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Posted Date: 18 August 2025

doi: 10.20944/preprints202508.1214.v1

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Dispersion, Polar, and Hydrogen-Bonding Contributions to Solvation Free Energies

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Abstract

A new method is presented for the estimation of contributions to solvation free energy from dispersion, polar and hydrogen-bonding (HB) intermolecular interactions. COSMO-type quantum chemical solvation calculations are used for the development of four new molecular descriptors of solutes for their electrostatic interactions. The new model needs one to three solvent –specific parameters for the prediction of solvation free energies. The widely used Abraham's LSER model is used for providing the reference solvation free energy data for the determination of the solvent-specific parameters. Extensive calculations in 80 solvent systems have verified the good performance of the model. The very same molecular descriptors are used for the calculation of solvation enthalpies. The advantages of the present model over Abraham's LSER model is discussed along with the complementary character of the two models. Enthalpy and free-energy solvation information for pure solvents is translated into partial solvation parameters (PSP) analogous to the widely used Hansen solubility parameters and enlarge significantly their range of applications. The potential and the perspectives of the new approach for further molecular thermodynamic developments is discussed.

Keywords: solvation thermodynamics; polarity / polarizability; molecular descriptos; sigma profiles; electrostatic interactions

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1. Introduction

Advances in modern molecular thermodynamic modelling requires a thorough understanding of the intermolecular interactions and their contributions to key thermodynamic quantities and important properties of the studied systems [1–6]. In this regard, solvation thermodynamics and solute transfer / partition studies between two immiscible or partly miscible phases are of key interest as they provide valuable information on solute–solvent and solvent–solvent interactions in fluid systems, especially at very low solute concentrations where interactions between two solute molecules are negligible. This information has been extensively used in a broad range of applications ranging from the rational design of physicochemical processes, products and equipment at the industrial scale down to stabilization or self-assembly of biomolecules, controlled drug delivery, and search of feasible metabolic pathways [1–16].

The key thermodynamic quantity of central interest in solvation thermodynamics is the free energy change, ΔG_{12}^{S}, upon solvation of solute 1 in solvent 2 or the associated equilibrium solvation constant K_{12}^{S}. Among others, ΔG_{12}^{S} plays an important role in molecular thermodynamics and computational chemistry, since it can make a significant contribution to the total free energy of chemical reactions in solution. This quantity and its components of solvation enthalpy, ΔH_{12}^{S} and entropy, ΔS_{12}^{S}, can be expressed in terms of more familiar and/or measurable properties as follows [7,16–19]:

$$-2.303 Log K_{12}^{S} = \frac{\Delta G_{12}^{S}}{RT} = \frac{\Delta H_{12}^{S} - T\Delta S_{12}^{S}}{RT} = \ln \frac{\varphi_1^0 P_1^0 V_{m2} \gamma_{1/2}^{\infty}}{RT} \quad (1)$$

V_{m2} in Equation (1) is the molar volume of the solvent (component 2) and $\gamma_{1/2}^{\infty}$ is the activity coefficient of solute (component 1) at infinite dilution in this solvent. P_1^0 is the vapor pressure of pure solute at temperature, T, and φ_1^0 its fugacity coefficient (typically, set equal to 1 at ambient conditions). For pure solvents at ambient conditions, equation 1 leads to the following simple expression for the self-solvation free energy:

$$\frac{\Delta G^{S}}{RT} = \ln \frac{P^0 V_m}{RT} \quad (2)$$

For pure solvent at ambient conditions the self-solvation enthalpy, $-\Delta H^{S}$, is equal to its heat of vaporization, ΔH_{vap} [20–22]. Combining, then, equations 1 – 2, the following equation is obtained for the self-solvation entropy:

$$\frac{\Delta S^{S}}{R} = \frac{\Delta H_{vap}}{RT} - \ln \frac{P^0 V_m}{RT} \quad (3)$$

Equations 1 – 3 may be viewed as the bridging equations between solvation thermodynamics and the classical thermodynamics of phase equilibria. As observed, self-solvation enthalpy, entropy and free energy are easily obtained from known or measurable properties of pure solvents. On the other hand, partition coefficients of solute 1 between two immiscible liquid solvents 2 and 3 are obtained from the ratio of the equilibrium solvation constants [7,12–14,16,17]. Thus, a large database of experimental information on solvation quantities was already available since the third and fourth quarter of the last century.

Kamlet and Taft [23–25], having recognized the importance of solvation thermodynamics in the above mentioned multitude of applications, have pioneered in the development of Linear Free-Energy Relationships (LFER) for the correlation of the available experimental solvation data by attributing to each solvent a set of molecular descriptors reflecting its interaction capacity via the corresponding various types of intermolecular interactions with solute molecules. Abraham [12,13,26–28] has further refined this approach and developed his highly successful LSER (Linear Solvation Energy Relationship) model, which is used in a remarkably broad and ever expanding range of applications, today.

The LSER model uses the following simple linear equation for the quantitative description of solvation or the solute transfer from the (ideal) gas state to the liquid solvent state:

$$Log K_{12}^{S} = \frac{-\Delta G_{12}^{S}}{2.303RT} = c_2 + e_2 E_1 + s_2 S_1 + a_2 A_1 + b_2 B_1 + l_2 L_1 \quad (4)$$

or, less often, the alternative equation:

$$Log K_{12}^{S} = \frac{-\Delta G_{12}^{S}}{2.303RT} = c_{v2} + e_{v2} E_1 + s_{v2} S_1 + a_{v2} A_1 + b_{v2} B_1 + v_2 V_1 \quad (5)$$

The upper-case letters in these equations indicate solute molecular LSER descriptors while the lower-case letters indicate the corresponding complementary but solvent-specific LFER coefficients. The descriptors *V, L, E, S, A*, and *B*, correspond to the McGowan's characteristic volume, the equilibrium constant for the gas–liquid partition in n-hexadecane at 298 K, the excess molar refraction, the polarity / polarizability, the hydrogen bonding acidity A, and hydrogen-bonding basicity B, respectively of the solute [12–14,26–28]. The solvent-specific LFER coefficients are determined by multilinear regression of experimental data. Those of equation 4 are known for about

80 solvents [28]. Solvation enthalpies have been correlated with similar linear equations and the corresponding LFER coefficients are known for about 40 solvents [20,21].

Further extension of the LSER model to more solvents is not easy and requires a number of critically compiled experimental data for the adequate determination of the six LFER parameters in each of equations 4 and 5. The additional problem is that all coefficients of equation 4 are, in general, different (and, often, very different) from the corresponding coefficients of equation 5. This introduces much ambiguity in the estimation of specific contributions to solvation quantities from the various types of intermolecular interactions. Significant efforts are made in the literature for resolving these problems [29–33]. The bulk of these efforts focuses on the prediction of LSER molecular descriptors leaving intact the LSER solvation equation and the procedure for obtaining the solvent-specific LFER coefficients of the solvation equation.

In series of recent publications [22,34–39], an alternative attempt is made to address the above problems and further augment the capacity of the LSER model by paying attention to the thermodynamic consistency while retaining the simplicity of the LSER linearity. First, the thermodynamic basis of the linearity of equations 4 or 5 had to be understood, especially, the terms accounting for the hydrogen-bonding contributions [34,35]. Subsequently [36–39], a solid basis for the electrostatic interactions had to be devised and this was done by extracting the pertinent information from widely available or easily obtained quantum chemical calculations of molecular surface charge distributions or sigma – profiles (**σ**-profiles) [40–48]. The hydrogen-bonding contributions to solvation enthalpy and free energy were discussed in ref. [38] and [39], respectively. The dispersion and polar contributions to solvation enthalpy are discussed in ref. [22].

The present work has a twofold scope and character. First, it continues our previous work and focuses on the dispersion and polar contributions to solvation free-energy. In this way, all major types of contributions to both, solvation enthalpy and solvation free-energy are addressed. Having a global picture of the contributions to solvation quantities, an integral presentation is made of this new approach to solvation thermodynamics. With this new approach, three parameters are needed for each organic solvent phase instead of six needed by the LSER model. The separate contributions are calculated now with relatively less ambiguity and this facilitates the exchange of information with other analogous QSPR-type models, hydrogen-bonding or polarity scales, and the transfer of important information for the development of molecular thermodynamic models.

Thus, the next section summarizes the rationale of the new approach, the new molecular descriptors and the new linear equations for the calculation of the solvation quantities. The results are discussed in subsequent sections along with examples for the exchange of information with other thermodynamic approaches.

2. The Model

This section consists of two subsections. The rationale of the approach, the new molecular descriptors and the key equations for the contributions to solvation free energy are discussed in the first subsection. The information from LSER estimations of the non-HB contributions to solvation free energy is used in the second subsection for the determination of the new molecular descriptors and the solvent specific parameters of the new solvation equations.

2.1. The Rationale of the Model, the New Molecular Descriptors and the Key Equations

As discussed previously [34–39] intermolecular interactions are difficult to divide into clear-cut ranges with sharp borderlines and one may find in the literature various alternative, often confusing, divisions [48–52]. This series of works has adopted the widely used division of intermolecular interactions into electrostatic and non-electrostatic or polar and non-polar [52–55]. Polar interactions often cover a broad range of interactions from strong-directional to relatively weak ones. Non-polar interactions often cover dispersion and/or cavitation ones. The measurable quantities are, in general, combined contributions from the various types of intermolecular interactions involved.

The probably unique value of Abraham's LSER model [12,13,25–28,56] is its development based on the highly successful selection of five physically sound molecular descriptors for the, very often, excellent correlation (multilinear, multi-parameter regression) of critically compiled experimental thermodynamic data sets. As mentioned already, although there is ambiguity on the physical content of each term of the linear LSER equations, it appears that it is rather safe to consider that the sum of the terms (aA + bB) reflects the overall hydrogen-bonding (HB) contribution to solvation quantities [38,39]. All other terms, then, of the linear LSER equation reflects the rest of the non-HB interactions, that is, the rest of the electrostatic or polar interactions and the non-electrostatic or dispersion interactions. Our first task, then, is to devise a physically sound separation of the sum of LSER terms ($c + eE + sS + lL$) or the sum ($c + eE + sS + vV$) into an equivalent sum of two terms, one for the polar contributions and one for the dispersion ones It should be kept in mind that there are no direct experimental data for these separate contributions for comparison with the above LSER estimations

Recently [37–39], we have introduced four new molecular descriptors based on quantum – chemical (QC) calculations and referred to as QC-LSER descriptors. These descriptors are based on the molecular surface charge densities or σ – profiles widely used by the quantum-mechanics based COSMO-RS model [40–48]. These σ - profiles are available, free of charge, for thousands of molecules in the open literature [48] but may be obtained also by using appropriate quantum-chemical calculation suite [57–59]. The essentials only will be summarized here. Details on the QC-LSER descriptors may be found in ref. {37-38].

In the frame of COSMO solvation calculations [6,40–48], a σ-profile is the distribution of probabilities $P_i(\sigma_i) = A_i/A$ to find a surface charge density σ_i on the surface (COSMO solvation cavity) of the studied molecule [40–48]. The sum of the partial surface areas A_i gives the total surface area, A, of the molecular cavity, while the sum of the partial charges $\sigma_i A_i$ gives the total charge of the molecule. Moments of these surface charge distributions are known as COSMOments [42,43]. The four QC-LSER descriptors are COSMOments with functional forms $\sigma_i^2 A_i$ (being charge by mirror charge over unit area, with units C^2m^{-2} or $e^2Å^{-2}$ and reflecting the strength of intermolecular forces) and are defined as follows [37–39]:

$$A_h = 10^6 \int_{-\infty}^{-0.01} A_i \sigma_i^2 d\sigma_i \tag{6}$$

$$A_p = 10^6 \int_{-0.01}^{0} A_i \sigma_i^2 d\sigma_i \tag{7}$$

$$B_p = 10^6 \int_{0}^{0.01} A_i \sigma_i^2 d\sigma_i \tag{8}$$

$$B_h = 10^6 \int_{0.01}^{\infty} A_i \sigma_i^2 d\sigma_i \tag{9}$$

A_h and B_h are the acidity and basicity QC-LSER descriptors, respectively, while Ap and Bp are the corresponding polarity / polarizability descriptors.

Of course, the intermolecular interactions are dictated not only by the plain interacting charges but also by the geometry and orientation of the interacting molecular surfaces. This spatial or 3-D information is lost in the σ-profiles and the QC-LSER descriptors must be corrected to account for this loss of spatial information. Thus, the hydrogen-bonding (HB) QC-LSER descriptors, A_h and B_h, are replaced by the corresponding effective acidity and basicity descriptors, $\alpha = f_A A_h$ and $\beta = f_B B_h$, respectively [20,21], where the correction factors f_A and f_B were considered to be molecular characteristics of the solute reflecting the efficiency or "availability" of the corresponding molecular surface charges of the solute to form a hydrogen bond. In addition, the conformer population in the ideal gas state of the very same molecule may be different from its prevailing conformer population in solution. This leaves open the possibility in solute molecules with complex molecular structure and/or complex multi-sited hydrogen-bonding capacity to have different effective acidity and basicity descriptors when they become solvents.

The above geometrical peculiarities, of course, affect also the polar interactions. Thus, similarly to HB interactions, the effective polarity / polarizability contributions to solvation enthalpy were considered analogous to the products of the complementary sums of descriptors, $(A_h + A_p) \times (B_p + B_h)$, of sites not participating in directional HB interactions [22]. Due to the lack of spatial information, the effective polarity descriptors, π_a and π_b, are considered analogous to the corresponding above sums, or

$$\frac{\pi_a}{\pi_b} = \frac{A_h + A_p}{B_h + B_p} \tag{10}$$

In direct analogy, then, with the HB interactions, the contribution of polar interactions to solvation free energy of solute 1 by solvent 2, in kJ/mol, will be considered to be given by

$$-\Delta G^S_{\mathrm{P},12} = \ln 10RT\left(\pi_{a1}\pi_{b2} + \pi_{b1}\pi_{a2}\right) = 5.71\left(\pi_{a1}\pi_{b2} + \pi_{b1}\pi_{a2}\right) \quad \text{(at 298 K)} \tag{11}$$

The last two equations are the definition of the new polarity / polarizability descriptors with a content analogous to the LSER descriptor S. On self-solvation of simple solutes (for which the molecular descriptors do not change when they become solvents) the polar and the hydrogen – bonding contributions to solvation free energy are given, respectively, by the following equations:

$$\begin{aligned} -\Delta G^S_{\mathrm{P},12} &= 11.4\pi_a\pi_b \\ -\Delta G^S_{\mathrm{H},12} &= 11.4\alpha\beta \end{aligned} \qquad \text{(self-solvation at 298 K)} \tag{12}$$

Exceptions, implying a different polarity of a solute molecule from the polarity of the same molecule when solvent, may also be expected as in HB interactions [38,39].

Regarding non-electrostatic interactions, the σ-profiles do not seem to be very useful but no other molecular descriptors will be introduced here. The dispersion contribution to solvation quantities is considered to be, primarily, dictated by the structural characteristics (molecular surface area or volume, polarizability, excess refractivity) and, secondarily of the interacting molecules. LSER model provides with such structural descriptors and, in the case of solvation enthalpy, it was verified that the dispersion contribution to solvation enthalpy could be well described by the sum of two linear terms involving the LSER descriptors E and V or the descriptors E and L [22]. A similar assumption will be adopted here and the following equation will be used for the dispersion contribution to solvation free energy:

$$-\Delta G^S_{\mathrm{D},12} = f_E E_1 + f_l L_1 \tag{13}$$

As previously [22], a universal value for the f_E coefficient will be sought. In contrast, the coefficient f_l will be treated as solvent-specific reflecting the solvent capacity to accommodate the solute molecule as well as the extend of the dispersion interactions with it.

As mentioned already, the LSER model correlates experimental data for the total solvation free energy since there are no data for the separate contributions to it. In the present approach, the equation for the total solvation free energy, including contributions from HB and non-HB interactions, takes the following form:

$$-\Delta G^S_{12} = 5.71\left(f_E E_1 + f_l L_1\right) + 5.71\left(\pi_{a1}\pi_{b2} + \pi_{b1}\pi_{a2} + \alpha_1\beta_2 + \beta_1\alpha_2\right) \tag{14}$$

This equation is the equivalent of the corresponding LSER equation and may, thus, replace the LSER equations 4 or 5. The descriptors α and β replace the LSER acidity and basicity descriptors A and B. The pair of descriptors π_a and π_b replaces the LSER polarity descriptor S. An updated list of these new molecular descriptors for a number of common solutes is reported in Table S1 of the

Supplementary Information (SI) file. Although in many cases, these descriptors remain the same regardless of whether the molecule is solute or solvent, for the sake of generality and ease of use of equation 14 in practice, we introduce here two solvent-specific parameters via the following ratios:

$$R_P = \frac{(\pi_a)_{solvent}}{(\pi_a)_{solute}} = \frac{(\pi_b)_{solvent}}{(\pi_b)_{solute}} \tag{15a}$$

And

$$R_H = \frac{(\alpha)_{solvent}}{(\alpha)_{solute}} = \frac{(\beta)_{solvent}}{(\beta)_{solute}} \tag{15b}$$

Then, the general form of equation 14 becomes:

$$-\Delta G_{12}^{S}/5.71 = f_E E_1 + f_{l2} L_1 + \left\{ R_{P2}\left(\pi_{a1}\pi_{b2} + \pi_{b1}\pi_{a2}\right) + R_{H2}\left(\alpha_1\beta_2 + \beta_1\alpha_2\right) \right\} \tag{16}$$

Thus, in general, each solvent phase is characterized by three parameters: one volume – or cavitation – parameter, f_l, one polarity ratio, R_P, and one hydrogen-bonding ratio, R_H. (Since f_{l2},R_{p2} and R_{H2} are solvent – specific parameters, the subscript 2 may be omitted for simplicity).

In the next subsection we will discuss the method for the determination of the unknown parameters in equation 16.

2.2. Determination of the New Molecular Descriptors and the Solvent-Specific Parameters

The methodology for the determination of the hydrogen –bonding and the polarity molecular descriptors of the solutes was presented in ref. [38,39] and [22], respectively. Since one single set of molecular descriptors will be used for both solvation enthalpy and solvation free-energy, it is advantageous to determine them from solvation free energy calculations due to the larger number of solvents with known LSER parameters [28,56]. Thus, the reported molecular descriptors in Table S1 of the SI file were obtained by a global minimization of deviations between calculations with equation 16 and the corresponding LSER estimations of solvation free energy for all known solvent systems [28]. The optimum sets of solvent-specific parameters, which are reported in Table 1, were also obtained from this global minimization process. Simultaneously, the universal value of -0.2 was obtained for the coefficient f_l. As observed in Table 1, in many cases, the solvent-specific parameter R_H is equal to one indicating that the capacity of the solute for hydrogen-bonding interactions remains unchanged when it becomes the solvent phase. In fact, this may be generalized for the electrostatic interactions on account of the very definitions of polarity descriptors. The polar contribution term in equation 16 may be rewritten as follows:

$$R_P\left(\pi_{a1}\pi_{b2} + \pi_{b1}\pi_{a2}\right) = 2R_P\left(\frac{\pi_{a1}}{\sqrt{2}}\frac{\pi_{b2}}{\sqrt{2}} + \frac{\pi_{b1}}{\sqrt{2}}\frac{\pi_{a2}}{\sqrt{2}}\right) \tag{17}$$

Thus, if all polarity descriptors in Table S1 were multiplied by the inverse of the square root of 2, the polarity ratio R_P in Table 1 would become 1 instead of 0,5 for many solvents. For these many solutes for which the capacity for electrostatic interactions remains unchanged when become solvents, the present model requires just one parameter, the f_l, for the estimation of the solvation free energies. It is important to point out again that, due to the lack of experimental data for the separate contributions to solvation quantities, our calculations were optimized against the two sets of LSER estimations for the hydrogen-bonding contributions and for the non-HB ones. Thus, the above minimization process was executed in two distinct and consecutive steps. In the first step, the sum of dispersion and polar (DP) contributions were optimized against the corresponding non-HB LSER estimations ($c_2 + e_2E_1 + s_2S_1 + l_2L_1$. The hydrogen-bonding parameters were obtained in the second step by optimization of calculations with equation 16 against corresponding LSER calculations of the total solvation free energy (equation 4).

By using the LSER estimations as reference data, not only the parameters reported in Table 1 but also the updated molecular descriptors reported in Table S1 are influenced by the quality of these LSER estimations for the dispersion and polar contributions and for the total solvation free energy. It is recalled that the LSER estimations of the total solvation free energy are well within the corresponding experimental uncertainties [28]. In the last two columns of Table 1 are reported the average absolute deviations (AAD) between present and LSER estimations in the above two steps of minimization process. As shown in the last row of Table 1, the mean AAD for the non-HB contributions is 0.43 kJ/mol, while the mean AAD for the total solvation free energy is 0.66 kJ/mol. These mean deviations are rather near or within the experimental uncertainties of solvation free-energy measurements [28,56]. Having the electrostatic molecular descriptors for the solutes and the solvent-specific parameters for a variety of solvents, we may proceed to the discussion of the results.

Table 1. The solvent-specific parameters f_i, R_P and R_H, and the average absolute deviations (AAD) of the predicted solvation free energies of 210 common solutes (cf. Table S1) from the corresponding LSER estimations [12] in kJ/mol at 298 K. Subscript *dp* indicates solvation free energies from dispersion and polar contributions while subscript *tot* indicates total solvation free energies.

SOLVENT	f_i	$2R_P$	R_H	AAD_{dp}	AAD_{tot}
n-HEXANE	1.03	1.00		0.55	0.55
n-HEPTANE	1.03	1.00		0.48	0.48
n-OCTANE	1.02	1.00		0.46	0.46
n-NONANE	1.02	1.00		0.43	0.43
n-DECANE	1.01	1.00		0.34	0.34
n-UNDECANE	1.01	1.00		0.29	0.29
n-DODECANE	1.00	1.00		0.19	0.19
n-HEXADECANE	1.00	1.00		0.00	0.00
CYCLOHEXANE	1.03	1.00		0.37	0.37
METHYLCYCLOHEXANE	1.04	1.00		0.60	0.60
BENZENE	1.06	1.00	0.83	0.31	0.40
TOLUENE	1.03	1.00	1.00	0.30	0.36
ETHYLBENZENE	1.05	1.00	1.00	0.31	0.45
o-XYLENE	1.05	1.00	1.00	0.29	0.44
m-XYLENE	1.06	1.00	1.00	0.43	0.40
p-XYLENE	1.03	1.00	1.00	0.33	0.44
CHLOROBENZENE	1.02	1.00	1.00	0.35	0.40
1,4-DIOXANE	0.90	1.00	1.00	0.38	0.61
TETRAHYDROFURAN	1.04	1.00	1.00	0.49	0.87
DIETHYL ETHER	0.97	1.00	2.12	0.20	0.54
DIISOPROPYL ETHER	1.05	1.00	1.43	0.40	0.91
DI-n-BUTYL ETHER	1.05	1.00	1.00	0.48	1.03
METHYL ACETATE	0.92	1.00	1.00	0.48	0.71
ETHYL ACETATE	0.95	1.00	1.00	0.46	0.70
n-PROPYL ACETATE	0.94	1.00	1.00	0.64	0.80
ISOPROPYL ACETATE	0.97	1.00	1.00	0.53	0.74
n-BUTYL ACETATE	0.98	1.00	1.00	0.40	0.62
DIETHYL CARBONATE	0.96	1.00	1.00	0.45	0.62
DIMETHYL CARBONATE	0.89	1.17	1.00	0.39	0.56
TRIBUTYL PHOSPHATE	0.89	0.70	0.91	0.29	0.63
ACETONE	0.89	1.00	1.00	0.42	0.64
METHYL ETHYL KETONE	0.94	1.00	1.08	0.42	0.66
CYCLOPENTANONE	0.94	0.86	1.00	0.38	0.61
ACETOPHENONE	0.85	1.00	1.00	0.50	0.54

N,N-DIMETHYLFORMAMIDE	1.01	0.59	1.00	0.71	1.12
METHANOL	0.80	1.00	1.00	0.44	0.61
ETHANOL	0.85	1.00	1.00	0.19	0.45
1-PROPANOL	0.84	1.00	0.97	0.33	0.56
1-BUTANOL	0.87	1.00	0.88	0.28	0.63
1-PENTANOL	0.90	0.73	0.89	0.23	0.57
1-HEXANOL	0.89	0.76	0.87	0.29	0.57
1-HEPTANOL	0.91	0.71	0.81	0.22	0.61
1-OCTANOL	0.92	0.57	0.79	0.27	0.61
1-DECANOL	0.92	0.58	0.78	0.39	0.82
2-METHYL-1-PROPANOL	0.89	0.78	1.00	0.21	0.43
2-METHYL-1-BUTANOL	0.89	0.75	0.93	0.24	0.60
3-METHYL-1-BUTANOL	0.91	0.66	0.87	0.22	0.53
2-ETHYL-1-HEXANOL	0.92	0.60	0.75	0.28	0.72
ISOPROPANOL	0.86	1.00	1.00	0.21	0.51
2-METHYL-2-PROPANOL	0.89	0.83	1.00	0.21	0.55
2-BUTANOL	0.88	1.00	1.00	0.25	0.47
2-PENTANOL	0.92	0.58	1.00	0.17	0.56
2-METHYL-2-BUTANOL	0.92	0.83	1.00	0.24	0.61
4-METHYL-2-PENTANOL	0.99	0.89	0.79	0.34	0.94
CYCLOPENTANOL	0.92	0.52	0.88	0.28	0.57
BENZYL ALCOHOL	0.82	0.71	0.75	0.51	0.62
2-METHOXYETHANOL c0	0.76	1.50	0.75	0.44	0.47
2-ETHOXYETHANOL c0	0.85	1.30	0.78	0.75	0.94
2-BUTOXYETHANOL	0.89	0.92	0.72	0.27	0.41
ETHYLENE GLYCOL c0	0.58	1.00	0.81	0.78	1.08
1,2-PROPYLENE GLYCOL	0.77	0.55	0.74	0.79	0.93
DIETHYLENE GLYCOL	0.65	1.00	0.56	0.78	0.78
TRIETHYLENE GLYCOL	0.68	0.67	0.46	0.93	0.81
ACETIC ACID	0.79	0.88	0.71	0.32	0.88
ANILINE	0.91	0.90	0.90	0.76	1.10
2-PYRROLIDONE	0.80	0.69	1.00	0.71	1.28
NITROMETHANE	0.80	1.32	1.65	1.34	1.81
NITROBENZENE	0.96	0.70	2.38	0.82	0.66
ACETONITRILE	0.74	1.08	1.63	0.45	0.56
PROPIONITRILE	0.82	0.96	2.32	0.41	0.80
BUTYRONITRILE	0.85	0.96	1.89	0.55	0.74
BENZONITRILE	0.87	0.73	2.50	0.42	0.40
PYRIDINE	0.96	1.00	1.94	0.45	0.90
DIMETHYL SULFOXIDE	0.77	0.66	1.46	0.76	0.88
FORMAMIDE	0.46	0.75	0.82	1.26	1.29
PROPYLENE CARBONATE	0.72	0.88	1.00	0.58	0.76
WATER	-0.21	2.73	1.03	0.91	1.61
Overall average absolute deviation				**0.43**	**0.66**

3. Results and Discussion

Extensive calculations of solvation free energies were conducted for a variety of solutes in all solvent phases reported in Table 1. Representative examples of these calculations are reported in the Supplementary Information (SI) file. Before going to these detailed calculations, it is worth discussing the results reported in Table 2. As seen in equation 2, the self-solvation free energy is rather easily calculated for common liquid solvents at ambient conditions since the required information may be found in freely accessible compilations, such as the NIST Chemistry Webbook [60] or the DIPPR compilation [61]. Large uncertainties are of course expected in the case of solvents with very low vapor pressure. As seen in Table 2, the predictions with the present approach follow closely the corresponding LSER estimations. In nearly all cases, these calculations are in good agreement with the experimental ones [60–62]. It is worth observing, however, the two noticeable exceptions of dimethyl sulfoxide and propylene carbonate. The predictions are close to LSER estimations but both deviate significantly from the experimental data. This was rather expected since the solvent-specific parameters reported in Table 1 were obtained by using the LSER estimations as reference data.

Table 2. The predicted (Pred) self-solvation free energies of common solvents, the corresponding LSER estimations [28] and the experimental ones [60–62] in kJ/mol at 298 K.

SOLVENT	ΔG^{S}		
	Pred	***LSER***	***Exper***
n-HEXANE	15.62	16.38	16.97
n-HEPTANE	18.56	18.82	18.65
n-OCTANE	21.44	21.43	23.34
n-NONANE	24.40	24.17	25.03
n-DECANE	26.23	26.93	27.85
n-UNDECANE	29.65	29.43	30.51
n-DODECANE	32.52	32.26	33.49
n-HEXADECANE	43.20	43.20	44.55
CYCLOHEXANE	17.20	17.86	18.54
METHYLCYCLOHEXANE	19.68	20.72	19.96
BENZENE	18.88	18.99	19.07
TOLUENE	21.80	21.60	21.63
ETHYLBENZENE	23.77	23.88	24.00
o-XYLENE	24.66	24.93	24.92
m-XYLENE	24.24	24.32	25.06
p-XYLENE	24.09	24.21	24.17
CHLOROBENZENE	23.45	24.17	23.88
1,4-DIOXANE	21.16	21.30	21.54
TETRAHYDROFURAN	18.16	18.82	17.70
DIETHYL ETHER	14.10	13.90	14.41
DIISOPROPYL ETHER	15.70	16.11	16.37
DI-n-BUTYL ETHER	24.39	22.78	23.99
METHYL ACETATE	16.17	16.36	17.31
ETHYL ACETATE	17.71	17.63	18.81
n-PROPYL ACETATE	20.74	20.17	21.06
ISOPROPYL ACETATE	18.87	19.01	19.52
n-BUTYL ACETATE	22.66	18.04	23.21
DIETHYL CARBONATE	23.55	23.85	23.89
DIMETHYL CARBONATE	17.78	17.33	24.59
TRIBUTYL PHOSPHATE	44.70	44.27	
ACETONE	16.02	16.40	17.33
METHYL ETHYL KETONE	18.06	18.66	19.19
CYCLOPENTANONE	23.87	24.30	24.59
ACETOPHENONE	30.02	31.66	32.63
N,N-DIMETHYLFORMAMIDE	29.17	29.83	27.48

METHANOL	20.01	19.94	20.29
ETHANOL	20.60	20.55	21.30
1-PROPANOL	22.88	22.58	23.31
ISOPROPANOL	20.58	20.23	21.39
1-BUTANOL	24.94	24.88	25.64
2-BUTANOL	22.78	23.43	23.17
1-PENTANOL	27.54	27.63	27.20
2-PENTANOL	26.42	25.96	25.35
1-HEXANOL	29.98	30.01	29.94
1-HEPTANOL	32.05	32.43	32.14
1-OCTANOL	34.12	34.48	34.14
1-DECANOL	39.59	40.10	38.30
2-METHYL-1-PROPANOL	23.82	23.77	24.22
2-METHYL-1-BUTANOL	26.34	26.71	26.74
3-METHYL-1-BUTANOL	26.89	26.94	26.87
2-ETHYL-1-HEXANOL	33.05	33.57	32.96
2-METHYL-2-PROPANOL	20.80	20.88	20.92
2-METHYL-2-BUTANOL	24.87	24.87	23.10
4-METHYL-2-PENTANOL	27.26	27.39	25.51
CYCLOPENTANOL	27.80	27.60	26.45
BENZYL ALCOHOL	35.43	35.43	36.25
2-METHOXYETHANOL c0	23.31	24.36	24.77
2-ETHOXYETHANOL c0	27.63	27.18	26.21
2-BUTOXYETHANOL	30.13	30.76	29.76
ETHYLENE GLYCOL c0	37.15	36.96	39.21
1,2-PROPYLENE GLYCOL	35.21	35.36	37.07
DIETHYLENE GLYCOL	38.98	38.30	45.60
TRIETHYLENE GLYCOL	49.87	50.03	
ACETIC ACID	28.26	27.72	24.73
ANILINE	28.84	31.98	31.58
2-PYRROLIDONE	42.70	41.64	42.70
NITROMETHANE	21.16	22.73	22.88
NITROBENZENE	32.53	33.96	33.65
ACETONITRILE	20.29	20.36	20.60
PROPIONITRILE	19.90	20.85	21.46
BUTYRONITRILE	21.86	21.98	23.07
BENZONITRILE	29.61	30.19	31.60
PYRIDINE	23.35	22.90	23.07
DIMETHYL SULFOXIDE	38.32	38.81	32.71
FORMAMIDE	42.55	40.97	
PROPYLENE CARBONATE	31.18	31.69	44.14
WATER	27.97	27.29	26.68

Detailed calculations for the solvation free energy of 210 common solutes in ethanol solvent are reported in Table S2. Dispersion, polar and hydrogen-bonding contributions are reported as calculated by LSER [28] and by the present approach. As observed, with few exceptions, the agreement is rather good for all three separate contributions to solvation free energy. It should be recalled that the reported LSER calculations were done using equation 4 only and they are not averages from calculations with equations 4 and 5 as was done previously in the case of solvation enthalpies [22].

Table S3 reports detailed calculations for the same quantities as Table S2 but for systems in acetic acid solvent. Here again the agreement is rather good for all three separate contributions to solvation free energy. The larger overall discrepancy is observed in the case of anthracene / acetic acid system. The separate deviations of dispersion and polar contributions for this particular system are larger but of opposite sign and, thus, the combined deviation of dispersion and polar contributions is 1.47 kJ/mol. Equally large is the discrepancy of hydrogen bonding contributions. The overall discrepancy for this anthracene / acetic acid system is 4.08 kJ/mol. We could not find experimental data for this system to judge the discrepancies.

Table S4 reports similar detailed calculations but for systems in acetone solvent. A rather good agreement is observed here, as well, for all three separate contributions throughout all solute / acetone systems. The overall agreement for the anthracene / acetone system is nearly perfect. The largest overall discrepancy is observed in the case of the acetol / acetone system. Although the agreement for the separate dispersion and polar contributions is nearly perfect, the discrepancy in the case of hydrogen-bonding contributions is significant leading to an overall deviation of 2.65 kJ/mol for the acetol / acetone system. We could not find experimental data for this system either to judge the discrepancies.

Table S5 reports detailed calculations of contributions to solvation free energy for systems in ethyl acetate solvent. Separate dispersion contributions are reported as well as combined dispersion plus polar and overall (dispersion plus polar plus hydrogen bonding) contributions. Rather good agreement is observed throughout all solute / ethyl acetate systems. The largest discrepancy is observed for the indole / ethyl acetate system. The overall discrepancy for this system is 2.54 kJ/mol. The major part of this overall discrepancy is due to the deviation of the combined dispersion plus polar contributions which is equal to 1.49 kJ/mol. No experimental data were found for this system also.

Table S6 reports detailed calculations for the same quantities as Table S5 but for systems in ethylene glycol solvent. Good agreement is observed throughout all solute / ethylene glycol systems. The largest discrepancy of 2.25 kJ/mol is observed for the p-ethylphenol / ethylene glycol system. The major part of this overall discrepancy is again due to the deviation of the combined dispersion plus polar contributions which is equal to 1.98 kJ/mol and more specifically to the deviation of polar contributions which is equal to 1.54 kJ/mol. No experimental data were found for this system either.

Table S7 reports similar calculations as Tables S5 and S6 but for systems in 2-pyrrolidone solvent. Good agreement is observed for most solute / 2-pyrrolidone systems. Larger discrepancies are observed for a couple of systems here. The largest overall discrepancy of 6.60 kJ/mol is observed for the anthracene / 2-pyrrolidone system. The major part of it is due to the deviation of the combined dispersion plus polar contributions which is equal to 5.87 kJ/mol (3,37 kJ/mol due to deviation of polar contributions and 2.50 kJ/mol to that of dispersion contributions). Again, no experimental data were found for this system.

Table S8 reports similar calculations as the above last three tables but for aqueous systems. In the last column it also includes experimental data [18] for the total solvation free energy. The peculiarity of these aqueous systems is the extensive hydrophobic interactions, which often lead to positive solvation free energies. These data are difficult to correlate with just the three solvent-specific parameters reported in Table 1. The f_E coefficient of equation 16 had to be changed from the universal value of -0.2 to 1.65. What is, however, more important is the role of the constant LFER coefficient (cf. equation 4) in these aqueous systems.

As mentioned already, one central question regarding the various linear free-energy relationships, such as equations 4 or 5, is the thermodynamic basis of their very linearity, especially the linearity of the terms reflecting the hydrogen bonding contribution to solvation free-energy. This question was addressed previously [34,35] and it was shown that, in the limit of infinite dilution, this hydrogen bonding contribution, ΔG_{H12}^{S}, takes the linear form

$$-\Delta G_{H12}^{S} = c_{12}\left(\alpha_1\beta_2 + \beta_1\alpha_2\right) + f\left(\alpha_2, \beta_2\right) \tag{18}$$

The functional form of the second term on the right hand side of this equation depends not only on the strength of the self-association interaction of the solvent but also on the multiplicity of the sites involved in its hydrogen-bonding interaction. The important point is that this second term depends exclusively on the nature of the solvent and may be treated as a solvent-specific constant. The direct consequence of this is a reconsideration of the constant term in equations 4 or 5 in the case of strongly self-associated solvents: A major part of it may be due to this self-association interaction of the solvent. With this in mind, let us return to Table S8.

Indeed, the LFER constant in aqueous systems makes a relatively high unfavorable contribution of 7.3 kJ/mol to the solvation free energy of any solute, including the non-associated or inert ones like hydrocarbons. Thus, in order to correlate properly the solvation data of Table S8 we have considered that the hydrogen bonding contribution is given by equation 18, which is rewritten as:

$$-\Delta G_{H12}^{S} = 5.71 R_H \left(\alpha_1 \beta_2 + \beta_1 \alpha_2\right) - c_H \tag{19}$$

The coefficient R_H is the ratio given in Table 1, while c_H in the case of water solvent is equal to 6.4 kJ/mol. Although not equal to the corresponding LSER coefficient of 7.3 kJ/mol, it indicates that the major part of it may be attributed to hydrogen-bonding interactions and a much smaller part of it to non-HB interactions. This is, in essence, the thermodynamic basis of the hydrophobic interaction.

As observed in Table S8, the above reinterpretation of the LFER constant results in a reasonably good estimation of the solvation free energy in aqueous systems. Again, we stress the point that in the present work we have not correlated the experimental data but the corresponding LSER estimations and this was done via the two-step minimization process discussed above.

However, water is not the only solvent in Table 1 which self-associates strongly. In fact, an inspection in the LSER solvent-specific coefficients of equation 4 [28] indicates that there are solvents, like ethylene glycol or 2-pyrrolidone, for which the constant LFER coefficient makes an appreciable unfavorable contribution to solvation free energy. In analogy with hydrophobic, this contribution may be referred to as solvophobic. In most cases the use of a solvophobic constant does not improve substantially the model performance. In cases, however, like ethylene glycol or 2-pyrrolidone an appreciable improvement was obtained by treating the LFER constant as solvophobic one. Thus, the results in Tables S6 and S7 were obtained by using the solvophobic constants 4.4 and 3.5 kJ/mol, respectively. Although this is not by any means a systematic treatment of solvophobicity, it indicates that care must be exercised in handling the LFER constants of the linearity equations 4 or 5 of the LSER model. This LFER constant should be considered consisting of two parts, one unfavorable (positive) due to hydrogen-bonding contribution and one favorable due to non-HB interactions. Systematic treatment of the LSER constant in this spirit exceeds the scope of the present work and is postpone for a future one. The main point is that the present approach with three solvent-specific parameters may estimate rather well the solvation free energy in most organic solvents. Systematic study of solvophobicity will require one additional parameter but this may introduce additional insight in the model.

For completion of the presentation of the model, in Table S9 are reported the three solvent-specific parameters for the estimation of the solvation enthalpies in a number of common solvents. It should be recalled that the reference data in this case were the averages of the corresponding LSER estimations by the analogous two equations 4 and 5 and the solvation enthalpy was given by the following equation [22]:

$$-\Delta H_{12}^{S} / 5.71 = f_E E_1 + f_v V_1^{1.07} + \left\{ R_P \left(\pi_{a1}\pi_{b2} + \pi_{b1}\pi_{a2}\right) + R_H \left(\alpha_1 \beta_2 + \beta_1 \alpha_2\right) \right\} \tag{20}$$

V_1 being the McGowan volume of the solute. The universal value of the f_E coefficient was 1.93 in that case of solvation enthalpy [22]. It is also recalled (cf. equation 3) that the self-solvation enthalpy is equal to the heat of vaporization of the liquid solvent. Thus, in Table S9 a comparison is also made of the predicted self-solvation enthalpies with the corresponding average LSER estimations [20,21] and the corresponding experimental vaporization enthalpies [60,61]. In the last column of Table S9 is reported the average absolute deviation between predicted and average LSER estimation of the total solvation enthalpy of 210 solutes in common solvents. Here again we should stress the point that the model has not correlated experimental data but the solvent-specific parameters in Table S9 were obtained by the above two-step minimization process using the corresponding average LSER estimations as reference data. In the first step, the estimation of dispersion plus polar contributions was made. Thus, in Table S10 are compared the non-HB contributions to self-solvation enthalpy calculated by the present approach and the two alternative LSER equations (analogous to equations 4 and 5). In the first two columns are compared the average absolute deviation $(AAD)_{pred}$ of the calculated dispersion (D) and polar (P) contributions to self-solvation enthalpies of 210 solutes in common solvents from the corresponding average LSER estimations [20,21], and the corresponding average absolute deviation between the two alternative LSER estimations $(AAD)_{LSER}$. The overall average $(AAD)_{pred}$ is 1.06 kJ/mol while the corresponding overall average $(AAD)_{LSER}$ is 2.09 kJ/mol. This deviation between the two alternative LSER estimations is larger than the overall average $(AAD)_{tot}$ which is 1.97 kJ/mol as shown in the last row of Table S9.

Table S10 consists of two parts. In the first part, the above estimations are also compared with the experimental heats of vaporization [60,61]. In self-associated solvents there is also a hydrogen-bonding contribution to solvation enthalpy. Thus, in the second part of the Table, the above estimations are compared with the corresponding estimation from Hansen solubility parameters(HSP) [62] given by the equation

$$\Delta E_{dp}^{coh} = V_m \left(\delta_d^2 + \delta_p^2 \right) \cong -\Delta H_{dp}^S \tag{21}$$

V_m is the molar volume of the solvent and δ_d and δ_p are the dispersion and polar HSPs, respectively, and ΔE_{dp}^{coh} is the cohesive energy contribution [22,62]. This indicates that the HSP and LSER models may exchange information. This exchange should be exercised with caution, as discussed previously [22], since HSPs give the cohesive energy contribution ΔE_{dp}^{coh}, which is not quite identical to the corresponding contributions to solvation enthalpy. In order to better understand this difference, it is recalled that the partial solvation parameters (PSP) [22] are defined either on the basis of solvation enthalpies (E-PSP) or on the basis of solvation free energy (G-PSP). The E-PSPs are defined by the following equations [22]:

$$\begin{aligned} \varepsilon_d^2 &= \frac{-\Delta H_d^S}{V_m} \qquad dispersion \quad E-PSP \\ \varepsilon_p^2 &= \frac{-\Delta H_p^S}{V_m} \qquad polar \quad E-PSP \\ \varepsilon_h^2 &= \frac{-\Delta H_h^S}{V_m} \qquad hydrogen-bonding \quad E-PSP \end{aligned} \tag{22}$$

$$\varepsilon^2 = \varepsilon_d^2 + \varepsilon_p^2 + \varepsilon_h^2 = \frac{\Delta H_{vap}}{V_m} \qquad total \quad E-PSP \tag{23}$$

Table S11 compares HSPs and the corresponding E-PSPs.

Similarly, the G-PSPs are defined by the following equations:

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$$\begin{aligned} \gamma_d^2 &= \frac{-\Delta G_d^S}{V_m} \qquad dispersion \quad G-PSP \\ \gamma_p^2 &= \frac{-\Delta G_p^S}{V_m} \qquad polar \quad G-PSP \\ \gamma_h^2 &= \frac{-\Delta G_h^S}{V_m} \qquad hydrogen-bonding \quad G-PSP \end{aligned} \tag{24}$$

$$\gamma^2 = \gamma_d^2 + \gamma_p^2 + \gamma_h^2 = \frac{-\Delta G^S}{V_m} = \frac{RT}{V_m}\ln\frac{RT}{\varphi^0 P^0 V_m} \qquad total \quad G-PSP \tag{25}$$

and

$$\varepsilon^2 - \gamma^2 = -\frac{T\Delta S^S}{V_m} \tag{26}$$

It is recalled that, for liquid solvents, the Hansen solubility parameters satisfy the following equation [:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 = \frac{\Delta H_{vap} - RT}{V_m} \tag{27}$$

Thus, the HSPs are closer to E-PSPs rather than to G-PSPs. In Table S11 are compared the HSPs and E-PSPs for common solvents. In Table S12 are reported the PSPs based on solvation free energies (G-PSP) of common solvents.

An attempt was made previously [63–67] to give some theoretical character and facilitate the calculation of HSPs over a range of external conditions. The advantage of PSPs is their clear thermodynamic definition and direct connection to solvation enthalpies and free-energies, as well as, to familiar or easily measurable thermodynamic properties. This augments significantly their range of applications and may facilitate the safe exchange of information between various QSPR-type models, polarity scales or databases. This, in turn, may be particularly useful in the development of molecular thermodynamic models for a broader range of applications well beyond solvation phenomena.

Analogous comments apply to the popular MOSCED (modified separation of cohesive energy density) model [68–70]. In contrast to what its name implies, this model is closer to G-PSP rather than to HSP or to E-PSP. MOSCED is focusing on $\gamma_{1/2}^{\infty}$, the activity coefficient at infinite dilution but, as shows equation 1, this is directly related to the solvation free energy and not to cohesion energy.(As shown in Tables S11 and S12, E-PSP of a solvent differ significantly from G-PSP of the same solvent). The pure solvent MOSCED parameters, then, should be closely related to solvation free energy PSPs or G-PSPs. This is essential for the reliable exchange of information between LSER and MOSCED and analogous models and databases in the literature.

It is essential to stress the point that the scope of this series of works is not to diminish in any way Abraham's LSER model but rather to enhance its predictive capacity for solvation quantities and related properties. In this sense, the present work complements the related efforts in the literature [29–33]. As discussed above, "complex" solvents like the strongly self-associated ones may require more than three solvent-specific parameters for the adequate estimation of solvation quantities. This may indicate that the original Abraham's LSER model still remains very useful for solvation calculations. In this spirit, it is hoped that the above developments will stir a broader interest and enhance collaborations in the literature.

4. Conclusions

An integral approach has been presented in this work for the estimation of solvation free energy by using four new molecular descriptors for the electrostatic interactions. These new descriptors are heavily based on the σ-profiles of molecular surface charge distributions obtained from rather cheap quantum chemical calculations. The very same molecular descriptors are used for both the solvation enthalpy and the solvation free energy of over 200 solutes in a variety of common solvents. One to three solvent-specific parameters are needed for the prediction of the solvation quantities, depending on the polar character of the solvent in the overwhelming majority of cases. This may be proved a significant advantage over Abraham's LSER model, which requires twice as many solvent specific parameters. Water is a special case and the hydrophobicity has been given a thermodynamic basis by using a thermodynamically consistent expression for the hydrogen bonding contribution to solvation free energy at infinite dilution. Analogous basis was given to the solvophobicity in strongly self-associated solvents. Solvophobicity introduces an additional solvent-specific parameter. The contributions to solvation quantities were split into dispersion, polar and hydrogen-bonding ones. For pure solvents, these contributions were translated into enthalpy – based and free energy – based partial solvation parameters (PSP) and their relation to the analogous and widely used partial or Hansen solubility parameters (HSP) and to MOSCED parameters was discussed. The clear definition and the comprehensive character of these PSPs may be proven particularly useful not only for the safe exchange of information between various QSPR-type models and databases in the literature but also for providing essential information to molecular thermodynamic model developers.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Supplementary Information File SI: The SI file consists of 12 Tables. An updated list of the new molecular descriptors for a variety of common solutes is reported in Table S1. Tables S2 to S8 report detailed calculations of the contributions to solvation free energy in representative solvents. Table S9 reports the new solvent-specific parameters for the prediction of solvation enthalpy in common solvents. Table S10 compares predicted solvation enthalpies with corresponding LSER estimations. Table S11 reports solvation enthalpy-based E-PSPs and compares them with corresponding HSPs. Table S12 reports the new solvation free-energy-based G-PSPs for a variety of common solvents.

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