals dimer and perhydrofullerenes and (4) a homologous series of phenyl alcohols.

In Section 2 we present the main features of the Hopfinger model for the calculation of the solvation Gibbs free energy. Following that, we describe a number of properties that can be estimated with the model, and then we present the universal solvation model which is the major subject of this work. The last two sections are devoted to the results, their discussion and our conclusions.

2. Solubilities and partition coefficient

We intend to get a universal organic solvation model to calculate the solubility in any organic solvent and in water as well as the organic solvent–water partition coefficient (P). The method is based on the model of Hopfinger [25] which uses the concept of the solvation sphere [26,27].

A brief account of the Hopfinger method and some of its applications follows. The molecule may be fragmented into atoms or groups. The starting hypothesis is that one can centre, independently, a solvation sphere on each group of the molecule. The size of this sphere depends on the solvent and on the group considered. This sphere is occupied by a certain number of solvent molecules. A variation of free energy, due to the extraction of a solvent molecule, is associated with each solvation sphere.

The intersecting volume, $V°$, is then calculated. It corresponds to the intersecting volume between the solvation sphere and the Van der Waals spheres of the remaining atoms in the molecule that are not bonded to the group under consideration. This volume allows the calculation of the effective volume of solvation of the group for a given conformation of the whole molecule. The model manages up to four parameters for a given solvent: (1) n=maximum number of solvent molecules allowed to fill the solvation sphere; (2) Δg=variation of Gibbs free energy associated with the extraction of one solvent molecule out of the solvation sphere; (3) R_v=radius of the solvation sphere and (4) V_f=free volume available for a solvent molecule in the solvation sphere. Another relevant parameter in the model is V_s, the volume of the solvent molecule.

In the present work, the values of n and R_v, have been taken from the minimization of the configuration energy in a force field [25] and the Δg values were taken from Gibson and Scheraga [27]. (Other additive fragment contributions have been proposed in the literature [28–38].)

The calculation of V_f is performed as follows. In the solvation sphere, part of the volume excludes the solvent molecules. This volume consists of the Van der Waals volume of the group at which the sphere is centred and of a volume representing the groups bonded to the central group. The latter volume is represented by a number of cylinders equal to the number of atoms bonded to the central group. The axes of the cylinders pass through the centre of the sphere. The radius of these cylinders is taken as 3/4 of the Van der Waals radius of the central group. Finally, the cylinders are disposed according to the valence geometry of the group (sp^2, sp^3, ...).

The difference between the total volume of the solvation sphere and the volume excluded to the solvent molecules represents the volume V' that is actually available for the n solvent molecules. Therefore, V_f can be calculated as

$$V_f = \frac{V'}{n} - V_s$$

The variation of Gibbs free energy associated with the extraction of all the solvent molecules out of the solvation sphere of a group, R, is

$$\Delta G_R = n\Delta g\left(1 - \frac{V^o}{V'}\right)$$

and for the extraction of all the solvent molecules out of the solvation spheres of a molecule, the result is

$$\Delta G_{extr} = \sum_{R=1}^{N} \Delta G_R$$

Finally, the solvation free energy of a molecule is

$$\Delta G_{solv} = -\Delta G_{extr}$$

Although this is a simple method, Pascal [23] has found important difficulties in recalculating the volume V'. For example, the value of V_f for the (CH) aromatic group solvated in water is 3.3 $Å^3$ (fitted parameter of Hopfinger) and 48.14 $Å^3$ (calculated using the geometric procedure indicated by Hopfinger). Hence, we have preferred to ensure the coherence of the calculations by calculating the values of V_f by means of SCAP, a computer program developed

by Pascal [23]; this program makes use of the KOROBO subprogram [39], which allows for the calculation of the surfaces and volumes by the numerical integration method of Korobov.

Once the ΔG_{solv} values have been estimated, one can use them for calculating other properties of biological interest. For instance, the partition coefficient, *P*, of a solute between a pair of immiscible solvents [generally 1-octanol (o) and water (w)] is critical for many phenomena in biological and medicinal chemistry [40–43]. The logarithm of *P*, log *P* of organic solutes has been found to be useful in correlating and predicting the biological activity of the solute [44–60]. Also, the hydropathicity (a term encompassing from hydrophobicity to hydrophilicity) [61,62] of a molecule can be quantified in terms of log *P* [63–80]. In principle, a great number of effects can be modelled from the knowledge of the free energies of solvation of the system at relevant sites. In this work we use the SCAP method to calculate solvation and partitioning free energies for organic solutes. A special advantage of this model is that it can predict the dependence of solvation free energy on the molecular conformation. Such information is important for modelling partitioning and binding phenomena, but it is only rarely available from experiment.

Another parameter of interest to experimentalists is the lipophilic parameter of Hansch et al. [81,82] π_X. It can be defined as:

$$\pi_x = \log\frac{P_X}{P_H}$$

where P_X is the partition coefficient of the molecule substituted by X and P_H is the partition coefficient of the reference molecule. It has been shown that its additivity is quite limited, e.g., it does not even hold for many benzene derivatives with two substituents [83].

The method that we use to calculate log *P* and π_X in terms of structural additive schemes is a generalization of the solvent-dependent conformational analysis (π-SCAP) method of Hopfinger [25,26]. π-SCAP was initially used to calculate the Gibbs free energy of solvation of molecules. From these data and with the equation

$$RT\ln P = \Delta G^{o}_{solv}(\text{water}) - \Delta G^{o}_{solv}(\text{1-octanol})$$

one can calculate the decimal logarithm log *P* at a given *T* which is taken as 298 K. *R* is the gas constant and ΔG^{o}_{solv} (1-octanol) and ΔG^{o}_{solv} (water) (in kJ mol^{-1}) are the standard-state free energies of solvation of a given solute considered in 1-octanol and water, respectively.

3. Solubilities, partition coefficients and related indices for general organic solvents

We have parametrized the method for general organic solvents [24]. The general SCAP (GSCAP) method that we propose here is designed to be employed for all organic solvents. We take the parameters n_s, Δg_s, $R_{v,s}$, and $V_{f,s}$, to be functions of the solvent relative dielectric constant ϵ_s and of the solvent molecular volume $V_{s,s}$. In the following, we use the subscripts w (water), o (1-octanol) and s (general organic solvent).

The n_s parameter of each group is corrected by the ratio of molecular volumes of both 1-octanol and the new organic solvent, and by an exponent which is obtained from the well-known data from water and 1-octanol.

$$n_s = n_o\left(\frac{V_{s,s}}{V_{S,O}}\right)^{\log\frac{n_o}{n_w}/\log\frac{V_{S,O}}{V_{s,w}}} \quad (1)$$

Note that the deviation from single proportionality between n_s and n_o is guessed from the deviation of direct proportionality between n_o and n_w. The quotient of logarithms is used to estimate the non-linear exponent.

The variation of Gibbs free energy parameter Δg_s is taken in first approximation as the electric polarization free energy of the solvent, due to solute–solvent interactions and the change in solvent–solvent interactions upon inserting the solute. It is calculated using the generalized Born equation [40–43]. We have improved this estimation by fitting experimental data for benzene. Assuming these conditions, we obtain

$$\Delta g_s = \Delta g_o\left[1 + 0.8\left(\frac{1-\frac{1}{\epsilon_s}}{1-\frac{1}{\epsilon_o}} - 1\right)\right]$$

$$= \Delta g_o\left\{1 + 0.8\left[\frac{\epsilon_o(\epsilon_s - 1)}{\epsilon_s(\epsilon_o - 1)} - 1\right]\right\} \quad (2)$$

The radius of the solvation sphere, $R_{v,s}$, is corrected by the molecular volumes of both 1-octanol and the new organic solvent. The exponent connects the radius of a sphere with its volume.

$$R_{V,S} = R_{V,O}\left(\frac{V_{S,S}}{V_{S,O}}\right)^{1/3} \quad (3)$$

The free volume, $V_{f,s}$, is directly corrected by the molecular volumes of both 1-octanol and the new organic solvent.

$$V_{f,s} = V_{f,O}\frac{V_{s,s}}{V_{s,O}} \quad (4)$$

The only needed parameters are the relative dielectric constant and molecular volume of the organic solvent. Molecular volumes for cyclohexane and chloroform have been calculated with the TOPO program developed by one of us (F.T.) [84–90]. In the present work we have used $\epsilon = 10.34$ for 1-octanol, 2.023 for cyclohexane, 4.806 for chloroform and $V_s = 155.0$ Å^3 for 1-octanol, 105.4 Å^3 for cyclohexane, 69.1 Å^3 for chloroform.

Starting from the SCAP program [23] we have implemented the following new features: (1) Estimation of parameters for any organic solvent following Eqs. (1)–(4). Any organic solvent–water log P can now be calculated provided that the relative dielectric constant of the solvent is known. (2) Other magnitudes of biological interest can now be calculated as (a) the molar concentration, C, of organic compound necessary to produce a 1:1 complex with bovine serum albumin (BSA) via equilibrium dialysis (b) the number of hydrophilic groups assuming that the molecule contains only one lipophilic group and (c) the hydrophile–lipophile balance (HLB). (3) One can select between Hopfinger and Pascal solvation parameter sets. (4) The calculation of the cavity volume and surface area in the organic solvent and in water is carried out. (5) An atom-to-atom or group-to-group partition of log P and all the other properties. This partition allows the analysis and display of local lipophilicity mapped on molecular surfaces. We have normalized the contribution to log P of each atom or group R to log P by a factor of V/V_R. So, we guarantee that the mean of log P_R is equal to the molecular value for molecules with similar group volumes. In this way, the values mapped at each point of a given group show the values that would correspond to a hypothetical molecule that were formed exclusively by several groups identical to this one.

We have compared the solvation descriptors log P with values obtained with a method developed by Kantola et al. [91] for the computation of conformationally dependent hydrophobic indices based on atomic contributions. The method of Kantola et al. uses the following expression for the 1-octanol–water partition coefficient:

$$\log P = \sum_i \alpha_i(N)S_i + \beta_i(N)S_i(\Delta q_i)^2 + \gamma_i(N)\Delta q_i \quad (5)$$

where S_i is the contribution of atom i to the molecular surface area; Δq is the total atomic charge [92,93]; and α, β and γ are fitting parameters dependent only on the atomic number of atom i. We have written a computer program called CDHI that uses the method of Kantola et al. and we have implemented in it an atom–atom partition analysis of log P near selected atoms. The contribution of each atom to the molecular surface area is calculated with the TOPO algorithm [84–88,90]. We have computed the atomic net charges Δq with the POLAR program which has been described elsewhere [84–90]. Note that the comparison between the SCAP method and the method of Kantola et al. has a special interest. The latter assigns a set of fitted parameters for each atom depending only on its atomic number and not on the surrounding atoms in the molecule. Instead, the SCAP method takes also into account the functional group to which each atom belongs in the molecule.

To compare our results with solvents other than 1-octanol, we have used the method proposed by Leo et al. [94]. They divided solute molecules in two general solute classes: class A (H-donor solutes) and class B (H-acceptor solutes). Then, they fitted regression equations (A and B) for log P of various organic solvent–water (s) systems as a function of the 1-octanol–water (o) values:

$$\log P_s = a\log P_o + b \quad (6)$$

In particular, for cyclohexane equation A gives log $P_{ch} = 0.675 \log P_o - 1.842$ for H-donors and equation B gives log $P_{ch} = 1.063 \log P_o - 0.734$ for H-acceptors. For chloroform, equation A gives log $P_{cf} =$

Table 1
Values for the 1-octanol–water partition coefficients log P_o of reference molecules

Compound	GSCAP	CDHI[a]	CDHI-Gasteiger[b]	Experimental[c]
Uracyl	−2.87	2.27	−0.49	−1.07
1,2-Oxazole	−0.93	1.08	0.07	0.08
Hydroquinone (1,4-benzenediol)	−0.92	0.20	0.56	0.59
Resorcinol (1,3-benzenediol)	−0.92	0.46	0.60	0.78
Pyrocatechol (1,2-benzenediol)	−0.82	0.43	0.75	0.88
Thymine	−0.67	2.68	−0.23	−0.62
Pyrazole (1,2-diazole)	−0.24	1.64	−0.43	0.26
Apigenin (4′,5,7-trihydroxyflavone)	−0.11	−1.22	1.18	1.24
Methanol	−0.01	−1.05	−0.37	−0.77
Pyrimidime (1,3-diazine)	0.33	2.00	−0.06	−0.40
Pyrazine (1,4-diazine)	0.34	1.48	−0.26	−0.22
Pyridazine (1,2-diazine)	0.36	1.42	−0.24	−0.72
Dihydrogen	0.38	−0.33	−0.01	0.45
Methane	0.44	1.71	0.88	1.09
Phenol	0.61	1.40	1.55	1.48
Ethene	0.88	1.55	1.61	1.13
Methylamine	0.95	0.78	−0.32	−0.57
Furan	1.39	1.46	1.48	1.34
2-Naphthol	2.14	2.41	2.54	2.89
Benzene	2.20	2.29	2.47	2.15
1-Naphthol	2.20	2.41	2.55	2.84
Oxirane	2.24	−0.95	0.08	−0.30
1-Propanol	2.45	−0.24	−0.63	−1.23
p-Cresol	2.55	1.80	1.72	1.94
m-Cresol	2.55	1.84	1.72	1.96
Propene	2.73	1.87	1.80	1.77
2-Naphthylamine	2.86	3.75	2.35	2.28
Quinoline	2.87	3.01	2.05	2.03
1-Naphthylamine	2.88	3.78	2.34	2.25
2-Propanol	3.07	0.03	−0.17	0.05
Caffeine (1,3,7-trimethylxantine)	3.08	4.49	−1.26	0.01
Propanone	3.38	0.69	0.30	−0.24
Cyclopropane	3.46	1.54	1.44	1.72
Naphthalene	3.71	3.34	3.48	3.36
Methyl ether	3.76	−0.54	0.60	0.10
Ethane	3.94	1.52	1.48	1.81
Toluene	4.12	2.77	2.97	2.69
Antipyrin	4.20	3.67	1.41	0.38
1,4-Dioxane	4.38	−1.88	0.65	−0.42
Tetrahydrofuran	4.45	−0.28	0.56	0.46
Trimethylamine	4.93	1.26	0.52	0.27
Phenanthrene	5.13	4.49	1.69	1.78
Cyclohexene	5.18	1.79	2.05	2.86
Anthracene	5.18	4.48	4.47	4.45
Fluorene	5.51	4.14	4.17	4.18
1-Methylnaphthalene	5.53	3.81	3.68	3.87
2-Methylnaphthalene	5.58	3.85	3.70	3.86
o-Xylene	5.92	3.23	2.87	2.77
m-Xylene	5.98	3.25	2.88	3.20
p-Xylene	6.02	3.25	2.92	3.15
2-Methylpropane	6.30	1.99	1.82	2.76
9,10-Dihydroanthracene	6.51	4.22	4.30	4.25
Mesitylene (1,3,5-trimethylbenzene)	7.77	3.74	3.13	3.42
Root-mean-square error	1.82	1.31	0.43	0.00

[a] CDHI: calculations carried out with a method developed by Kantola et al. [91].
[b] CDHI calculations with charges computed using the Gasteiger method; results taken from [91].
[c] Experimental data taken from [91].

1.126 log $P_o - 1.343$ for H-donors and equation B gives log $P_{cf} = 1.276$ log $P_o + 0.171$ for H-acceptors.

4. Calculation results and discussion

Table 1 compares the performance of GSCAP and our version of the CDHI model using as a reference the CDHI series of values taken from Kantola et al. [91]. A set of 53 reference molecules built from H, C, N and O atoms have been selected from the whole set of fitting systems used by Kantola et al. [91]. The difference between both CDHI calculations in Table 1 comes from the different atomic net charges and surface areas used in Eq. (5). Comparing to experiment, the method of Kantola et al. outperforms the GSCAP results. In particular, the root-mean-square error (RMSE) is 1.31 log *P* units for CDHI and 1.82 log *P* units for SCAP. However, note that all the 53 molecules in Table 1 have been selected from the parametrization set of CDHI, while the parameters used in GSCAP are generated in a completely different way that does not depend on the set of molecules (see above).

The GSCAP results in Table 1 show that those molecules with low log *P* values (first entries in Table 1) are treated with more accuracy than those with large log *P* values (last entries). In particular, the mean unsigned error (MUE) for the first 10 molecules is 1.11 log *P* units.

In spite of the lower quality of the GSCAP results, we preferred to generalize it because it is based on a physical model in which the parameters have a physical meaning (e.g., the molecular volume of the solvent) and are easier to change from one organic solvent to another. Instead, trying to use CDHI with a new solvent would imply that all of the parameters must be fitted again. This fitting would be difficult because there are not enough data available for most organic solvents [40–43]. If it is not indicated otherwise, the CDHI calculations presented in this work have been performed with our version. In it the atomic contributions to the molecular surface area are calculated with the TOPO algorithm [84–88,90], and the atomic net charges are computed with the POLAR program [84–90]. These results have been used as reference calculations when experimental data are not available.

The solvation descriptors for porphin (H_2Por, Fig. 1a), iron and manganese porphyrins (M^{II}Por), their chlorine derivatives (M^{III}PorCl) and phthalocyanine (Ptc, Fig. 1b) and phthalocyanine tetrasulphonate (Ptctsp) are reported in Table 2. Starting from porphin, minus Gibbs free energies of solvation in water ($-\Delta G_{solv,w}$), 1-octanol ($-\Delta G_{solv,O}$), cyclohexane ($-\Delta G_{solv,ch}$) and chloroform ($-\Delta G_{solv,cf}$) for metalloporphyrins are, in general, slightly decreased by the presence of the metal atom and slightly increased by the addition of Cl. This last variation can be related to a big increase in the hydrophilic

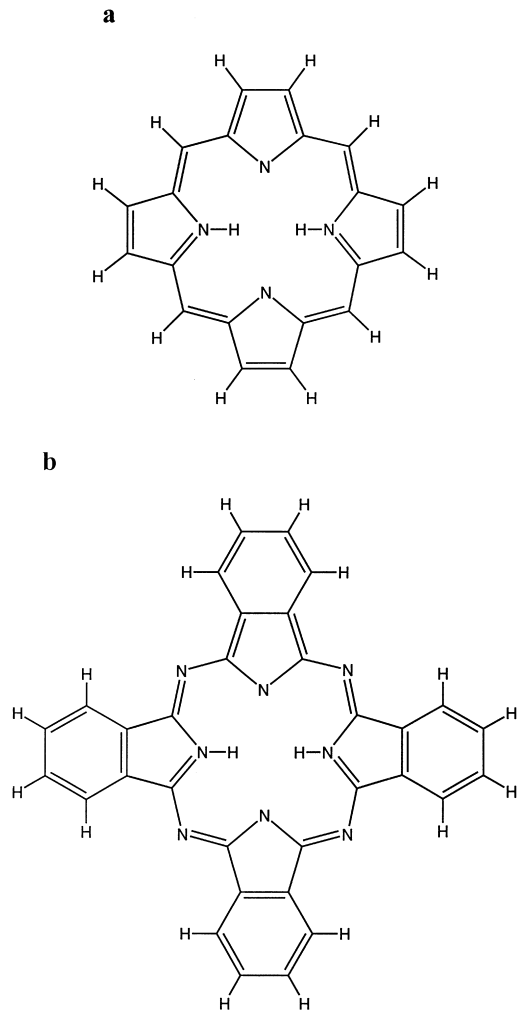

Fig. 1. Molecular structures of (a) porphin (H_2Por) and (b) phthalocyanine molecules.

Table 2
Solvation descriptors for porphin, porphyrins and phthalocyanines

Molecule	$\Delta G^{a}_{solv,w}$	$\Delta G^{b}_{solv,o}$	$\Delta G^{c}_{solv,ch}$	$\Delta G^{d}_{solv,cf}$	Log P_o (GSCAP)	Log P_o (CDHI)	Log P_{ch} (GSCAP)[f]	Log P_{ch}[g]	Log P_{cf} (GSCAP)[h]	Log P_{cf}[g]
Porphin	−31.45	−62.63	−41.63	−59.80	5.48	7.16	1.79	1.86	4.98	4.82
Fe^{II}porphyrin	−29.73	−62.02	−41.08	−58.74	5.67	6.14	2.00	1.99	5.10	5.04
Mn^{II}porphyrin	−29.60	−61.94	−41.06	−58.72	5.68	5.89	2.01	1.99	5.12	5.05
Fe^{III}porphyrinCl	−29.63	−63.18	−41.64	−59.53	5.89	10.6	2.11	2.14	5.25	5.29
Mn^{III}porphyrinCl	−29.63	−63.19	−41.68	−59.61	5.89	10.5	2.12	2.14	5.27	5.29
Phthalocyanine	−52.57	−99.24	−65.30	−92.48	8.20	12.4	2.24	3.69	7.01	7.89
Phthalocyanine tetrasulphonate	−45.67	−124.2	−79.42	−108.5	13.8	[i]	5.93	7.47	11.0	14.2

[a] Gibbs free energy of solvation in water (kJ mol^{-1}).
[b] Gibbs free energy of solvation in 1-octanol (kJ mol^{-1}).
[c] Gibbs free energy of solvation in cyclohexane (kJ mol^{-1}).
[d] Gibbs free energy of solvation in chloroform (kJ mol^{-1}).
[e] P_o is the 1-octanol–water partition coefficient.
[f] P_{ch} is the cyclohexane–water partition coefficient.
[g] Calculations carried out with a method developed by Leo et al. [94].
[h] P_{cf} is the chloroform–water partition coefficient.
[i] This method is not parameterized for molecules containing sulphur.

accessible-surface area (from 27.52 to 51.25 $Å^2$) [86]. Hence, the 1-octanol–water partition coefficient is minimal for the metal free porphin (log $P_o = 5.48$) and maximal for the Cl metalloporphyrins (log $P_o = 5.89$). The log P_o results vary similarly as the CDHI reference calculations. The cyclohexane–water partition coefficient, log P_{ch} falls in the range 1.8–2.1. The chloroform–water partition coefficient, log P_{cf}, falls in the range 5.0–5.3. Both indices follow the same trend as P_o. The log P_{ch} and log P_{cf} results are in good agreement with reference calculations carried out with the method of Leo et al. [94]. For both phthalocyanines, the increase in log P_o from 8.20 to 13.8 can be also explained by a big increase in the hydrophilic accessible-surface area (from 75.91 to 483.17 $Å^2$). That increment is also shown in log P_{ch} and log P_{cf}. The range of more than 8 log P units in log P_o going from H_2Por to Ptctsp implies a variation of 8 orders of magnitude in P_o ($10^{5.48}$–$10^{13.8}$).

The three organic solvents show different ranges of calculated log P values. On one hand, 1-octanol shows the greatest log P value because it is able to form hydrogen bonds with porphyrins and phthalocyanines. On the other hand, cyclohexane shows the lowest log P because it lacks this ability. Thus, the difference between log P_o and log P_{ch} has been proposed as a measure of hydrogen bonding [95,96]. In spite of the intermediate value of the dielectric constant, chloroform is predicted to present an intermediate behaviour, but clearly closer to that of 1-octanol.

The atom-to-atom partition for the metal atom of the solvation descriptors of porphyrins and phthalocyanines is summarized in Table 3. For porphin and phthalocyanines, results are referred to each central H atom. This contribution to normalized, log P_o, log P_{ch}, log P_{cf} is increased by the substitution of metal for both central H atoms and by the addition of the Cl. It should be noted that, for the same central atom (Fe, Mn or two H atoms), the three normalized partition coefficients are rather sensitive to the presence in the molecule of neighbouring (Cl) or distant (tetrasulphonate) groups.

The normalized atomic partition of log P_o vs. distance (in angstroms) to the centre of the molecule for the atoms in porphin and phthalocyanine is shown in Fig. 2. Porphin shows a central hydrophilic region (at a distance of 2 Å). In addition to this hydrophilic region, phthalocyanine also presents a peripheral hydrophobic region (near 6 Å, see Fig. 2), resulting in an amphipathic molecule. This result can be explained by the increase of the atomic net charges on going from the central N atoms (ab initio STO-3G $q_N = -0.341e$) to the peripheral benzenic ring C atoms (q_C in the range $-0.055e$ to $-0.047e$).

The solvation descriptors for the benzothiazole

Table 3
Solvation descriptors for porphin, porphyrins and phthalocyanines — atom-to-atom partition for the metal atom

Molecule	Log P_o[a]	Log P_{ch} (GSCAP)[b]	Log P_{ch}[c]	Log P_{cf} (GSCAP)[d]	Log P_{cf}[c]
Porphin[e]	−3.2	−4.6	−4.1	−2.4	−3.9
Fe^{II}porphyrin	0.0	−1.7	−1.8	0.1	0.2
Mn^{II}porphyrin	−0.1	−1.8	−1.9	0.0	0.0
Fe^{III}porphyrinCl	0.8	−1.0	−1.3	0.7	1.2
Mn^{III}porphyrinCl	1.0	−0.8	−1.2	0.9	1.4
Phthalocyanine[e]	−5.4	−7.6	−6.5	−3.9	−6.7
Phthalocyanine tetrasulphonate[e]	−8.8	−13	−10	−6.4	−11

[a] P_o is the normalized 1-octanol–water partition coefficient.
[b] P_{ch} is the normalized cyclohexane–water partition coefficient.
[c] Calculations carried out with a method developed by Leo et al. [94].
[d] P_{cf} is the normalized chloroform–water partition coefficient.
[e] In the case of porphin and phthalocyanines, results refer to each H atom.

(A)–benzobisthiazole (B) linear oligomers in the series A–A to A–B_{13}–A (see Fig. 3a) are given in Table 4. Minus Gibbs free energy of solvation in water is increased with the number of units in the oligomer from the monomeric unit ($-\Delta G_{solv} = 8.90$ kJ mol^{-1}) to A–B_{13}–A ($-\Delta G_{solv,w} = 122.6$ kJ mol^{-1}). However, minus Gibbs free energy of solvation in 1-octanol increases more quickly, so the 1-octanol–water partition coefficient, P_o, is rather incremented with the number of units in the oligomer. Both in GSCAP and in the CDHI reference calculations the change implies various tens in the order of magnitude in P_o. It should be noted that for values of log $P_o > 3$ (entries A–A to A–B_{13}–A in Table 4), more than 99.9% of the solute is in the organic phase. So, both methods agree qualitatively in predicting a negligible quantity of solvent in water. The cyclohexane–water and chloroform–water partition coefficients show the same trend as P_o. Some values are greater than Avogadro number exponent 23 ($P > 10^{23}$). This would mean that no solvent molecules would be present in water to allow experiments for validation. However, all figures are kept in Table 4

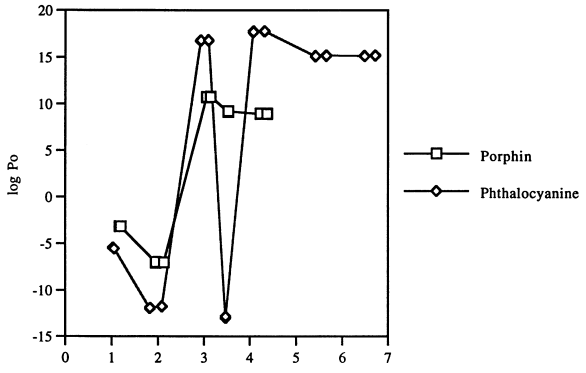

Fig. 2. Atom-to-atom partition of the decimal logarithm of the 1-octanol–water normalized partition coefficient vs. distance (in angstroms) to the centre of the molecule for the atoms in porphin and phthalocyanine computed with SCAP.

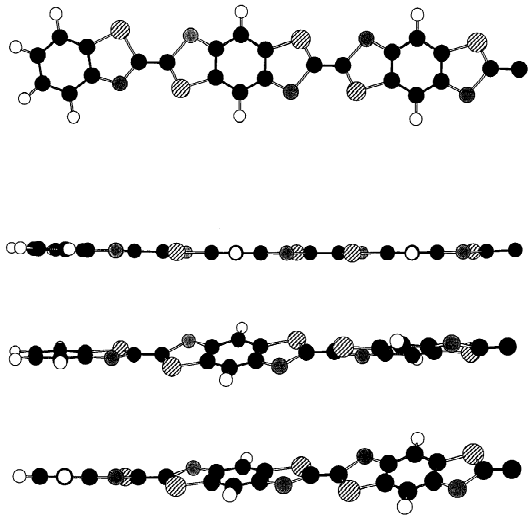

Fig. 3. Image of fragment A–B–B– of the benzothiazole (A)–benzobisthiazole (B) linear oligomer A–B_{13}–A: (a) front view of the 000 rotational isomer; (b) top view of the 000 rotational isomer; (c) top view of the + − + rotational isomer; and (d) top view of the + + + rotational isomer. The rotation angles have been slightly enhanced (to 20°) to make clearer the torsional effects.

Table 4
Solvation descriptors for benzothiazole (A)–benzobisthiazole (B) linear oligomers

Oligomer	$\Delta G^{a}_{solv,w}$	$\Delta G^{b}_{solv,o}$	$\Delta G^{c}_{solv,ch}$	$\Delta G^{d}_{solv,cf}$	Log P_o (GSCAP)[e]	Log P_o (CDHI)	Log P_{ch} (GSCAP)[f]	Log P^{g}_{ch}	Log P_{cf} (GSCAP)[h]	Log P^{g}_{cf}
A	−8.90	−21.97	−14.60	−20.88	2.30	2.35	1.00	−0.29	2.11	1.24
AA	−15.03	−42.08	−27.67	−39.02	4.75	4.24	2.22	1.36	4.21	4.01
ABA	−23.35	−64.76	−41.94	−58.16	7.28	6.01	3.27	3.07	6.12	6.85
AB_2A	−31.65	−87.43	−56.18	−77.32	9.80	7.78	4.31	4.77	8.02	9.69
AB_3A	−39.95	−110.1	−70.39	−96.49	12.3	9.59	5.35	6.47	9.93	12.5
AB_4A	−48.24	−132.7	−84.58	−115.7	14.8	11.4	6.38	8.18	11.9	15.4
AB_5A	−56.53	−155.4	−98.74	−134.9	17.4	13.2	7.42	9.88	13.8	18.2
AB_6A	−64.81	−178.0	−112.9	−154.1	19.9	15.0	8.44	11.6	15.7	21.1
AB_7A	−73.09	−200.6	−127.0	−173.4	22.4	16.7	9.47	13.3	17.6	23.9
AB_8A	−81.36	−223.2	−141.1	−192.6	24.9	18.5	10.5	15.0	19.5	26.7
AB_9A	−89.63	−245.8	−155.1	−211.9	27.4	20.3	11.5	16.7	21.5	30.0
$AB_{10}A$	−97.89	−268.4	−169.2	−231.2	30.0	22.1	12.5	18.4	23.4	32.4
$AB_{11}A$	−106.1	−291.0	−183.2	−250.5	32.5	23.9	13.5	20.1	25.4	35.2
$AB_{12}A$	−114.4	−313.6	−197.2	−269.8	35.0	25.7	14.5	21.8	27.3	38.1
$AB_{13}A$	−122.6	−336.1	−211.1	−289.2	37.5	27.5	15.6	23.5	29.3	40.9

[a] Gibbs free energy of solvation in water (kJ mol^{-1}).
[b] Gibbs free energy of solvation in 1-octanol (kJ mol^{-1}).
[c] Gibbs free energy of solvation in cyclohexane (kJ mol^{-1}).
[d] Gibbs free energy of solvation in chloroform (kJ mol^{-1}).
[e] P_o is the 1-octanol–water partition coefficient.
[f] P_{ch} is the cyclohexane–water partition coefficient.
[g] Calculations carried out with a method developed by Leo et al. [94].
[h] P_{cf} is the chloroform–water partition coefficient.

with the only purpose of comparison along the homologous series of molecules. For entry A in Table 4, log P_{ch} in cyclohexane–water is negative, which implies preferential solubility in water for this system. Even in this case, all the oligomers, starting from the smaller ones, show a clear preferential solubility in the organic phase.

The solvation descriptors for fullerene-60, -70, -82, -60 Van der Waals dimer and perhydrobuckminsterfullerene ($C_{60}H_{60}$) have been calculated. On one hand, C_{60} (buckminsterfullerene) is especially symmetric with all 60 atoms occupying equivalent sites in a truncated icosahedron configuration [97]. The molecular structure contains 12 pentagonal rings and 20 hexagonal rings constituting a roughly spherical molecule. The pentagonal rings sit as far as possible from each other, at the vertices of an icosahedron; they may be viewed as defects compared to the un-strained hexagonal rings. Each carbon is equivalent to every other carbon, and all of them occur at the vertex joining a pentagon and two hexagons. C_{60} has icosahedral point group symmetry [98]. On the other hand, C_{70}, is similar to C_{60}, with the ten extra carbons inserted in a band of hexagons around the middle of the truncated icosahedron, producing a prolate, ellipsoidal structure. For this fullerene, a substructure is shown in Fig. 4 where the five non-equivalent carbons are labelled a–e following a notation used in previous works [99,100]. It should be remarked that atoms labelled a to d join one pentagon with two hexagons while the type e atoms join three hexagons, and that, on going from atom a to e, the distance from the nearest pentagon gradually increases.

The fully saturated perhydrogenated buckminsterfullerene, $C_{60}H_{60}$, is an interesting system that has deserved the attention of theoretical chemists [101–103]. One would expect that the hydrogens introduced by chemical reduction of C_{60} would lie on the outside of the cluster. The symmetric structure produced in this way was predicted to be highly strained. Some endohedral $C_{60}H_{60}$ isomers with one or more CH bonds pointing inside the cavity were shown to be more stable than their all-out counterparts. Mizoguchi computed the optimum number of inside hydrogen atoms and geometry with the AM1

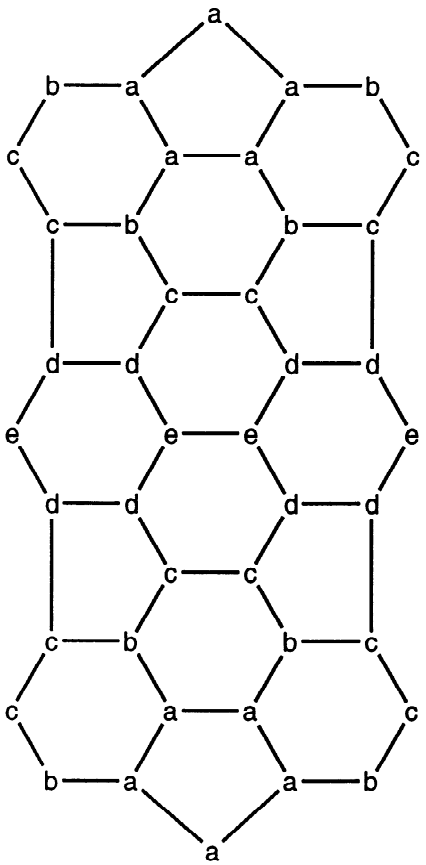

Fig. 4. Flat projection of approximately 3/10 of the structure of (D_{5h})fullerene-70 showing the five non-equivalent carbon atom types. The five-fold symmetry axis of rotation is through the centre of the top and bottom pentagons.

method, finding the most stable isomer [103]. The calculations in the present work refer to the most stable isomer of Mizoguchi, that has ten endohedral H atoms [103].

The solvation descriptors for these fullerenes are resumed in Table 5. The negative Gibbs free energy of solvation is slightly increased on going from C_{60} (15.60 kJ mol^{-1}) to C_{82} (20.86 kJ mol^{-1}). However, the negative Gibbs free energy of solvation in 1-octanol is rather increased from C_{60} (128.7 kJ mol^{-1}) to C_{82} (172.4 kJ mol^{-1}). Hence, the 1-octanol–water partition coefficient P_o, increases with the number of carbons (change of 7 orders of magnitude in P_o). The transfer free energy to 1-octanol from water $\Delta\Delta G_{solv}^{\circ}$ (1-octanol←water), can be easily obtained by subtracting ΔG_{solv}° (water) from ΔG_{solv}° (1-octanol). The cyclohexane–water and chloroform–water partition coefficients show the same trend as P_o.

The results for the C_{60} Van der Waals dimer show a value of log $P_o = 39$, indicating that a negligible quantity remains in water. As these dimers are only stable in concentrated solutions, we have repeated the calculation imposing the condition that the water phase must be entirely assigned to the monomer form. In this case, the organic phase is more favoured, in addition, by 2.7 log P units. This effect is similar in the other organic solvents.

The results for $C_{60}H_{60}$ show that no important effect on the log P values is expected related to the all-exo or partially endo position of the H atoms. In both cases, the GSCAP log P values indicate that all the $C_{60}H_{60}$ molecules would remain in the organic phase. The most noticeable feature in Table 5 is the sharp discrepancy in the orders of magnitude predicted by the CDHI method for the 1-octanol–water system (log $P \sim 3$–4). The CDHI results would indicate a preferential solubility in 1-octanol of only 10^3 times that in water, a prediction which seems unlikely for a system that can be thought as a fully saturated system of cyclic tertiary carbon atoms. These spurious results of CDHI illustrate well the danger of using parameter-fitted methods out of the range of molecules that were used in the fitting.

The atom-to-atom partition for each carbon of the solvation descriptors of the fullerene systems are listed in Table 6. The contribution of the C_{70}-a–c carbons to normalized log P_o, log P_{ch} and log P_{cf} is slightly greater than for d–e. This result can be explained because the distances from the nearest pentagon vary gradually from atom a to e.

The solvation descriptors for phenol, benzyl alcohol and a homologous series of phenyl alcohols (from 2-phenylethanol to 7-phenylheptanol) are reported in Table 7. The log P_o values show the expected deviations from the experimental values according to the discussion of Table 1. A few data are available for the other two solvents in cyclohexane (-1.00 for phenol and -0.62 for benzyl alcohol) and chloroform (0.36 for phenol) [22]. The log P values vary gradually in this series (i.e., change of 7 orders of magnitude in P_o) that has been selected because it has been proposed as a model for

Table 5
Solvation descriptors for fullerene systems

Fullerene	$\Delta G^{a}_{solv,w}$	$\Delta G^{b}_{solv,o}$	$\Delta G^{c}_{solv,ch}$	$\Delta G^{d}_{solv,cf}$	Log P_o (GSCAP)[e]	Log P_o (CDHI)	Log P_{ch} (GSCAP)[f]	Log P^{g}_{ch}	Log P_{cf} (GSCAP)[h]	Log P^{g}_{cf}
C_{60}	−15.60	−128.7	−78.48	−103.2	19.9	13.8	11.1	11.6	15.4	21.0
C_{60} dimer	−30.82	−250.0	−153.1	−202.4	38.5	27.6	21.5	24.2	30.1	42.0
C_{60} dimer[i]	−15.60	−250.0	−153.1	−202.4	41.2	−	24.2	26.0	32.8	45.0
$C_{60}H_{60}$ (10 H inside)	35.43	−122.3	−72.09	−91.44	27.7	2.76	18.9	16.9	22.3	29.8
$C_{60}H_{60}$ all-out	38.04	−124.5	−75.04	−97.67	28.6	4.07	19.9	17.4	23.8	30.8
C_{70}	−18.09	−148.4	−91.20	−119.9	22.9	15.8	12.8	13.6	17.9	24.4
C_{82}	−20.86	−172.4	−106.2	−139.2	26.6	17.6	15.0	16.1	20.8	28.6

[a] Gibbs free energy of solvation in water (kJ mol^{-1}).
[b] Gibbs free energy of solvation in 1-octanol (kJ mol^{-1}).
[c] Gibbs free energy of solvation in cyclohexane (kJ mol^{-1}).
[d] Gibbs free energy of solvation in chloroform (kJ mol^{-1}).
[e] P_o is the 1-octanol–water partition coefficient.
[f] P_{ch} is the cyclohexane–water partition coefficient.
[g] Calculations carried out with a method developed by Leo et al. [94].
[h] P_{cf} is the chloroform–water partition coefficient.
[i] Here, fullerene-60 is calculated as monomer in water and Van der Waals dimer in the organic phase.

transdermal delivery drugs. Various linear correlations between log *P*, quadrupole moment and fractal dimension point not only to a homogeneous molecular structure of phenyl alcohols but also to the utility of log P_o to predict and tailor drug properties. The latter is a nontrivial but very exciting problem in pharmacology [104].

5. Conclusions

We propose a tentative universal organic solvation model to calculate the solubility (ΔG_{solv}) in any organic solvent and in water as well as the organic solvent–water partition coefficient (*P*). The model is based on the modification of a previously established model known as SCAP and proposed by Hopfinger [25,26]. The hallmark of the model is that it is designed to be employed for all organic solvents without previous fitting parametrization. It is based in the division of ΔG_{solv} in order to obtain a system of increments by atoms or by groups. From the preceding results and discussion the following conclusions can be drawn.

(1) Although in the present form the GSCAP method is far from showing the accuracy of the CDHI method,

Table 6
Solvation descriptors for fullerene systems — atom-to-atom partition for each carbon atom

Fullerene	Atom type	Log P_o (GSCAP)[a]	Log P_o (CDHI)	Log P_{ch} (GSCAP)[b]	Log P^{c}_{ch}	Log P_{cf} (GSCAP)[d]	Log P^{c}_{cf}
−60	a	20.0	13.8	11.0	11.7	15.3	21.2
−70	a	23.7	15.8	13.3	14.2	18.2	25.3
	b	23.5	15.9	13.2	14.0	18.2	25.1
	c	23.2	15.8	12.9	13.8	17.9	24.8
	d	22.6	15.9	12.6	13.4	17.8	24.1
	e	22.1	15.9	12.5	13.1	17.4	23.5
−60 dimer	average	39.6	27.6	22.0	24.9	30.7	43.2

[a] P_o is the normalized 1−octanol–water partition coefficient.
[b] P_{ch} is the normalized cyclohexane–water partition coefficient.
[c] Calculations carried out with a method developed by Leo et al. [94].
[d] P_{cf} is the normalized chloroform–water partition coefficient.

Table 7
Solvation descriptors for phenol and phenyl alcohols

Molecule	$\Delta G^{a}_{solv,w}$	$\Delta G^{b}_{solv,o}$	$\Delta G^{c}_{solv,ch}$	$\Delta G^{d}_{solv,cf}$	Log P_o (GSCAP)[e]	Log P_o (CDHI)	Experimental[f]	Log P_{ch} (GSCAP)[g]	Log P^{h}_{ch}	Log P_{cf} (GSCAP)[i]	Log P^{h}_{cf}
Phenol	−19.29	−22.77	−15.72	−23.40	0.61	1.40	1.48	−0.63	−1.43	0.72	−0.66
Benzyl alcohol	−17.80	−27.12	−18.58	−27.45	1.64	0.69	1.10	0.14	−0.74	1.69	0.50
2-Phenylethanol	−16.51	−31.68	−21.67	−31.98	2.67	1.02	1.36	0.91	−0.04	2.72	1.66
3-Phenylpropanol	−15.04	−36.10	−24.68	−36.36	3.70	1.24	1.88	1.69	0.66	3.75	2.82
4-Phenylbutanol	−13.57	−40.57	−27.70	−40.77	4.74	1.48	–	2.48	1.36	4.78	4.00
5-Phenylpentanol	−12.14	−45.08	−30.74	−45.16	5.79	1.63	–	3.27	2.06	5.80	5.17
6-Phenylhexanol	−10.66	−49.53	−33.77	−49.54	6.83	1.84	–	4.06	2.77	6.83	6.35
7-Phenylheptanol	−9.26	−54.05	−36.80	−53.93	7.87	2.08	–	4.84	3.47	7.85	7.52

[a] Gibbs free energy of solvation in water (kJ mol^{-1}).
[b] Gibbs free energy of solvation in 1-octanol (kJ mol^{-1}).
[c] Gibbs free energy of solvation in cyclohexane (kJ mol^{-1}).
[d] Gibbs free energy of solvation in chloroform (kJ mol^{-1}).
[e] P_o is the 1-octanol–water partition coefficient.
[f] Experimental data taken from [22].
[g] P_{ch} is the cyclohexane–water partition coefficient.
[h] Calculations carried out with a method by Leo et al. [94].
[i] P_{cf} is the chloroform–water partition coefficient.

our results show that GSCAP is actually a general solvent method and can be applied to very big systems with log *P* values covering more than 5 log *P* units. Since GSCAP is an accumulative method, it can overestimate the results for very big systems. This is a defect to be corrected in the future and various damping strategies can be considered. Important qualitative errors (e.g. those related to the sign of log *P*) need also to be considered. Note, as an example of possible refinement, that other additive fragment contributions than that by Gibson and Scheraga [27] exist in the literature. It should be worth exploring their effect in the results. Notwithstanding, the authors consider that the goal of showing that a method based on physically obtainable parameters, as SCAP is, and which can be generalized to other solvents has been achieved.

(2) We have written GSCAP as a version of Pascal's SCAP program implementing the modelling of the solubility in any organic solvent and the calculations of organic solvent–water log *P*. The only needed parameters are the dielectric constant and molecular volume of the organic solvent of interest. No fitted parameters are included in the model.

(3) The method differentiates the log *P* values of metalloporphyrins and phthalocyanines, fullerenes and perhydrofullerenes, and shows a gradual variation in the homologous series of benzothiazole-benzobisthiazole oligomers and phenyl alcohols. This property is predicted for molecules where the values change in 35 orders of magnitude.

(4) The GSCAP method allows the analysis of atom or group partial contributions to log *P*. The results show that, for a given atom, the normalized partition coefficients are rather sensitive to the presence in the molecule of other atoms or groups. As an example, both porphin and phthalocyanine show a central hydrophilic region, but only phthalocyanine presents a peripheral hydrophobic region, resulting in an amphipathic molecule. Another example is provided by C_{70}, where the contribution of the a–c carbons to normalized log *P* is slightly greater than for d–e; this result can be correlated with the gradual variation in distances from the nearest pentagon ring.

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