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PAPER

Redefining solubility parameters: the partial solvation parameters

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The present work reconsiders a classical and universally accepted concept of physical chemistry, the solubility parameter. Based on the insight derived from modern quantum chemical calculations, a new definition of solubility parameter is proposed, which overcomes some of the inherent restrictions of the original definition and expands its range of applications. The original single solubility parameter is replaced by four partial solvation parameters reflecting the dispersion, the polar, the acidic and the basic character of the chemical compounds as expressed either in their pure state or in mixtures. Simple rules are adopted for the definition and calculation of these four parameters and their values are tabulated for a variety of common substances. In contrast, however, to the well known Hansen solubility parameters, their design and evaluation does not rely exclusively on the basic rule of “similarity matching” for solubility but it makes also use of the other basic rule of compatibility, namely, the rule of “complementarity matching”. This complementarity matching becomes particularly operational with the sound definition of the acidic and basic components of the solvation parameter based on the third σ -moments of the screening charge distributions of the quantum mechanics-based COSMO-RS theory. The new definitions are made in a simple and straightforward manner, thus, preserving the strength and appeal of solubility parameter stemming from its simplicity. The new predictive method has been applied to a variety of solubility data for systems of pharmaceuticals and polymers. The results from quantum mechanics calculations are critically compared with the results from Abraham's acid/base descriptors.

1. Introduction

The unprecedented ease of performing *ab initio*, quantum-chemical, and molecular simulations, today, has led to a profound change in the face and character of modern chemical thermodynamics turning it, once again, into a most exciting and attractive field in research and academia. Cornerstones of the lofty thermodynamic edifice, that still “inspire solemnity and awe”,¹ are looked upon with the new insights and modern perspectives in an effort to further enhance their capacity and strength, and expand the range of their applications. This is particularly true when thermodynamics is envisioned and used as a secure way and tool for the rational design of new processes and new products.

Apart from the stringent process and product quality specifications, the production of chemicals, such as pharmaceuticals, cosmetics, coatings, and foodstuffs often involves highly non-ideal multicomponent mixtures. In this regard, there is very much interest today in the development of reliable methods for the prediction of key physicochemical properties

of processed or designed materials including their miscibility with other substances, their interaction with their environment, and their effect on human and animal health. Numerous multivariate linear or non-linear quantitative structure–property or structure–activity relationships (QSPR/QSAR) and related methodologies have been developed and are currently used.^{2,3} In specific fields, such as in pharmaceutical and biological sciences, today's QSPR/QSAR methods have gone a long way and are advanced to high levels of specialization, leading to cross-terms fragment descriptors and to modern fragnomics.⁴ In the field of chemical and related sciences much emphasis is given to advancing various basic categories of predictive methods, such as the functional group-contribution techniques,^{5,6} the linear free energy relationships or the linear solvation energy relationships (QSPR/LFER or LSER),^{2,3,7} or the neural network algorithms.^{8,9} The character of the molecular descriptors used in these methods varies from purely empirical to computationally derived and to purely theoretical one.

One relatively simple and of the most widely used approaches is through the calculation of solubility parameters that reflect the contributions to the cohesion of materials. The cohesive energy density (ced) of a liquid was originally defined by Hildebrand and Scott¹⁰ as the energy of vaporization per unit

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volume and reflects the strength of attractive forces holding the molecules together. The solubility parameter, δ , is, simply, the square root of $c\epsilon d$. The conceptual simplicity of the solubility parameter makes it most attractive in industry and in academia. In spite of its moderate success, it remains today one of the key parameters for selecting solvents in industry, for predicting polymer compatibility, chemical resistance and permeation rates, for characterizing surfaces, and for rationally designing new products and processes.^{10–16} An excellent historical account of the developments in solubility parameter, until recently, may be found in ref. 14.

The central principle behind the use of δ is the old classical rule of solubility, “like dissolves like”. This rule can, indeed, be a good guide in the selection of an appropriate solvent for a given solute, as long as we can also define with sufficient precision the degree of likeness in the solute–solvent pair. An important step, in this regard, was taken by Hansen with the division of δ into its partial components or Hansen solubility parameters (HSP),^{11,14} δ_d , δ_p , and δ_{hb} , for the dispersion, the polar, and the hydrogen-bonding contribution, respectively. With this division, the “similarity matching” rule would imply that liquids with similar δ_d , δ_p , and δ_{hb} are very likely to be miscible. Indeed, the division of δ into its HSP components has very much improved its success in solvent selection and in related applications.^{13,14}

However, a solute does not interact with a solvent in the same way it interacts with itself in its pure state. Because of this, the “similarity matching” rule is not always successful and it is now recognized that the disregard of the other principle of compatibility, namely, the “complementarity matching” of properties is contributing to this failure.^{17–19} With this in mind, the hydrogen bonding component, δ_{hb} , has been proposed to be further subdivided into an acidic component, δ_a , and a basic component, δ_b , in order to account for the Lewis-acid and Lewis-base character of the substance.^{18,19} These attempts have their analogues in the widely used multivariate LFER/LSER methods with their theoretical molecular descriptors, where the hydrogen-bonding scales are also divided into acidity and basicity scales.^{7,20–25} The sources of experimental information for the construction of these latter scales include the enthalpy of hydrogen-bond formation^{20,25} solvatochromic studies,^{21–24} or NMR shifts.⁷

In the case of expanded solubility parameters, Karger *et al.*^{18,26} have used the corresponding acidity and basicity scales of Kamlet *et al.*^{22–24} and developed simple linear relations for δ_a and δ_b , respectively. The adopted key equation for their relation to the Hansen hydrogen-bonding δ_{hb} parameter is the following

$$2\delta_a\delta_b = \delta_{hb}^2 \quad (1)$$

This equation was also adopted invariably in later studies.^{19,27,28} A major drawback of eqn (1) arises when one of the δ_a and δ_b is zero or very small, forcing the other to be intolerably high. As a consequence, eqn (1) cannot apply to the very common case where a compound has only acidic or only basic character, namely, when either δ_a or δ_b is zero. A similar problem was faced in the construction of hydrogen bonding scales in the LSER approach.⁷

Apart from this drawback, the expanded Hansen solubility parameter approach was more successful over the plain

Hansen approach.²⁹ Yet, the vast majority of users prefer the plain Hansen approach because there are no extensive databases available for the separate δ_a and δ_b parameters, neither are established robust and simple methods for their unequivocal determination. On the contrary, over the years, the plain Hansen partial solubility parameters were determined for a very large number of substances and led to critical compilations available in the literature.^{12,14,30} This type of compilations is a most valuable source of information for the nature of the substances and their intermolecular interactions with other substances, especially, since the variation of HSPs with external conditions may be estimated and they may easily be integrated in modern process simulators for the rational design of new products and processes.³¹ Recently,³² we have also presented a robust and reliable new methodology for the calculation of group contributions for HSPs based on the Conjugation theory^{33,34} and, more recently³⁵ we provided with further improved updated and extensive tables with the first- and second-order group contributions to HSPs.

In the above recent work³⁵ we have proposed a new scheme for splitting the hydrogen bonding solubility parameter, δ_{hb} , into its acidic and basic components, δ_a and δ_b , respectively, leaving intact the HSPs for dispersion and polarity, δ_d and δ_p , respectively, and preserving their adherence to cohesive energy density, or

$$\text{ced} = \delta_d^2 + \delta_p^2 + \delta_{hb}^2 = \delta_d^2 + \delta_p^2 + \delta_a^2 + \delta_b^2 = \delta_{\text{total}}^2 \quad (2)$$

This splitting was based on the third moments of screening charge density profiles of the COSMO-RS theory³⁶ for their hydrogen bonding acceptor and donor parts. The predictive conductor-like screening model for real solvents, COSMO-RS, combines in an eloquent manner the strength of quantum chemistry with concepts of dielectric continuum models and group–surface interactions leading to a powerful tool of modern chemical thermodynamics. Thus, Ikeda *et al.*³⁷ could satisfactorily predict, with COSMO-RS, the solubility of a number of drugs in polar solvents. In another recent work³⁸ we have turned the COSMO-RS model into an equation-of-state model increasing, thus, substantially the range of external conditions in which it can be applied. However, the implementation and performance of this kind of relatively sophisticated calculations are not highly favored methods for the majority of scientists and engineers. It is worth pointing out here that the COSMO-RS theory was also successfully transformed into an LSER model³⁶ along the lines of Abraham's model.⁷ Abraham's acid/base descriptors⁷ were recently used to split predetermined δ_{hb} parameters into their acidic and basic components.³⁰ It is also worth mentioning that in a very recent interesting work⁹ a multivariate non-linear method based on an artificial neural network technique has used the COSMO-RS σ -moments or COSMOments³⁶ as molecular descriptors for the prediction of HSPs but their success was inferior to the above group-contribution method.³²

In the present work, the concept of solubility parameter is reconsidered and the restrictions imposed by its defining equation (2) are re-examined. This reconsideration will lead to the division of the chemical compounds into two major classes depending on whether they meet eqn (2) or not. It will

also lead to an equation analogous to eqn (2) but without the restrictions of it. The central objective is to define molecular descriptors or parameters analogous to HSPs, which can be calculated independently in a simple and straightforward manner and which will properly accommodate both of the above-mentioned solubility criteria, namely, the “similarity matching” and the “complementarity matching” ones. In other words, the focus will be on the solvation rather than on the cohesion of matter, thus, freeing the new parameters from the restrictions of eqn (2). In fact, the calculation of the four new molecular descriptors does not require the availability of any specific experimental information for the various compounds that may interact with polar or strong specific interactions. The COSMO-RS theory³⁶ is the key source for these developments. An alternative route for obtaining the acidic and basic parameters from the corresponding Abraham's descriptors⁷ is presented in the Appendix and the results are compared with those obtained from COSMOments.³⁶ The new 4-parameter method is compared, subsequently, with the 3-parameter HSP approach¹⁴ against a variety of experimental solubility data for systems of practical interest. A discussion follows on the relation of this predictive methodology with the classical QSPR/LSER methodologies.^{2,3,7}

2. Definition of partial solvation parameters

In this section we will define four new molecular descriptors along two principal lines: first, we will retain as much as possible the analogy with the four solubility parameters appearing in eqn (2). Second, the definition will be done in a manner which will permit their calculation without requiring, in principle, any experimental information, that is, it can be made even for molecules not yet synthesized. The former furnishes a more or less clear physical meaning to the descriptors while the latter augments the potential of the new method for the design of new molecules and for its implementation in modern process simulators. Of course, our main concern is to propose a simple to use method and avoid unnecessary sophistications and complexities. The above requirements are ably met by adopting the quantum-mechanics based

COSMO-RS theory³⁶ as the principal source of needed information. This information is available, today, in tabulated form for thousands of compounds in extensive databases either commercial³⁹ or free of charge.⁴⁰ They can be, also, rather easily calculated *via* widely available quantum chemical calculation software suites such as the Dmol³ density functional theory (DFT) module embodied in the Materials Studio suite of Accelrys[®] or the TURBOMOLE suite.⁴¹

Since our focus is on molecular solvation, the first quantity that we will need is the cavity volume of the molecule. A measure of it is provided with the cosmo volume, V_{cosm} , of the COSMO-RS theory.³⁶ The second needed quantity is a measure of the polar character of the molecule. This is provided by the dipole moment, t , of the theory and is also provided by the above COSMO databases or computation suites.

A most important feature of the COSMO-RS theory is the evaluation of the sigma (σ) profiles for the charge density distribution on the surface of the molecules, which enable the calculation of molecular interactions even in complex and highly non-ideal multicomponent mixtures. These profiles are unique properties of pure compounds and can be calculated or found in the above-mentioned databases.^{39–41} The distribution of molecular surface charges, as provided by the σ -profiles (Fig. 1 and 2) or by the corresponding 3-D coloured graphs^{36,39} give, in a pictorial manner, valuable information on the capacity of the molecule to interact with dispersion, polar, or hydrogen bonding forces. A cutoff of $\pm 0.01 \text{ e nm}^{-2}$ is typically set³⁶ beyond which the surface charge may participate in hydrogen bond formation if the complementary (opposite) charge is available in the interacting system. Thus, from the σ -profile of a compound, one may evaluate the acidic and/or basic character of the compound and foresee the capacity and strength of its hydrogen bonding interactions. In Fig. 1 are shown the σ -profiles of acetone and chloroform. As observed, acetone has only basic character as depicted by the pronounced peak in the right hand side of the profile (the σ -charges, as screening charges, are the opposite of the real molecular surface charges), while chloroform has only acidic character as depicted by the tail in the left-hand side of its σ -profile. Similarly, from the

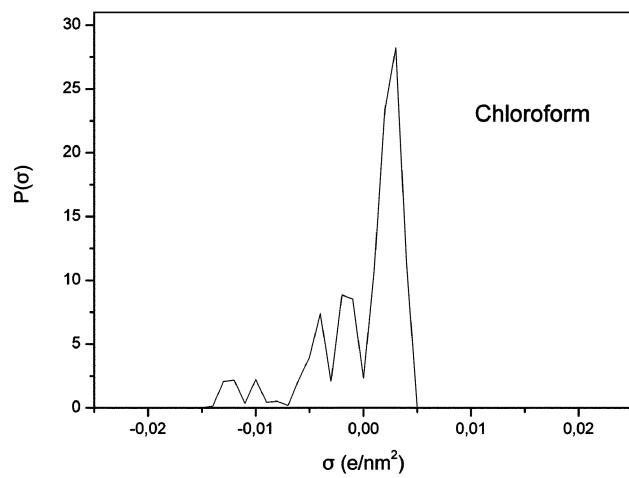
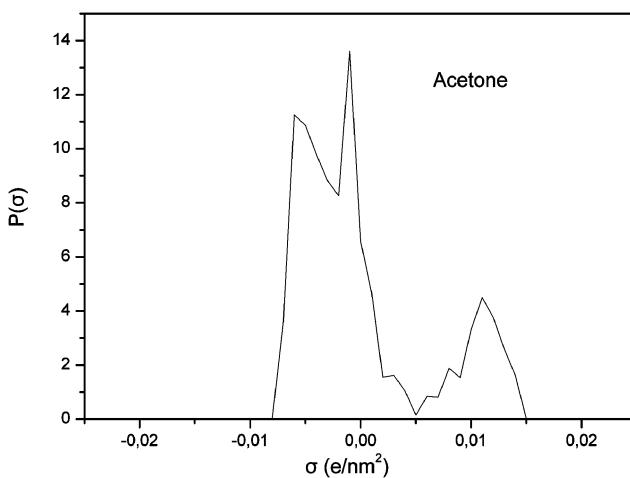


Fig. 1 The sigma profiles of acetone and chloroform clearly indicating that the former has basic (proton acceptor) character, while the latter has acidic (proton donor) character.

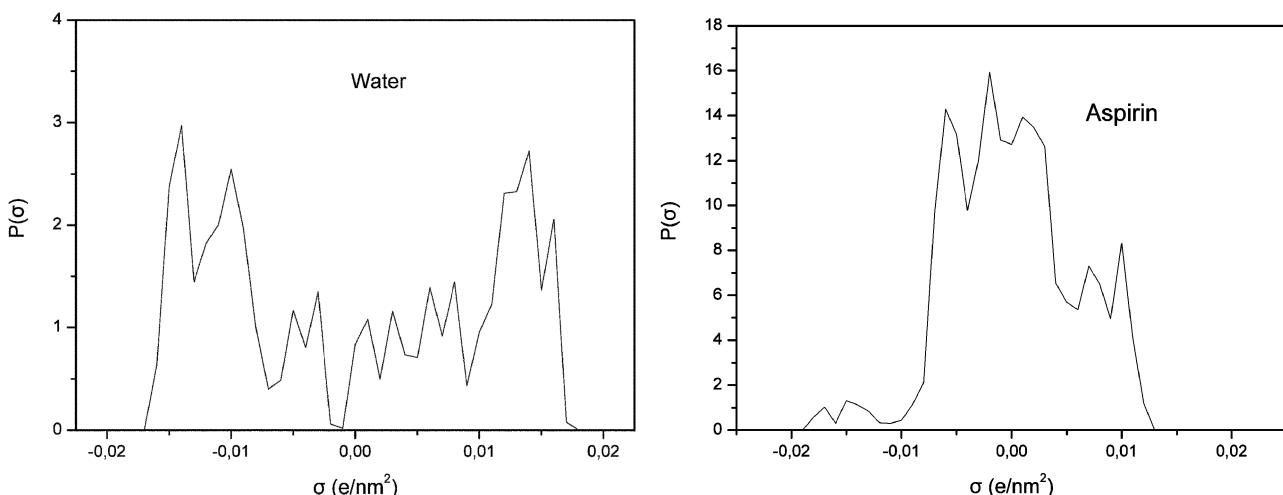


Fig. 2 The sigma profiles of water and aspirin clearly indicating the predominance of hydrogen bonding interactions in water. Both compounds are exhibiting acidic as well as basic character.

σ -profiles in Fig. 2, one may observe that water has both basic and acidic character and a near symmetric screening charge distribution. Aspirin (acetyl salicylic acid), on the other hand, does have the pronounced acidic tail, but it also has a basic character. The predominance of hydrogen-bonding interactions is clear in water while in aspirin the dispersion and polar forces weigh much more in its intermolecular interactions.

From the σ -profiles, being continuous distributions, one may obtain the various moments of the distributions. These moments are measures of key features of the surface charge distributions, such as the total charge, the electrostatic interaction energy, or the kind of skewness of the distribution. These σ -moments were proved very good linear descriptors in an LSER model implementation.³⁶ Of interest to us here are the third moments of screening (polarization) charge density profiles for their hydrogen bonding acceptor and donor parts, HB_acc3 and HB_don3 , respectively.^{9,36} This information will be used for obtaining our molecular descriptors for the strong acidic and basic character of the various compounds.

Having available the above information on V_{cosm} , t , HB_acc3 and HB_don3 , we may now proceed to the definition of our molecular descriptors. As already mentioned, in this definition we will closely adhere to the physical meaning of the four partial solubility parameters of eqn (2). Since the focus is on molecular solvation, our four molecular descriptors will be called *Partial Solvation Parameters* (PSPs) in order to distinguish them from the corresponding solubility parameters. As we will see below, quantum mechanical evidence will force us to abandon eqn (2) as often being too restrictive that solubility parameters, especially δ_{hb} , lose their physical meaning. The new partial solvation parameters are precisely introduced in an attempt to preserve this physical meaning.

The first parameter to be defined is s_d , the partial solvation parameter for the dispersion intermolecular forces exhibited by the molecule either in its pure state (self-solvation) or in solution. s_d is entirely analogous to δ_d and identical to it for hydrocarbons. Values of δ_d s for hydrocarbons may be

obtained from available compilations^{12,14,30,42} or may easily be calculated from reliable group-contribution schemes.^{30,32} For all other non-hydrocarbon molecules, the calculation of s_d is based on the corresponding value of their *homomorph* hydrocarbons. The homomorph with its various definitions is an old concept⁴³ but still very useful. The homomorph hydrocarbon is considered here to retain the structure and types of bonds of the non-hydrocarbon molecule and to simulate as close as possible its volume or solvation cavity. For this purpose, the atoms of O, N, S, F and P of the compound of interest are replaced by carbon atoms or CH or CH_2 or CH_3 groups as valences and bonds require. Bulkier atoms, such as the halogens, are replaced by more than one CH_x groups. Thus, Cl is replaced by an ethyl group while I by a propyl group. On the basis of the dispersion solubility parameter of its homomorph, $\delta_{d,hom}$, the corresponding partial solvation parameter for dispersion, s_d , of the non-hydrocarbon molecule is defined by the following equation:

$$s_d = \delta_{d,hom} \sqrt{\frac{V_{cosm,hom}}{V_{cosm}}} \quad (3)$$

Values of the partial solvation parameter, s_d , for some common solvents and pharmaceuticals are reported in Table 1 along with the dispersion solubility parameter and the cosmo volume, $\delta_{d,hom}$ and $V_{cosm,hom}$, respectively, of their homomorphs. For comparison purposes, in Table 1 are also reported the corresponding δ_d parameters of the non-hydrocarbon molecule. As observed, the two parameters, s_d and δ_d , are comparable in most cases. We may then consider s_d as been equal to δ_d of its hydrocarbon homomorph brought at similar cavity volumes. Table 1 includes numerous examples of implementation of the concept of a homomorph molecule. Alternatively, one might use molar volumes instead of cosmo volumes in eqn (3). However, the molar volumes are not always known and, of course, they cannot be measured for not synthesized molecules.

As shown in Table 1, the replacement of bulkier atoms by CH_x groups needs some refinement. Better results could have

Table 1 The dispersion component of solvation parameter, s_d , of common compounds based on their homomorphs

Compound	$V_{\text{cosm}}^{39}/\text{nm}^3$	δ_d Hansen ¹⁴ or SP ^a	$s_d/\text{MPa}^{1/2}$	Homomorph	$V_{\text{cosm homom}}/\text{nm}^3$	δ_d homom
Formaldehyde	0.0433	12.80	13.87	Ethylene	0.0538	12.44
Acetaldehyde	0.0643	14.70	14.20	Propylene	0.075	13.15
Acrolein	0.0804	15.00	15.80	1,3-Butadiene	0.0916	14.80
1-Butanal	0.1074	14.70	14.62	1-Pentene	0.1188	13.90
1-Pentanal	0.1294	15.93	15.33	1-Hexene	0.1408	14.70
1-Hexanal	0.1512	15.80	15.57	1-Heptene	0.1629	15.00
1-Heptanal	0.1734	15.95	15.78	1-Octene	0.1845	15.30
1-Octanal	0.195	15.96	15.30	1-Nonene	0.2063	14.87
1-Nonanal	0.2172	15.97	16.20	1-Decene	0.2284	15.80
1-Decanal	0.2398	15.98	15.24	1-Undecene	0.2512	14.89
1-Undecanal	0.2618	15.99	15.22	1-Dodecene	0.2732	14.90
1-Dodecanal	0.2839	15.99	15.20	1-Tridecene	0.2953	14.91
1-Tridecanal	0.3057	16.00	15.20	1-Tetradecene	0.3173	14.92
Ketene	0.0587	15.40	15.26	Propadiene	0.0696	14.01
Acetone	0.0863	15.50	15.40	Isobutene	0.0974	14.50
Methyl ethyl ketone	0.107	16.00	14.96	2-Methyl-1-butene	0.1187	14.20
2-Pentanone	0.1287	16.00	15.08	2-Methyl-1-pentene	0.1395	14.48
3-Pentanone	0.1285	15.80	15.42	2-Ethyl-1-butene	0.1376	14.90
Cyclohexanone	0.1329	17.80	17.00	Methylcyclohexane	0.1501	16.00
2-Hexanone	0.1508	15.30	15.06	2-Methyl-1-hexene	0.1629	14.49
3-Hexanone	0.1498	15.98	14.86	2-Ethyl-1-pentene	0.1631	14.24
2-Heptanone	0.1726	16.20	15.02	2-Methyl-1-heptene	0.1851	14.50
3-Heptanone	0.1717	16.20	14.78	2-Ethyl-1-hexene	0.1848	14.25
Methanol	0.0484	15.10	13.64	Ethane	0.0586	12.40
Ethanol	0.07	15.80	14.06	Propane	0.0806	13.10
1-Propanol	0.0918	16.00	14.48	<i>n</i> -Butane	0.1025	13.70
1-Butanol	0.1139	16.00	15.05	<i>n</i> -Pentane	0.1244	14.40
1-Pentanol	0.1355	15.90	15.45	<i>n</i> -Hexane	0.1457	14.90
1-Hexanol	0.1578	15.90	15.77	<i>n</i> -Heptane	0.1676	15.30
1-Heptanol	0.1794	16.00	15.83	<i>n</i> -Octane	0.1895	15.40
1-Octanol	0.2014	16.00	15.98	<i>n</i> -Nonane	0.2113	15.60
1-Nonanol	0.2236	15.92	16.04	<i>n</i> -Decane	0.2333	15.70
1-Decanol	0.2449	16.00	16.26	<i>n</i> -Undecane	0.256	15.90
1-Undecanol	0.2675	15.94	16.17	<i>n</i> -Dodecane	0.2768	15.90
1-Dodecanol	0.2888	16.00	16.40	<i>n</i> -Tridecane	0.2995	16.10
1-Tridecanol	0.3114	15.96	16.33	<i>n</i> -Tetradecane	0.3204	16.10
1-Tetradecanol	0.3334	15.97	16.44	<i>n</i> -Pentadecane	0.3433	16.20
1-Pentadecanol	0.3553	15.97	16.45	<i>n</i> -Hexadecane	0.3664	16.20
1-Hexadecanol	0.3773	15.98	16.31	<i>n</i> -Heptadecane	0.387	16.10
1-Eicosanol	0.465	16.02	16.37	<i>n</i> -Heneicosane	0.4746	16.20
Allyl alcohol	0.0863	16.20	14.47	1-Butene	0.0969	13.66
Isopropanol	0.0921	15.80	15.75	Isobutane	0.1036	14.85
2-Butanol	0.1138	15.80	14.31	Isopentane	0.1241	13.70
2-Methyl-1-propanol	0.1141	15.10	14.29	Isopentane	0.1241	13.70
2-Methyl-2-propanol	0.1152	15.20	15.20	Neopentane	0.1258	14.54
2,2-Dimethyl-1-propanol	0.1358	15.27	14.00	Neopentane	0.1258	14.54
3-Methyl-1-butanol	0.1359	15.80	15.31	3-Methylpentane	0.1451	14.82
2-Pentanol	0.1354	15.60	15.47	2-Methylpentane	0.1465	14.87
3-Pentanol	0.1345	15.66	15.39	3-Methylpentane	0.1451	14.82
2-Ethyl-1-butanol	0.1567	15.80	15.31	3-Ethylpentane	0.1673	14.82
2-Hexanol	0.1576	15.67	15.36	2-Methylhexane	0.168	14.88
2-Methyl-1-pentanol	0.1575	15.54	15.28	3-Methylhexane	0.1674	14.82
4-Methyl-2-pentanol	0.1581	15.40	15.06	2,4-Dimethylpentane	0.1687	14.58
2-Heptanol	0.1795	15.68	15.34	2-Methylheptane	0.1905	14.89
5-Methyl-1-hexanol	0.18	15.61	15.32	2-Methylheptane	0.1905	14.89
2-Ethyl-1-hexanol	0.2023	15.90	15.14	3-Ethylheptane	0.2105	14.84
2-Octanol	0.2016	16.10	15.26	2-Methyloctane	0.2115	14.90
2-Nonanol	0.2231	15.70	15.28	2-Methylnonane	0.2343	14.91
8-Methyl-1-nonanol	0.2462	15.63	14.45	3-Methylnonane	0.233	14.85
Cyclohexanol	0.1391	17.40	16.62	Methylcyclohexane	0.1501	16.00
1-Methylcyclohexanol	0.1619	17.19	16.11	1,1-Dimethylcyclohexane	0.171	15.67
cis-2-Methylcyclohexanol	0.1604	17.08	16.80	cis-1,2-Dimethylcyclohexane	0.1714	16.25
trans-2-Methylcyclohexanol	0.1611	17.08	16.31	trans-1,2-Dimethylcyclohexane	0.1721	15.78
cis-3-Methylcyclohexanol	0.1613	17.08	16.21	cis-1,3-Dimethylcyclohexane	0.1732	15.64
trans-3-Methylcyclohexanol	0.1625	17.08	16.52	trans-1,3-Dimethylcyclohexane	0.1724	16.04
cis-4-Methylcyclohexanol	0.1626	17.08	16.50	cis-1,4-Dimethylcyclohexane	0.1734	15.98
trans-4-Methylcyclohexanol	0.1615	17.08	16.06	trans-1,4-Dimethylcyclohexane	0.1734	15.50
Phenol	0.1207	18.00	18.81	Toluene	0.1318	18.00
Benzyl alcohol	0.1429	18.40	18.47	Ethylbenzene	0.1539	17.80
m-Cresol	0.1422	18.00	18.90	<i>m</i> -Xylene	0.1533	18.20
<i>o</i> -Cresol	0.1422	15.93	18.43	<i>o</i> -Xylene	0.1524	17.80

Table 1 (continued)

Compound	$V_{\text{cosm}}^{39}/\text{nm}^3$	δ_d Hansen ¹⁴ or SP ^a	$s_d/\text{MPa}^{1/2}$	Homomorph	V_{cosm} homom/ nm^3	δ_d homom
2-Phenylethanol	0.1655	18.42	18.26	<i>n</i> -Propylbenzene	0.1762	17.70
2,4-Xylenol	0.1646	18.43	18.78	1,2,4-Trimethylbenzene	0.1747	18.23
1-Phenyl-1-propanol	0.1864	17.15	17.93	<i>n</i> -Butylbenzene	0.1980	17.40
Ethylene glycol	0.0805	16.79	15.46	<i>n</i> -Butane	0.1025	13.70
1,2-Propylene glycol	0.1031	16.80	15.03	Isopentane	0.1241	13.70
Glycerol	0.1118	17.40	16.88	3-Methylpentane	0.1451	14.82
1,2-Butanediol	0.1242	16.45	16.01	3-Methylpentane	0.1451	14.82
1,4-Butanediol	0.1216	16.60	16.31	<i>n</i> -Hexane	0.1457	14.90
1,5-Pantanediol	0.1472	16.61	16.33	<i>n</i> -Heptane	0.1676	15.30
1,6-Hexanediol	0.1689	16.62	16.31	<i>n</i> -Octane	0.1895	15.40
Triethylene glycol	0.1911	16.00	17.35	<i>n</i> -Decane	0.2333	15.70
Formic acid	0.0534	14.60	15.58	Propylene	0.075	13.15
Acetic acid	0.0743	14.50	16.60	Isobutene	0.0974	14.50
Propionic acid	0.0954	14.70	15.84	2-Methyl-1-butene	0.1187	14.20
<i>n</i> -Butyric acid	0.1175	15.70	15.78	2-Methyl-1-pentene	0.1395	14.48
<i>n</i> -Pentanoic acid	0.1398	15.00	15.64	2-Methyl-1-hexene	0.1629	14.49
<i>n</i> -Hexanoic acid	0.1614	16.30	15.53	2-Methyl-1-heptene	0.1851	14.50
<i>n</i> -Heptanoic acid	0.1833	15.76	16.00	2-Methyloctane	0.2115	14.90
<i>n</i> -Octanoic acid	0.2052	15.10	15.93	2-Methylnonane	0.2343	14.91
<i>n</i> -Tetradecanoic acid	0.3381	15.83	16.32	<i>n</i> -Pentadecane	0.3433	16.20
Oxalic acid	0.0883	17.71	17.70	2,3-Dimethyl-1,3-butadiene	0.1334	14.40
Benzoic acid	0.1461	18.20	18.70	α -Methylstyrene	0.1686	17.41
Methyl formate	0.0759	15.30	15.43	1-Butene	0.0969	13.66
Ethyl formate	0.0967	15.50	15.41	1-Pentene	0.1188	13.90
<i>n</i> -Propyl formate	0.1188	16.28	16.00	1-Hexene	0.1408	14.70
Methyl acetate	0.0968	15.50	15.72	2-Methyl-1-butene	0.1187	14.20
Ethyl acetate	0.1173	15.80	15.79	2-Methyl-1-pentene	0.1395	14.48
<i>n</i> -Propyl acetate	0.1393	15.30	15.67	2-Methyl-1-hexene	0.1629	14.49
<i>n</i> -Butyl acetate	0.1611	15.80	15.54	2-Methyl-1-heptene	0.1851	14.50
Methyl propionate	0.1182	15.50	16.08	2-Ethyl-1-butene	0.1376	14.90
Ethyl propionate	0.1394	15.50	15.40	2-Ethyl-1-pentene	0.1631	14.24
Dimethyl ether	0.0717	15.20	13.89	Propane	0.0806	13.10
Diethyl ether	0.1134	14.50	15.08	<i>n</i> -Pentane	0.1244	14.40
Methyl- <i>n</i> -propyl ether	0.1144	15.63	15.02	<i>n</i> -Pentane	0.1244	14.40
Ethyl propyl ether	0.1350	15.23	15.48	<i>n</i> -Hexane	0.1457	14.90
Di- <i>n</i> -propyl ether	0.1573	15.10	15.79	<i>n</i> -Heptane	0.1676	15.30
Methyl- <i>n</i> -butyl ether	0.136	15.64	15.42	<i>n</i> -Hexane	0.1457	14.90
Di- <i>n</i> -butyl ether	0.2001	15.20	16.03	<i>n</i> -Nonane	0.2113	15.60
Di- <i>n</i> -hexyl ether	0.2882	15.29	16.41	<i>n</i> -Tridecane	0.2995	16.10
Anisole	0.1427	17.80	18.49	Ethylbenzene	0.1539	17.80
Ethylene oxide	0.0620	15.60	15.41	Cyclopropane	0.0713	14.37
Trioxane	0.1005	18.61	18.83	Cyclohexane	0.1263	16.80
Furan	0.0877	17.80	17.57	Cyclopentadiene	0.0965	16.75
Tetrahydrofuran	0.0991	16.80	17.18	Cyclopentane	0.1088	16.40
1,3-Dioxane	0.1094	18.01	18.05	Cyclohexane	0.1263	16.80
1,4-Dioxane	0.1102	17.50	17.99	Cyclohexane	0.1263	16.80
Carbon tetrachloride	0.1284	17.80	18.59	3,3-Diethylpentane	0.2085	14.59
Chloroform	0.1057	17.80	18.64	3-Ethylpentane	0.1673	14.82
Dichloromethane	0.0827	17.00	17.66	<i>n</i> -Pentane	0.1244	14.40
Methyl chloride	0.0601	15.30	15.17	Propane	0.0806	13.10
<i>trans</i> -1,2-Dichloroethylene	0.0982	16.70	18.33	<i>trans</i> -3-Hexene	0.1397	15.37
Ethyl chloride	0.0816	15.70	15.35	<i>n</i> -Butane	0.1025	13.70
<i>n</i> -Propyl chloride	0.1039	16.00	15.76	<i>n</i> -Pentane	0.1244	14.40
<i>n</i> -Butyl chloride	0.1258	16.20	16.04	<i>n</i> -Hexane	0.1457	14.90
1-Chloropentane	0.1478	16.45	16.29	<i>n</i> -Heptane	0.1676	15.30
Monochlorobenzene	0.1326	19.00	19.18	Ethylbenzene	0.1539	17.80
Benzyl dichloride	0.1778	19.90	17.62	<i>n</i> -Propylbenzene	0.1762	17.70
Dibromomethane	0.0954	19.00	20.28	<i>n</i> -Heptane	0.1676	15.30
1-Bromobutane	0.1316	16.80	17.27	<i>n</i> -Heptane	0.1676	15.30
Bromobenzene	0.1388	20.50	19.94	<i>n</i> -Propylbenzene	0.1762	17.70
Isopropyl iodide	0.1204	16.97	16.40	2-Methylpentane	0.1465	14.87
Iodobenzene	0.1492	19.50	19.23	<i>n</i> -Propylbenzene	0.1762	17.70
Fluorobenzene	0.1186	18.70	18.98	Toluene	0.1318	18.00
Methylamine	0.0529	13.00	13.05	Ethane	0.0586	12.40
Ethylamine	0.0751	15.00	13.57	Propane	0.0806	13.10
<i>n</i> -Propylamine	0.0968	15.67	14.10	<i>n</i> -Butane	0.1025	13.70
<i>n</i> -Butylamine	0.1186	16.20	14.75	<i>n</i> -Pentane	0.1244	14.40
<i>n</i> -Pentylamine	0.1405	15.69	15.17	<i>n</i> -Hexane	0.1457	14.90
<i>n</i> -Hexylamine	0.1623	15.70	15.55	<i>n</i> -Heptane	0.1676	15.30
<i>n</i> -Heptylamine	0.1840	15.71	15.63	<i>n</i> -Octane	0.1895	15.40
<i>n</i> -Octylamine	0.2059	15.72	15.80	<i>n</i> -Nonane	0.2113	15.60

Table 1 (continued)

Compound	$V_{\text{cosm}}^{39}/\text{nm}^3$	δ_d Hansen ¹⁴ or SP ^a	$s_d/\text{MPa}^{1/2}$	Homomorph	$V_{\text{cosm homom}}/\text{nm}^3$	δ_d homom
<i>n</i> -Nonylamine	0.2278	15.73	15.89	<i>n</i> -Decane	0.2333	15.70
<i>n</i> -Decylamine	0.2497	15.74	16.10	<i>n</i> -Undecane	0.2560	15.90
Undecylamine	0.2716	15.75	16.05	<i>n</i> -Dodecane	0.2768	15.90
<i>n</i> -Dodecylamine	0.2934	15.75	16.27	<i>n</i> -Tridecane	0.2995	16.10
Dimethylamine	0.0757	15.30	13.52	Propane	0.0806	13.10
Trimethylamine	0.0982	16.39	15.26	Isobutane	0.1036	14.85
Diethylamine	0.1187	14.90	14.74	<i>n</i> -Pentane	0.1244	14.40
Triethylamine	0.1601	15.50	15.15	3-Ethylpentane	0.1673	14.82
Di- <i>n</i> -butylamine	0.2056	15.93	15.81	<i>n</i> -Nonane	0.2113	15.60
Pyridine	0.1049	19.00	18.84	Benzene	0.1100	18.40
Aniline	0.1250	20.10	18.48	Toluene	0.1318	18.00
Benzylamine	0.1472	18.27	18.20	Ethylbenzene	0.1539	17.80
<i>N</i> -Methylaniline	0.1470	18.87	18.21	Ethylbenzene	0.1539	17.80
<i>m</i> -Toluidine	0.1465	19.65	18.62	<i>m</i> -Xylene	0.1533	18.20
<i>o</i> -Toluidine	0.1462	19.40	18.17	<i>o</i> -Xylene	0.1524	17.80
<i>p</i> -Toluidine	0.1466	19.65	18.21	<i>p</i> -Xylene	0.1535	17.80
Quinoline	0.1627	19.40	19.48	Naphthalene	0.1674	19.20
Acridine	0.218	21.70	20.34	Anthracene	0.2255	20.00
Allylamine	0.0907	15.65	14.12	1-Butene	0.0969	13.66
Pyrrole	0.0913	19.20	17.68	Cyclopentadiene	0.0965	17.20
Pyrrolidine	0.1046	18.11	16.73	Cyclopentane	0.1088	16.40
Piperazine	0.1173	18.85	17.43	Cyclohexane	0.1263	16.80
Piperidine	0.1222	18.12	17.08	Cyclohexane	0.1263	16.80
Cyclohexylamine	0.1438	17.20	16.35	Methylcyclohexane	0.1501	16.00
Indole	0.1482	19.80	19.82	Indene	0.1546	19.41
Acetonitrile	0.0637	15.30	15.86	Methylacetylene	0.0703	15.10
Nitrobenzene	0.1413	20.00	19.02	α -Methylstyrene	0.1686	17.41
<i>n</i> -Butyl mercaptan	0.1317	17.42	14.00	<i>n</i> -Pentane	0.1244	14.40
<i>n</i> -Pentyl mercaptan	0.1537	17.43	14.51	<i>n</i> -Hexane	0.1457	14.90
<i>n</i> -Hexyl mercaptan	0.1757	17.44	14.94	<i>n</i> -Heptane	0.1676	15.30
Thiophene	0.1029	18.90	16.22	Cyclopentadiene	0.0965	16.75
Lactic acid DL	0.1054	17.00	17.24	2,3-Dimethyl-1-butene	0.1411	14.90
2-Methoxyethanol	0.1033	16.00	15.80	<i>n</i> -Pentane	0.1244	14.40
2-Butoxyethanol	0.1682	16.00	16.35	<i>n</i> -Octane	0.1895	15.40
Formamide	0.0575	17.20	15.02	Propylene	0.075	13.15
Acetamide	0.0787	17.30	16.13	Isobutene	0.0974	14.50
<i>N</i> -Methylformamide	0.0801	17.40	15.02	1-Butene	0.0969	13.66
Acrylamide	0.0950	15.80	16.51	3-Methyl-1,2-butadiene	0.1136	15.10
<i>N,N</i> -Dimethylformamide	0.1018	17.40	15.11	3-Methyl-1-butene	0.1186	14.00
<i>N</i> -Methylacetamide	0.1010	16.90	15.39	2-Methyl-1-butene	0.1187	14.20
Diethanolamine	0.1402	17.20	16.73	<i>n</i> -Heptane	0.1676	15.30
Morpholine	0.1136	18.00	17.71	Cyclohexane	0.1263	16.80
<i>p</i> -Chlorophenol	0.1433	19.08	19.60	<i>p</i> -Ethyltoluene	0.1753	17.72
Water	0.0256	15.50	14.08	Methane	0.0377	11.60

^a Calculated with the group-contribution method.³²

been obtained if we could replace a Cl atom not by an entire ethyl group but by *ca.* 0.85 of an ethyl group and similarly for the other bulkier atoms. As an example, if 3-methyl,3-ethylpentane were chosen as the homomorph of carbon tetrachloride, instead of the 3,3-diethylpentane, the calculated s_d would have been 17.65 instead of 18.59, much closer to the DIPPR⁴² total solubility parameter of 17.55, which is the expected value for s_d in this case. As another example, let us consider chloroform, whose 3-D structure can be considered to fall between the structures of 3-ethylpentane and 3-methylpentane. If 3-methylpentane were chosen as the homomorph of chloroform instead of the 3-ethylpentane, the calculated s_d would have been 17.36 instead of 18.64. Both are rather exaggerations and the correct value should be in between, as is the proposed δ_d (17.80) by Hansen.¹⁴

We will now proceed to the definition of s_{hb} , the partial solvation parameter for the hydrogen-bonding intermolecular interactions exhibited by the molecule either in its pure state

(self-solvation) or in solution. s_{hb} is analogous to the Hansen solubility parameter δ_{hb} but, as we will see shortly, they differ rather substantially. The method that we will follow for the definition of s_{hb} will let us define simultaneously its two components, namely, the partial solvation parameters s_a and s_b for the acidic (proton donor) and basic (proton acceptor) character, respectively, of the compound.

As already mentioned, we will base the new definitions on the third moments of the σ -profiles for their hydrogen bonding donor and acceptor parts. Our central assumption here is that the division of the hydrogen bonding solubility parameter into its acidic and basic components should reflect the ratio of the COSMO donor and acceptor functions, HB_don3 and HB_acc3 , respectively. This is not, however, sufficient for the calculation of the absolute values of s_a and s_b . Unfortunately, there is no absolute and universally accepted measure of this Lewis-acidic or Lewis-basic character, to which one has to comply, not even for a single reference substance. Our proposal, although it may

suffer from a similar degree of arbitrariness, has at least a sound basis and a reliable source of consistent information. With this in mind, we will adopt water as our reference compound for two reasons. First, we will follow the common chemistry practice and consider water as the reference “neutral” substance of balanced acidity and basicity. Second, due to this balanced acidic and basic character, the water molecule will be considered to exhibit its full hydrogen bonding capacity not only in solution but also in its pure state, or, in the self-solvation state. The first of the above reasons implies, as we will see, a universal shift of the HB_don3 functions in order to reflect the water neutrality. The second implies that in water, our reference substance, the cohesive forces are highly representative of the intermolecular solvation forces in, both, pure state and solution. This is the basis for the rationale of our method.

As seen in Table 2, the acceptor and donor σ -moments, HB_acc3 and HB_don3 for water, are equal to 5.758 and 3.858, respectively. Obviously, these numbers do not reflect the above-mentioned symmetry and neutrality of water, not even the balanced picture that emerges at first sight from Fig. 1. Although we may proceed with these numbers and weigh accordingly the acidic and basic character of the various compounds, for convenience we will follow a different route. Since our interest in using the functions HB_acc3 and HB_don3 is to develop a scale of acidity and a scale of basicity relative to water, the relative position of the various compounds in these scales will not change if we multiply the acceptor and/or the donor σ -moments by a universal factor. These functions for water become equal by multiplying the donor function by 1.492. This is the universal factor by which we must multiply the HB_don3 values of all substances and have one scale of acidity and one scale of basicity which reflect the presumed neutrality of water. This modified HB_don3 value when added to the corresponding HB_acc3 value gives the m-SUM value for each substance and is reported in the 4th column of Table 2.

Having the acidity and basicity scales established, we must now provide with a reference value against which we will obtain the absolute values of the partial solvation parameters for hydrogen bonding. Our reference compound, water, provides with this reference value since its cohesive forces may adequately represent its solvation forces in solution as well. In other words, the partial solvation parameters of water are considered identical to its corresponding partial solubility parameters. Our proposal, then, amounts to adopting the following defining equations:

$$\frac{s_b^2}{s_{hb}^2} = 1 - \frac{s_a^2}{s_{hb}^2} = \frac{\text{HB_acc3}}{\text{m-SUM}} \quad \text{for all compounds} \quad (4)$$

or

$$s_{hb}^2 = s_a^2 + s_b^2 \quad (5)$$

and

$$\begin{aligned} s_{hb} &= \delta_{hb,\text{water}} \sqrt{\frac{\text{m-SUM}}{\text{m-SUM}_{\text{water}}}} \sqrt{\frac{V_{\text{cosm},\text{water}}}{V_{\text{cosm}}}} \\ &= 1.994 \sqrt{\frac{\text{m-SUM}}{V_{\text{cosm}}}} \cong 2 \sqrt{\frac{\text{m-SUM}}{V_{\text{cosm}}}} \end{aligned} \quad (6)$$

The numerical factor in eqn (6) results from the replacements $\delta_{hb,\text{water}} = 42.3$, $V_{\text{cosm},\text{water}} = 0.0256$, $\text{m-SUM}_{\text{water}} = 11.5152$. For water, of course, $s_{hb} = \delta_{hb}$ and $s_a = s_b$. The above simple equations are sufficient for calculating s_{hb} of the hydrogen-bonded compounds and for splitting it into its acidic and basic components s_a and s_b , respectively. It is worth pointing out that the defining equation (5) does not have the problem mentioned in the Introduction in relation with eqn (1). Eqn (5) shows that zero or negligibly small values for the acidic or basic component can be tolerated without causing the other component to adopt intolerably high values.

In the last three columns of Table 2 are reported the hydrogen bonding partial solvation parameter, s_{hb} , for common solvents along with its acidic and basic components, s_a and s_b , as calculated with eqn (4) and (5). For comparison purposes, the corresponding Hansen δ_{hb} parameters are also reported in Table 2. As observed, the solvation parameter is, in general, different from the corresponding solubility parameter. This is in particular true for classes of compounds such as ketones or ethers. In contrast, for compounds such as *n*-alkanols or the higher carboxylic acids, the two parameters have comparable values. The inherent basic character in ethers or ketones is not fully pronounced in the cohesive interactions in their pure state but it is pronounced in their solvation interactions when in solution. This is expressed by the higher values of their solvation parameters compared to their corresponding solubility parameters, as shown in Table 2. In contrast, alkanols and higher carboxylic acids possess both acidic and basic character at a sufficient degree to be shown up in their cohesive interactions. An inspection of the values of s_a and s_b for ethanol and phenol verifies that both have acidic as well as basic character though in phenol the acidic character clearly prevails. We will return to the comments regarding Table 2 after we complete the definitions of solvation parameters.

The proposed method for the calculation of hydrogen bonding solvation parameters can be applied to any similar quantum- or molecular-mechanics based functions or even to experimentally determined acidity and basicity molecular descriptors. This would provide with an alternative test of the validity of our method. In the Appendix, our method is applied to the widely used Abraham's QSPR/LSER acid/base descriptors.⁷ As shown in the Appendix, the calculated hydrogen bonding solvation parameters on the basis of Abraham's acid/base descriptors are very similar to the quantum-mechanics based calculations reported in Table 2.

The last parameter to be defined is s_p , the partial solvation parameter for the polar intermolecular forces exhibited by the molecule either in its pure state (self-solvation) or in solution. s_p is entirely analogous to the partial solubility parameter δ_p . This is the most difficult to define solvation parameter and, necessarily, the definition will be an approximation. In view of this, we will follow a simplified approach. The first choice for this definition could be a most simple equation, analogous to the extensively used one for Hansen's¹⁴ δ_p , or

$$s_p = \mu \frac{1.385}{\sqrt{V_{\text{cosm}}}} \quad (7)$$

where, μ is the “experimental” dipole moment in Debye units.⁴² The numerical factor in eqn (7) accounts for the units

Table 2 The hydrogen bonding partial solvation parameter, s_{hb} , and its acidic and basic components of common compounds as calculated from the σ -moments of COSMO-RS theory³⁹

Compound	HB_acc3	HB_don3	Sum_m	δ_{hb} Hansen ¹⁴	s_{hb}	s_a	s_b
Formaldehyde	0.8531	0	0.8531	15.4	8.85	0.00	8.85
Acetaldehyde	1.8694	0	1.8694	11.3	10.75	0.00	10.75
Acrolein	1.8689	0	1.8689	8.6	9.62	0.00	9.62
1-Butanal	1.8279	0	1.8279	7	8.23	0.00	8.23
1-Pentanal	1.7273	0	1.7273	—	7.29	0.00	7.29
1-Hexanal	1.8303	0	1.8303	5.4	6.94	0.00	6.94
1-Heptanal	1.783	0	1.7830	—	6.40	0.00	6.40
1-Octanal	1.8366	0	1.8366	—	6.12	0.00	6.12
1-Nonanal	1.7884	0	1.7884	—	5.72	0.00	5.72
1-Decanal	1.7944	0	1.7944	—	5.46	0.00	5.46
1-Undecanal	1.7805	0	1.7805	—	5.20	0.00	5.20
1-Dodecanal	1.7873	0	1.7873	—	5.00	0.00	5.00
1-Tridecanal	1.7854	0	1.7854	—	4.82	0.00	4.82
Ketene	0	0.0177	0.0264	5.8	1.34	1.34	0.00
Acetone	2.7924	0	2.7924	7.0	11.35	0.00	11.35
Methyl ethyl ketone	2.7702	0	2.7702	5.1	10.15	0.00	10.15
2-Pentanone	2.7193	0	2.7193	4.7	9.17	0.00	9.17
3-Pentanone	2.5967	0	2.5967	4.7	8.97	0.00	8.97
Cyclohexanone	3.009	0	3.0090	5.1	9.49	0.00	9.49
2-Hexanone	2.7399	0	2.7399	4.1	8.50	0.00	8.50
3-Hexanone	2.5977	0	2.5977	—	8.31	0.00	8.31
2-Heptanone	2.7015	0	2.7015	4.1	7.89	0.00	7.89
3-Heptanone	2.6044	0	2.6044	4.1	7.77	0.00	7.77
Methanol	4.2629	1.939	7.1568	22.3	24.25	15.42	18.72
Ethanol	3.9826	1.54	6.2810	19.43	18.89	11.43	15.04
1-Propanol	3.8477	1.578	6.2028	17.4	16.39	10.10	12.91
1-Butanol	3.7771	1.5483	6.0879	15.8	14.58	8.98	11.49
1-Pentanol	4.0006	1.8334	6.7369	13.9	14.06	8.96	10.84
1-Hexanol	4.0323	1.8452	6.7862	12.5	13.08	8.33	10.08
1-Heptanol	3.9997	1.832	6.7339	11.7	12.22	7.79	9.42
1-Octanol	3.9967	1.8306	6.7288	11.2	11.53	7.35	8.88
1-Nonanol	3.995	1.8334	6.7313	10.6	10.94	6.98	8.43
1-Decanol	4.0498	1.8315	6.7832	10.5	10.50	6.66	8.11
1-Undecanol	4.0025	1.831	6.7352	—	10.01	6.37	7.71
1-Dodecanol	4.047	1.8324	6.7818	9.3	9.66	6.14	7.47
1-Tridecanol	3.9955	1.8326	6.7306	—	9.27	5.91	7.14
1-Tetradecanol	3.9967	1.8309	6.7292	—	8.96	5.71	6.91
1-Pentadecanol	3.9932	1.8319	6.7272	—	8.68	5.53	6.69
1-Hexadecanol	3.999	1.8306	6.7311	—	8.42	5.37	6.49
1-Eicosanol	3.9953	1.8309	6.7278	—	7.59	4.83	5.85
Allyl alcohol	3.2796	1.6759	5.7808	16.8	16.32	10.74	12.30
Isopropanol	4.1004	1.4338	6.2403	16.4	16.42	9.61	13.31
2-Butanol	3.5429	1.4114	5.6494	14.5	14.05	8.58	11.13
2-Methyl-1-propanol	3.4092	1.7926	6.0846	15.9	14.56	9.66	10.90
2-Methyl-2-Propanol	3.8355	1.1345	5.5287	14.7	13.82	7.65	11.51
2,2-Dimethyl-1-propanol	3.1458	1.244	5.0024	—	12.10	7.37	9.60
3-Methyl-1-butanol	4.0818	1.8044	6.7748	13.3	14.08	8.88	10.93
2-Pentanol	3.568	1.4252	5.6950	13.3	12.93	7.91	10.24
3-Pentanol	3.2102	1.0668	4.8024	—	11.92	6.86	9.74
2-Ethyl-1-butanol	3.087	1.6256	5.5131	13.5	11.83	7.85	8.85
2-Hexanol	3.5949	1.3602	5.6249	—	11.92	7.16	9.53
2-Methyl-1-pentanol	3.294	1.7782	5.9479	—	12.26	8.19	9.12
4-Methyl-2-pentanol	3.3807	1.1268	5.0624	12.3	11.29	6.50	9.22
2-Heptanol	3.4708	1.1419	5.1750	—	10.71	6.15	8.77
5-Methyl-1-hexanol	4.0651	1.8288	6.7945	—	12.25	7.77	9.48
2-Ethyl-1-hexanol	3.1525	1.7341	5.7406	11.8	10.62	7.13	7.87
2-Octanol	3.5736	1.4121	5.6811	11	10.59	6.45	8.40
Cyclohexanol	3.9142	1.3132	5.8741	13.5	12.96	7.49	10.58
1-Methylcyclohexanol	3.3351	0.9911	4.8143	—	10.88	6.03	9.05
cis-2-Methylcyclohexanol	3.4411	1.3581	5.4680	—	11.64	7.09	9.24
trans-2-Methylcyclohexanol	3.8591	1.1148	5.5229	—	11.68	6.41	9.76
cis-3-Methylcyclohexanol	3.2825	1.0676	4.8758	—	10.97	6.27	9.00
trans-3-Methylcyclohexanol	3.3978	1.2751	5.3008	—	11.39	6.83	9.12
cis-4-Methylcyclohexanol	3.8924	1.4188	6.0099	—	12.13	7.20	9.76
trans-4-Methylcyclohexanol	3.44	1.22	5.2608	—	11.38	6.70	9.20
Phenol	0.6949	3.6429	6.1318	14.9	14.22	13.39	4.79
Benzyl alcohol	2.8374	1.7521	5.4523	13.7	12.32	8.53	8.89
m-Cresol	0.7596	3.52	6.0130	12.9	12.97	12.12	4.61
<i>o</i> -Cresol	0.5326	3.4692	5.7102	—	12.64	12.03	3.86
2-Phenylethanol	3.2434	1.8704	6.0349	—	12.04	8.19	8.83

Table 2 (continued)

Compound	HB_acc3	HB_don3	Sum_m	δ_{hb}	Hansen ¹⁴	s_{hb}	s_a	s_b
2,4-Xylenol	0.62	3.3488	5.6179	—	11.65	10.99	3.87	
1-Phenyl-1-propanol	2.6722	1.2114	4.4802	—	9.78	6.21	7.55	
Ethylene glycol	5.5454	2.9481	9.9453	26	22.17	14.75	16.55	
1,2-Propylene glycol	5.1838	2.4399	8.8252	21.3	18.45	11.85	14.14	
Glycerol	6.4593	2.6388	10.3976	27.2	19.23	11.84	15.16	
1,2-Butanediol	5.0894	2.4143	8.6926	—	16.69	10.74	12.77	
1,4-Butanediol	6.0619	2.3871	9.6245	20.9	17.74	10.80	14.08	
1,5-Pentanediol	7.924	3.7403	13.5062	—	19.10	12.28	14.63	
1,6-Hexanediol	7.9627	3.6957	13.4784	—	17.82	11.40	13.69	
Triethylene glycol	9.1158	1.3017	11.0585	18.6	15.17	6.36	13.78	
Formic acid	1.2344	4.7411	8.3103	14	24.88	22.96	9.59	
Acetic acid	1.9745	3.8304	7.6912	13.5	20.29	17.49	10.28	
Propionic acid	1.938	3.7186	7.4879	12.4	17.67	15.21	8.99	
<i>n</i> -Butyric acid	1.8841	3.7063	7.4156	12	15.84	13.68	7.99	
<i>n</i> -Pentanoic acid	1.8719	3.7043	7.4004	10.3	14.51	12.54	7.30	
<i>n</i> -Hexanoic acid	1.8581	3.6956	7.3736	11.5	13.48	11.66	6.77	
<i>n</i> -Heptanoic acid	1.8687	3.6935	7.3811	—	12.66	10.94	6.37	
<i>n</i> -Octanoic acid	1.8542	3.6889	7.3597	8.2	11.94	10.33	6.00	
<i>n</i> -Tetradecanoic acid	1.9065	3.6896	7.4131	—	9.34	8.05	4.74	
Oxalic acid	0.3182	7.2358	11.1173	—	22.38	22.06	3.79	
Benzoic acid	1.3605	4.0224	7.3638	9.8	14.16	12.78	6.09	
Methyl formate	1.4214	0	1.4214	10.2	8.63	0.00	8.63	
<i>n</i> -Propyl formate	1.5761	0	1.5761	—	7.26	0.00	7.26	
Methyl acetate	2.0952	0	2.0952	7.6	9.28	0.00	9.28	
Ethyl acetate	2.2925	0	2.2925	7.2	8.82	0.00	8.82	
<i>n</i> -Propyl acetate	2.2582	0	2.2582	7.6	8.03	0.00	8.03	
<i>n</i> -Butyl acetate	2.2577	0	2.2577	6.3	7.47	0.00	7.47	
Methyl propionate	2.0009	0	2.0009	7.7	8.21	0.00	8.21	
Ethyl propionate	2.264	0	2.2640	4.9	8.04	0.00	8.04	
Dimethyl ether	2.6431	0	2.6431	5.7	12.11	0.00	12.11	
Diethyl ether	2.6171	0	2.6171	4.6	9.58	0.00	9.58	
Methyl- <i>n</i> -propyl ether	2.5797	0	2.5797	—	9.47	0.00	9.47	
Ethyl propyl ether	2.7228	0	2.7228	—	8.96	0.00	8.96	
Methyl- <i>n</i> -butyl ether	2.6625	0	2.6625	—	8.82	0.00	8.82	
Di- <i>n</i> -butyl ether	2.6998	0	2.6998	4.2	7.33	0.00	7.33	
Di- <i>n</i> -hexyl ether	2.6658	0	2.6658	—	6.07	0.00	6.07	
Anisole	0.4264	0	0.4264	6.9	3.45	0.00	3.45	
Ethylene oxide	1.8446	0	1.8446	11	10.88	0.00	10.88	
Trioxane	2.3264	0	2.3264	8.6	9.60	0.00	9.60	
Furan	0.0115	0.0031	0.0161	5.3	0.86	0.46	0.72	
Tetrahydrofuran	3.5159	0	3.5159	8	11.88	0.00	11.88	
1,3-Dioxane	3.683	0	3.6830	9.3	11.57	0.00	11.57	
1,4-Dioxane	4.2449	0	4.2449	9	12.38	0.00	12.38	
Carbon tetrachloride	0	0	0.0000	0.6	0.00	0.00	0.00	
Chloroform	0	1.378	2.0566	5.7	8.80	8.80	0.00	
Dichloromethane	0	0.2261	0.3374	7.1	4.03	4.03	0.00	
Methyl chloride	0	0	0.0000	3.9	0.00	0.00	0.00	
<i>trans</i> -1,2-Dichloroethylene	0	0.1481	0.2210	3.3	2.99	2.99	0.00	
Ethyl chloride	0	0	0.0000	2.9	0.00	0.00	0.00	
<i>n</i> -Propyl chloride	0	0	0.0000	2	0.00	0.00	0.00	
<i>n</i> -Butyl chloride	0	0	0.0000	2	0.00	0.00	0.00	
1-Chloropentane	0	0	0.0000	0	0.00	0.00	0.00	
Monochlorobenzene	0	0	0.0000	2	0.00	0.00	0.00	
Benzyl dichloride	0	0.2334	0.3483	2.4	2.79	2.79	0.00	
Dibromomethane	0	0.2497	0.3727	7	3.94	3.94	0.00	
1-Bromobutane	0	0	0.0000	0	0.00	0.00	0.00	
Bromobenzene	0	0	0.0000	4.1	0.00	0.00	0.00	
Iodobenzene	0	0	0.0000	6.1	0.00	0.00	0.00	
Fluorobenzene	0	0	0.0000	2	0.00	0.00	0.00	
Methylamine	5.8147	0.0484	5.8869	17.3	21.04	2.33	20.91	
Ethylamine	5.6478	0.0321	5.6957	10.7	17.37	1.59	17.30	
<i>n</i> -Propylamine	5.5609	0.0338	5.6113	8.6	15.19	1.44	15.12	
<i>n</i> -Butylamine	5.5366	0.0327	5.5854	8	13.69	1.28	13.63	
<i>n</i> -Pentylamine	5.5268	0.0331	5.5762	—	12.56	1.18	12.51	
<i>n</i> -Hexylamine	5.5238	0.0323	5.5720	—	11.69	1.09	11.64	
<i>n</i> -Heptylamine	5.4367	0.0352	5.4892	—	10.89	1.07	10.84	
<i>n</i> -Octylamine	5.4345	0.0361	5.4884	—	10.30	1.02	10.25	
<i>n</i> -Nonylamine	5.4216	0.0361	5.4755	—	9.78	0.97	9.73	
<i>n</i> -Decylamine	5.4187	0.0366	5.4733	—	9.34	0.93	9.29	
Undecylamine	5.4178	0.0363	5.4720	—	8.95	0.89	8.91	
<i>n</i> -Dodecylamine	5.4152	0.0358	5.4686	—	8.61	0.85	8.57	

Table 2 (continued)

Compound	HB_acc3	HB_don3	Sum_m	δ_{hb} Hansen ¹⁴	s_{hb}	s_a	s_b
Dimethylamine	4.4988	0.0609	4.5897	11.2	15.53	2.19	15.38
Trimethylamine	3.1797	0	3.1797	1.8	11.35	0.00	11.35
Diethylamine	3.9622	0.0112	3.9789	6.1	11.55	0.75	11.52
Triethylamine	2.9345	0	2.9345	1	8.54	0.00	8.54
Di-n-butylamine	3.9082	0.0134	3.9282	—	8.72	0.62	8.70
Pyridine	3.394	0	3.3940	5.9	11.34	0.00	11.34
Aniline	1.1961	1.1233	2.8726	11.2	9.56	7.30	6.17
Benzylamine	3.7887	0.076	3.9021	—	10.27	1.75	10.12
N-Methylaniline	0.2863	0.6949	1.3234	—	5.98	5.30	2.78
m-Toluidine	1.2522	1.0178	2.7712	—	8.67	6.42	5.83
o-Toluidine	1.1392	0.8949	2.4748	9.4	8.21	6.03	5.57
p-Toluidine	1.4279	0.9656	2.8690	—	8.82	6.25	6.22
Quinoline	3.0441	0	3.0441	7.6	8.63	0.00	8.63
Acridine	2.7909	0	2.7909	2	7.14	0.00	7.14
Allylamine	4.878	0.0726	4.9864	10.6	14.79	2.18	14.63
Pyrrole	0.0818	2.5619	3.9053	6.7	13.04	12.91	1.89
Pyrrolidine	4.9994	0.0394	5.0582	7.4	13.87	1.50	13.79
Piperazine	8.1764	0.1137	8.3461	8	16.82	2.40	16.65
Piperidine	4.2586	0.0415	4.3205	8.9	11.86	1.42	11.77
Cyclohexylamine	5.0823	0.0225	5.1159	6.5	11.90	0.96	11.86
Indole	0	2.587	3.8610	6.5	10.18	10.18	0.00
Acetonitrile	1.3469	0	1.3469	6.1	9.17	0.00	9.17
Nitrobenzene	0.2432	0	0.2432	4.1	2.62	0.00	2.62
n-Butyl mercaptan	0.3787	0.001	0.3802	—	3.39	0.21	3.38
n-Pentyl mercaptan	0.3918	0.0008	0.3930	—	3.19	0.18	3.18
n-Hexyl mercaptan	0.3919	0.0009	0.3932	—	2.98	0.17	2.98
Thiophene	0	0	0.0000	7.8	0.00	0.00	0.00
Dimethyl sulfoxide	9.7406	0.003	9.7451	10.2	19.81	19.80	0.42
Lactic acid DL	2.7713	4.2661	9.1383	28.4	18.57	15.50	10.23
2-Methoxyethanol	4.5265	0.7446	5.6378	15	14.73	6.54	13.20
2-Butoxyethanol	4.5867	0.5667	5.4325	12.3	11.33	4.47	10.42
Formamide	5.8181	3.6157	11.2144	19	27.85	19.32	20.06
Acetamide	7.0216	2.941	11.4109	22.4	24.02	14.89	18.84
N-Methylformamide	6.2741	2.0625	9.3523	15.9	21.55	12.36	17.65
Acrylamide	5.7615	3.3095	10.7008	12.8	21.17	14.38	15.53
N,N-Dimethylformamide	6.0094	0	6.0094	11.3	15.32	0.00	15.32
N-Methylacetamide	7.4237	1.5928	9.8009	13	19.65	9.68	17.10
Diethanolamine	7.6463	1.8292	10.3763	19	17.16	8.80	14.73
Morpholine	6.2626	0.0957	6.4054	11	14.98	2.24	14.81
p-Chlorophenol	0.4928	4.008	6.4746	—	13.41	12.89	3.70
Acetylsalicylic acid	1.8024	4.1882	8.0531	9.3	12.46	5.90	10.98
Paracetamol	4.4608	5.7717	13.0748	13.9	16.87	9.86	13.69
Water	5.7576	3.8578	11.5152	42.3	42.30	29.91	29.91

(nm³ per molecule) of V_{cosm} and of s_p (MPa^{1/2}). But, these experimental dipole moments are not always available for the compounds of interest and, of course, cannot be obtained for not synthesized compounds. The dipole moments, however, can be obtained computationally today with quantum/molecular mechanics software of various levels of approximation (such as with Schrödinger's Jaguar and Gaussian, GAMESS Pro 12.0, or MOPAC 2009, which can be used either as stand-alone software or can be found as interfaced modules in widely used software suites such as the ChemOffice of Perkin-Elmer[®]). The cosmo files of COSMO-RS³⁶ provide with the dipole moment, t , for thousands of compounds and the corresponding sources^{39–41} will be used for our calculations. They are obtained in a conductor and not in gas-phase and, thus, they incorporate the additional back-polarization. The defining equation, in this case, for the polar solvation parameter is:

$$s_p = t \left(\frac{1.29}{\sqrt{V_{cosm}}} - 1.10 \right) \quad (8)$$

The numerical factors in eqn (8) have two main sources. First, they should properly render the SI units of MPa^{1/2} to the partial solvation parameter, as the units of cosmo volume are nm³ per molecule, while the experimental⁴² values of dipole moment in Debyes are, on the average, about 70% of the corresponding t values in Debyes. Second, eqn (8) should properly account for the polar solvation parameter of water which has been chosen as our reference compound. The results obtained by using eqn (8) are similar to the corresponding results with eqn (7).

The polar solvation parameters, as calculated with eqn (8), are reported in Table 3 for a number of common solvents. For comparison purposes, the corresponding Hansen polar solubility parameters are reported in the same table. As observed, the solvation and solubility parameters are, in general, of comparable size but, not rarely, they may differ significantly. Three examples of exception are the symmetric molecules of oxalic acid, *trans*-1,2-dichloroethylene, and piperazine, for each of which there are two rows in Table 3. The calculations in the first row are done with eqn (8) and the

cosmo dipole moments, which are near zero for their symmetric conformer. The calculations in the second row are done with eqn (7) and the experimental⁴² dipole moment. The calculations with eqn (7) are much closer to the δ_p values reported by Hansen.¹⁴ These examples point to the need for a further refinement of the dipolar s_p parameter in the future. Most likely, polarizability should be involved explicitly in this refinement but physicochemical insight should be given a priority over complex correlations of s_p with dipole moment.

In Table 3 are also compared the square root of cohesive energy density (ced) or the total solubility parameter of the DIPPR compilation⁴² obtained from the heat of vaporization and the molar volume of the compound, the total Hansen solubility parameter (eqn (2)), and the total solvation parameter given by the equation:

$$s_{\text{total}} = \sqrt{s_d^2 + s_p^2 + s_{\text{hb}}^2} = \sqrt{s_d^2 + s_p^2 + s_a^2 + s_b^2} \quad (9)$$

Table 3 The *polar* component of the solvation parameter, s_p , of common compounds obtained from eqn (7), and comparison of total solubility and solvation parameters

Compound	$\sqrt{\text{ced}}$ DIPPR ⁴²	δ_{total} Hansen ¹⁴	s_{total}	δ_p Hansen ¹⁴	s_p
Formaldehyde	23.82	24.66	22.48	14.40	15.32
Acetaldehyde	19.91	22.36	23.54	12.50	15.38
Acrolein	20.18	18.38	24.59	7.20	16.21
1-Butanal	18.66		19.93		10.76
1-Pentanal	18.44	19.39	19.49	9.40	9.58
1-Hexanal	18.15	18.74	19.02	8.50	8.44
1-Heptanal	17.95		18.93		8.28
1-Octanal	17.92		17.88		6.94
1-Nonanal	17.76		18.53		6.93
1-Decanal	17.71		17.40		6.37
1-Undecanal	17.64		17.14		5.93
1-Dodecanal	17.63		16.93		5.50
1-Tridecanal	17.56		16.76		5.17
Ketene	18.06	18.00	17.61	7.30	8.70
Acetone	19.73	19.94	23.68	10.40	13.96
Methyl ethyl ketone	18.88	19.05	21.65	9.00	11.91
2-Pentanone	18.29	18.33	20.39	7.60	10.21
3-Pentanone	18.41	18.15	20.61	7.60	10.32
Cyclohexanone	20.14	20.33	22.57	8.40	11.42
2-Hexanone	18.14		19.63	6.10	9.30
3-Hexanone	17.90		19.24		8.97
2-Heptanone	17.88	17.66	18.83	5.70	8.17
3-Heptanone	18.11	17.44	18.64	5.00	8.29
Methanol	29.59	29.61	29.83	12.30	10.73
Ethanol	26.13	26.54	25.13	8.80	8.77
1-Propanol	24.45	24.60	23.08	6.80	7.38
1-Butanol	23.35	23.20	21.92	5.70	6.42
1-Pentanol	22.58	21.93	21.49	5.90	5.05
1-Hexanol	21.62	21.04	21.03	5.80	4.75
1-Heptanol	21.37	20.52	20.41	5.30	4.08
1-Octanol	20.87	20.16	20.09	5.00	3.92
1-Nonanol	21.23		19.71	4.80	3.41
1-Decanol	20.56	19.71	19.64	4.70	3.34
1-Undecanol	20.67		19.24		2.92
1-Dodecanol	20.28	18.93	19.25	4.00	2.88
1-Tridecanol	19.76	18.58	18.95	3.10	2.54
1-Tetradecanol	19.43		18.89		2.51
1-Pentadecanol	19.07		18.73		2.23
1-Hexadecanol	18.88		18.49		2.21
1-Eicosanol	18.06		18.12		1.75
Allyl alcohol	24.66	25.72	22.86	10.80	6.84
Isopropanol	23.41	23.58	23.90	6.10	7.31
2-Butanol	22.54	22.19	20.99	5.70	6.18
2-Methyl-1-propanol	22.91	22.66	21.15	5.70	5.59
2-Methyl-2-propanol	21.60	21.75	21.47	5.10	6.24
2,2-Dimethyl-1-propanol	19.27		19.29	6.50	5.44
3-Methyl-1-butanol	22.16	21.30	21.49	5.20	5.38
2-Pentanol	21.70	21.48	20.88	6.40	5.42
3-Pentanol	21.12		20.24		5.54
2-Ethyl-1-butanol	20.90	21.22	19.87	4.30	4.53
2-Hexanol	21.11		20.03		4.82
2-Methyl-1-pentanol	21.05	21.16	20.06	4.90	4.33
4-Methyl-2-pentanol	19.29	19.98	19.39	3.30	4.68
2-Heptanol	20.60	20.30	19.20	5.40	4.34
5-Methyl-1-hexanol	20.45		20.09		4.34
2-Ethyl-1-hexanol	20.04	20.07	18.89	3.30	3.83

Table 3 (continued)

Compound	\sqrt{ced} DIPPR ⁴²	δ_{total} Hansen ¹⁴	s_{total}	δ_p Hansen ¹⁴	s_p
2-Octanol	20.11	20.11	18.99	4.90	3.98
Cyclohexanol	23.74	22.40	21.81	4.10	5.61
1-Methylcyclohexanol	20.69	22.19	19.97	6.40	4.61
cis-2-Methylcyclohexanol	21.35		21.02	6.50	4.91
trans-2-Methylcyclohexanol	21.46		20.64	6.50	4.88
cis-3-Methylcyclohexanol	21.61		20.16	6.40	4.86
trans-3-Methylcyclohexanol	21.59		20.52	6.40	4.30
cis-4-Methylcyclohexanol	22.09		21.08	6.30	4.98
trans-4-Methylcyclohexanol	21.88		20.19	6.30	4.48
Phenol	24.63	24.10	24.09	5.90	4.93
Benzyl alcohol	24.70	23.79	22.73	6.30	4.86
m-Cresol	23.90	22.72	23.59	5.10	5.57
<i>o</i> -Cresol	22.87		22.61	4.70	3.44
2-Phenylethanol	21.99	23.17	22.48	5.80	5.18
2,4-Xylenol	22.14		22.27		2.74
1-Phenyl-1-propanol	20.53		20.98		4.80
Ethylene glycol	33.70	32.85	29.19	11.00	11.03
1,2-Propylene glycol	29.52	30.22	25.90	9.40	10.21
Glycerol	34.12	34.21	26.32	11.30	6.14
1,2-Butanediol	27.25		24.91		9.25
1,4-Butanediol	28.85	28.87	27.30	11.00	12.81
1,5-Pantanediol	26.45		26.96		9.75
1,6-Hexanediol	25.16		24.16		0.04
Triethylene glycol	24.96	27.54	23.57	12.50	4.96
Formic acid	21.46	22.56	30.87	10.00	9.53
Acetic acid	19.01	21.37	27.60	8.00	8.64
Propionic acid	19.41	19.95	24.78	5.30	7.15
<i>n</i> -Butyric acid	20.24	20.34	23.14	4.80	5.94
<i>n</i> -Pentanoic acid	21.81	18.65	22.03	4.10	5.49
<i>n</i> -Hexanoic acid	21.33	20.39	21.10	4.20	4.71
<i>n</i> -Heptanoic acid	22.79		20.89		4.48
<i>n</i> -Octanoic acid	22.24	17.50	20.29	3.30	3.90
<i>n</i> -Tetradecanoic acid	19.79		18.97		2.51
Oxalic acid	35.98	31.26	28.53	14.30	0.10
Oxalic acid	35.98	31.26	31.05	14.30	12.25 ^a
Benzoic acid	24.59	21.79	24.42	6.90	6.78
Methyl formate	20.50	20.22	19.97	8.40	9.28
<i>n</i> -Propyl formate	18.47		19.33	7.10	8.05
Methyl acetate	19.35	18.70	19.86	7.20	7.82
Ethyl acetate	18.35	18.15	19.57	5.30	7.47
<i>n</i> -Propyl acetate	17.89	17.62	18.89	4.30	6.85
<i>n</i> -Butyl acetate	17.59	17.41	18.26	3.70	6.01
Methyl propionate	18.63	18.49	19.21	6.50	6.59
Ethyl propionate	17.74	17.36	18.57	6.10	6.56
Dimethyl ether	15.12	17.34	19.69	6.10	6.93
Diethyl ether	15.42	15.49	18.51	2.90	4.85
Methyl- <i>n</i> -propyl ether	15.66		18.35		4.65
Ethyl propyl ether	15.41		18.33		4.03
Di- <i>n</i> -propyl ether	15.55	16.10	18.12	4.20	3.38
Methyl- <i>n</i> -butyl ether	15.83		18.30		4.37
Di- <i>n</i> -butyl ether	15.75	16.13	17.91	3.40	3.17
Di- <i>n</i> -hexyl ether	16.47		17.65	0.00	2.32
Anisole	20.11	19.59	19.33	4.40	4.49
Ethylene oxide	21.72	21.55	21.76	10.00	10.84
Trioxane	22.27	22.47	23.07	9.20	9.25
Furan	18.52	18.66	17.82	1.80	2.87
Tetrahydrofuran	18.97	19.46	22.36	5.70	7.96
1,3-Dioxane	20.67		23.22	6.60	8.91
1,4-Dioxane	20.54	20.47	17.99	1.80	0.01
Chloroform	18.92	18.95	21.15	3.10	4.71
Carbon tetrachloride	17.55	17.81	18.59	0.00	0.01
Dichloromethane	20.37	19.82	19.90	7.30	8.23
Methyl chloride	19.72	16.93	18.90	6.10	11.28
<i>trans</i> -1,2-Dichloroethylene	18.59	18.72	18.57	7.80	0.03
<i>trans</i> -1,2-Dichloroethylene	18.59	18.72	18.83	7.80	3.09 ^a
Ethyl chloride	17.77	17.09	18.68	6.10	10.64
<i>n</i> -Propyl chloride	17.08	17.91	18.24	7.80	9.19
<i>n</i> -Butyl chloride	17.30	17.22	18.05	5.50	8.28
1-Chloropentane	16.95		17.88		7.36
Monochlorobenzene	19.35	19.58	20.17	4.30	6.25
Benzyl dichloride	19.13	21.10	19.19	6.60	7.08

Table 3 (continued)

Compound	\sqrt{ced} DIPPR ⁴²	δ_{total} Hansen ¹⁴	s_{total}	δ_p Hansen ¹⁴	s_p
Dibromomethane	22.34	21.24	21.75	6.40	6.81
1-Bromobutane	18.42		19.17		8.32
Bromobenzene	19.94	21.62	20.86	5.50	6.11
Isopropyl iodide	17.78		19.03		9.64
Iodobenzene	20.45	21.19	19.98	5.60	5.41
Fluorobenzene	18.44	19.77	19.82	6.10	5.73
Methylamine	23.10	22.84	26.23	7.30	8.67
Ethylamine	19.49	19.26	23.08	5.60	6.84
<i>n</i> -Propylamine	18.55	18.54	21.58	4.90	6.03
<i>n</i> -Butylamine	18.31	18.62	20.75	4.50	5.08
<i>n</i> -Pentylamine	17.89		20.25		4.67
<i>n</i> -Hexylamine	17.63		19.87		4.06
<i>n</i> -Heptylamine	17.33		19.38		3.55
<i>n</i> -Octylamine	17.18		19.16		3.37
<i>n</i> -Nonylamine	17.01		18.89		2.98
<i>n</i> -Decylamine	16.91		18.83		2.86
Undecylamine	16.78		18.56		2.56
<i>n</i> -Dodecylamine	16.63		18.57		2.48
Dimethylamine	19.00	19.56	21.29	4.80	5.43
Trimethylamine	15.18	16.84	19.23	3.40	2.89
Diethylamine	16.61	16.26	19.15	2.30	4.01
Triethylamine	15.17	15.54	17.51	0.40	2.07
Di- <i>n</i> -butylamine	16.60		18.25		2.64
Pyridine	21.57	21.75	23.99	8.80	9.58
Aniline	24.12	23.73	21.72	5.80	6.22
Benzylamine	21.69		21.38		4.52
<i>N</i> -Methylaniline	21.69	23.42	20.24	6.00	6.49
<i>m</i> -Toluidine	22.10		21.13		4.96
<i>o</i> -Toluidine	22.49	22.54	20.83	5.80	6.01
<i>p</i> -Toluidine	21.74		20.73		4.48
Quinoline	21.94	21.57	22.40	5.60	6.93
Acridine	20.18	22.58	22.28	5.90	5.62
Allylamine	19.93	19.74	21.31	5.70	6.01
Pyrrole	24.86	21.64	23.62	7.40	8.66
Pyrrolidine	20.51	19.24	22.45	6.50	5.64
Piperazine	17.96	19.66	24.23	5.60	0.00
Piperazine	17.96	19.66	24.94	5.60	5.94*
Piperidine	18.94	18.67	21.13	4.50	3.74
Cyclohexylamine	18.83	21.32	20.70	10.80	4.46
Indole	23.43	22.15	23.48	7.50	7.39
Acetonitrile	24.05	24.40	27.81	18.00	20.92
Nitrobenzene	22.61	22.15	24.48	8.60	15.19
<i>n</i> -Butyl mercaptan	17.80		15.68		6.21
<i>n</i> -Pentyl mercaptan	17.65		15.80		5.38
<i>n</i> -Hexyl mercaptan	17.45		16.06		5.06
Thiophene	20.12	20.59	16.34	2.40	2.01
Lactic acid	33.11	34.12	30.26	8.30	16.54
Salicylic acid	24.21	27.95	24.34	10.10	7.11
2-Methoxyethanol	23.20	23.41	23.43	8.20	9.07
2-Butoxyethanol	20.25	20.82	20.95	5.10	6.57
Formamide	38.57	36.65	39.59	26.20	23.78
Acetamide	31.73	33.92	34.79	18.70	19.32
<i>N</i> -Methylformamide	30.50	30.15	32.99	18.80	19.95
Acrylamide	28.45	23.66	31.49	12.10	16.46
<i>N,N</i> -Dimethylformamide	23.96	24.86	27.72	13.70	17.47
<i>N</i> -Methylacetamide	27.21	28.78	30.08	18.70	16.79
Diethanolamine	29.26	26.57	25.69	7.00	9.26
Morpholine	21.79	21.66	23.97	4.90	6.03
<i>p</i> -Chlorophenol	22.62		24.95		7.66
Acetylsalicylic acid	22.39	22.16	22.41	6.60	6.03
Paracetamol	24.91	24.91	24.98	10.50	6.73
Water	47.81	47.81	47.80	16.00	17.24

^a Obtained from eqn (8).

From the comparison of these total parameters, a number of points can be made. In general, the three parameters are of comparable size, although we often encounter noticeable differences between them. What is essential is the fact that

even the total Hansen solubility parameter is sometimes significantly different from \sqrt{ced} . This is important because, to a large extent, the Hansen solubility parameters have been determined experimentally and reflect the real behavior of solvents.

Yet, to a large extent, the missing information (usually, the value of δ_p and/or δ_{hb}) was obtained as a difference from the cohesive energy density, eqn (2).¹⁴ As already mentioned, the underlying concept in the present work is the inadequacy of cohesive energy density to fully reflect the solvation characteristics of a compound. This is especially true when the compound is either acidic only (chloroform, indole, *etc.*) or basic only (ethers, ketones, *etc.*) or the pure state favors particular inter/intra-molecular associates (acid dimerization, *etc.*) that mask the solvation character of the compound. In these cases, eqn (2) is an unnecessary and misleading restriction. It should be pointed out that the above definitions for the four partial solvation parameters are entirely independent and their determination does not require any compromise or compliance with experimental measurements or external restrictive equations.

The above discussion might be facilitated if we could separate in an unequivocal manner the various compounds in two categories. In the first category would fall the compounds whose cohesion in their pure state does reflect adequately their solvation character. We could call them *homo-solvated* compounds. In the second category would fall the compounds that need another solvating compound to adequately show up their solvation character. We could call them *hetero-solvated* compounds. In the case of homo-solvated compounds the total solvation parameter should be close to the square root of c_{ed} . For this class of compounds we could then correct the s_p values accordingly (subtract s_d and s_{hb} from s_{total} all squared), especially, in the cases where different conformers of the same compound have drastically different dipole moments and their computation does not take them properly into account. In any case, the applications and the gained experience will guide us to properly refine the above definitions. We will come back to the definitions of partial solvation parameters after we present the applications.

3. Applications

In this section we will evaluate the capacity of partial solvation parameters to predict the solubility of various solutes of interest to the Pharmaceutical and Polymer community in a variety of solvents. For this purpose we must first select the tests to be performed. Since the comparison will also be made against partial solubility parameters, the prediction of solubility will be done through an adaptation of Hansen's criterion of solubility.¹⁴ Hansen's criterion for a solute 2 to be soluble in a solvent 1 is a small value (ideally equal to zero) of the following radius of solubility function:

$$R^2 = 4(\delta_{d1} - \delta_{d2})^2 + (\delta_{p1} - \delta_{p2})^2 + (\delta_{hb1} - \delta_{hb2})^2 \quad (\text{Hansen}) \quad (10)$$

The underlying idea behind this test is the similarity of solute and solvent as regards each of their dispersion, polar, and hydrogen bonding interactions as expressed by the corresponding solubility parameters. In other words, eqn (10) is a mathematical expression of the "similarity" principle for solubility, as discussed previously. As observed, the minimum value of Hansen's function-criterion is zero and negative values are not allowed.

The partial solvation parameters of this work are developed in an effort to account for both criteria of solubility, namely, the "similarity" and the "complementarity" of solute and solvent. The acidic and/or basic character of solute and solvent will primarily dictate their complementarity. An acidic solute will favor a basic solvent over an acidic one if all others remain the same. In this respect, the last term in eqn (10) should drastically change in order to favor complementary acid-base or hydrogen bonding interactions between the solute and the solvent. Various relevant equations have been proposed in the past.^{27,30,35} In general, such a term could be expressed as follows:

$$\Delta s_{hb} = c_1(s_{hb1} - s_{hb2})^2 + c_2(s_{a1} - s_{a2})(s_{b1} - s_{b2}) \\ + c_3(s_{a1} - s_{b1})(s_{a2} - s_{b2}) \quad (11)$$

When $c_1 = 1$ and $c_2 = c_3 = 0$, we recover the analog of eqn (10). When $c_1 = c_3 = 0$ and $c_2 = 2$, we recover the analog of Beerbower *et al.*²⁷ term. When $c_1 = 0$ and $c_2 = c_3 = 1$, we recover an earlier expression of ours.³⁵ Extensive testing is obviously needed for establishing a reliable and all-purpose form of eqn (11). In any case, care must be exercised in the use of this equation in order to avoid absurd results.

For the purposes of the present work we will adopt the suggestion of Beerbower *et al.*²⁷ and, thus, the analog of eqn (10) becomes:

$$\Delta s = 4(s_{d1} - s_{d2})^2 + (s_{p1} - s_{p2})^2 + 2(s_{a1} - s_{a2})(s_{b1} - s_{b2}) \quad (\text{PSP}) \quad (12)$$

There are some points to be made as regards eqn (12). As seen, the presence of complementary acidic and basic groups in compounds 1 and 2 does favor their miscibility as the product of the complementary components ($s_{a1}s_{b2} + s_{b1}s_{a2}$) are subtracted from the rest of the terms and, thus, reduce Δs . In fact, when the solute–solvent interactions lead to the formation of strong hydrogen bonds, one may expect that this might be the most important factor and that would lead even to negative values of Δs . The polar components may also contribute to the complementary matching criterion, though typically to a lesser extent. Thus, the first two terms in the rhs of eqn (12) may be considered as representing the similarity matching while the last term as expressing the complementarity matching criterion.

In Table 4 are compared the radii of solubility R^2 , as calculated by eqn (10), with the solvation differences Δs , as calculated by eqn (12), for pairs of paracetamol with 24 solvents. The miscibility data for these systems and for all systems reported in Tables 4 to 7 are obtained from the critical compilations of Jouyban.⁴⁴ There is one third criterion of solubility which is also compared in these tables and which reads:

$$\Delta s,2 = 4(\delta_{d1} - \delta_{d2})^2 + (\delta_{p1} - \delta_{p2})^2 \\ + 2(s_{a1} - s_{a2})(s_{b1} - s_{b2}) \quad (\text{Combined}) \quad (13)$$

As seen, in this equation the similarity matching is expressed through Hansen's dispersion and polar components of solubility parameter while the complementarity matching through the acidic and basic partial solvation parameters of this work.

Table 4 Evaluation of the solubility of PARACETAMOL in various solvents (*solubility limit* 100 g per kg solvent)

Solvent	Solubility ⁴⁴ g /kg of solvent	R ² HSP	Δs	Δs,2	Results
WATER	17.39	857.97	803.21	701.88	I,Y,Y,Y*
METHANOL	371.61	112.24	101.05	72.36	S,N,N,N
ETHANOL	232.75	49.14	23.58	-4.56	S,Y,N,Y
ETHYLENE GLYCOL	144.3	150.74	46.60	18.45	S,N,N,Y
1-PROPANOL	132.77	38.9	11.09	4.75	S,Y,N,Y
ISOPROPANOL	135.01	41.61	-17.83	7.25	S,Y,Y,Y
1-BUTANOL	93.64	39.61	5.61	20.70	I,N,Y,Y
1-PENTANOL	67.82	35.6	7.71	26.36	I,N,Y,Y
1-HEXANOL	49.71	38.49	11.29	34.15	I,N,Y,Y
1-HEPTANOL	37.43	44.84	21.27	45.23	I,N,Y,Y
1-OCTANOL	27.47	50.5	27.56	55.58	I,Y,Y,Y
ACETONE	111.65	68.78	26.41	-19.49	S,N,N,Y
METHYL ETHYL KETONE	69.99	92.65	41.50	7.32	I,Y,Y,N
METHYL ISOBUTYL KETONE	17.81	140.4	51.74	91.76	I,Y,Y,Y
TETRAHYDROFURAN	155.37	61.85	-53.69	-28.26	S,N,Y,Y
1,4-DIOXANE	17.08	100.06	-22.12	7.09	I,Y,N,N
ETHYL ACETATE	10.73	87.93	38.58	71.59	I,Y,Y,Y
ACETONITRILE	32.83	142.09	228.90	100.11	I,Y,Y,Y
DIETHYLAMINE	1316.9	161.72	-8.83	57.84	S,N,Y,N
N,N-DIMETHYLFORMAMIDE	1012.02	17.64	-14.50	-138.72	S,Y,Y,Y
DIMETHYL SULFOXIDE	1132.56	49.94	-125.65	-227.56	S,Y,Y,Y
ACETIC ACID	82.72	49.97	8.97	53.02	I,N,Y,Y
DICHLOROMETHANE	0.32	59.04	193.20	203.32	I,Y,Y,Y
CHLOROFORM	1.54	122	107.46	151.24	I,Y,Y,Y
Limited Radius of Solubility (squared) or Solvation Limit		50	5	19	
Successful Predictions		14/24	18/24	20/24	

*The first letter indicates whether the compound is soluble (S) or insoluble (I) in the given solvent. The second letter indicates whether the plain Hansen test (eqn (10)) is successful (Y) or unsuccessful (N). The third letter indicates whether the present PSP criterion (eqn (11)) test is successful (Y) or unsuccessful (N) and the fourth letter whether the combined test (eqn (12)) is successful (Y) or unsuccessful (N).

For a given solubility limit (in the case of paracetamol it is set equal to 100 g per kg of solvent) the limited radius of solubility, R^2 , or the solvation limits, Δs and $\Delta s,2$, for soluble and insoluble pairs are selected so that they give the maximum number of successful predictions. Thus, for paracetamol in Table 4, the selected criteria are $R^2 = 50$, $\Delta s = 5$ and $\Delta s,2 = 19$ as shown at the bottom of the table. For soluble systems, one prediction is successful when the calculated R^2 or Δs is smaller than the limited radius of solubility or the solvation limit. For insoluble systems, the prediction is successful when R^2 or Δs are bigger than the limited radius of solubility or the solvation limit. As an example, paracetamol is insoluble in water (solubility lower than 100 g per kg solvent) and this is correctly predicted by all three criteria since the calculated R^2 , Δs , and $\Delta s,2$ are bigger than the corresponding limiting values for

solubility. As a second example, paracetamol is soluble in diethylamine (solubility bigger than 100 g per kg solvent) but this is correctly predicted only with PSP and the criterion of eqn (12). The first case is indicated in the last column of Table 4 by the quadruplet I, Y, Y, Y (insoluble system, successful guess with Hansen criterion, successful guess with PSP criterion, successful guess with Combined criterion) in the corresponding row for water. The second case is indicated in the last column of Table 4 by the quadruplet S, N, Y, N (soluble system, unsuccessful guess with Hansen criterion, successful guess with PSP criterion, unsuccessful guess with Combined criterion) in the corresponding row for diethylamine.

As observed in Table 4, the Hansen criterion (eqn (10)) is successful in 14 cases, the PSP criterion (eqn (12)) is successful in 18 cases, while the Combined criterion (eqn (13)) is

successful in 20 cases out of the 24 total tests. It is also observed that the solvation limit Δs is significantly smaller than the limited radius of solubility.

In Table 5 are compared the radii R^2 and the solvation differences Δs and $\Delta s,2$ for pairs of aspirin with 23 solvents. In this case and for the set limit of solubility, the limited radius of solubility and the solvation limits are $R^2 = 40$, $\Delta s = 32$, and $\Delta s,2 = 14.8$, while the successful guesses are 14, 16 and 16, respectively, out of the 23 total tests with a variety of solvents. Negative values of Δs and $\Delta s,2$ are typically associated with soluble solute/solvent pairs but there may be insoluble cases with negative Δs and $\Delta s,2$ values. Similarly, high positive values are typically associated with low solubilities. Of interest in the case of aspirin is the solubility in acetone and in ethyl acetate, two typical hetero-solvated compounds. In both cases, their basic character complements the acidic character of aspirin. This is brought up by the PSP and

combined tests and predict it successfully while the plain Hansen fails to predict it.

Results for the solubility of benzoic acid in 29 solvents are reported in Table 6. The limiting values for the three criteria in this case are $R^2 = 100$, $\Delta s = 47$, and $\Delta s,2 = 60$, while the successful guesses are 18, 22 and 22, respectively, out of the 29 total tests. The corresponding results for salicylic acid are reported in Table 7, for which the limiting values for the three criteria are $R^2 = 81$, $\Delta s = 31$, and $\Delta s,2 = 1$, while the successful guesses are 13, 15 and 16, respectively, out of the 19 total tests. In both acid solutes there are cases of negative Δs and $\Delta s,2$ values associated with insoluble solute/solvent pairs. Particularly surprising are the highly negative values for the insoluble pairs benzoic acid/tetrahydrofuran and benzoic acid/*n*-methyl-2-pyrrolidone. The negative values in both cases are due to the large negative product of the s_a value of benzoic acid (12.78) with the large s_b values of tetrahydrofuran (11.88)

Table 5 Evaluation of the solubility of ASPIRIN in various solvents (*solubility limit: X_{ASPIRIN} = 0.044*)

Solvent	Solubility ⁴⁴ (Mole fraction of Aspirin, 25 C)	R ² HSP	Δs	Δs,2	Results
METHANOL	0.0719	275.45	278.84	220.32	S,N,N,N*
ETHANOL	0.0855	147.81	139.52	54.00	S,N,N,N
ISOPROPANOL	0.05232	91.62	41.21	20.97	S,N,N,N
1-BUTANOL	0.0453	79.06	61.42	14.51	S,N,N,Y
1-PENTANOL	0.0395	60.09	50.57	19.01	I,Y,Y,Y
1-HEXANOL	0.0393	49.32	38.84	16.93	I,Y,Y,Y
1-HEPTANOL	0.03892	43.45	38.86	15.22	I,Y,Y,Y
1-OCTANOL	0.0386	42.17	35.78	16.87	I,Y,Y,Y
ACETONE	0.0828	68.73	14.36	-56.13	S,N,Y,Y
TETRAHYDROFURAN	0.1904	21.86	-103.84	-111.14	S,Y,Y,Y
1,4-DIOXANE	0.0516	32.13	-95.22	-110.23	S,Y,Y,Y
ETHYL ACETATE	0.0448	47.06	-3.33	-21.41	S,N,Y,Y
ACETONITRILE	0.0185	194.96	206.42	112.89	I,Y,Y,Y
CHLOROFORM	0.206	30.97	31.29	43.76	S,Y,Y,N
1-DECANOL	0.03652	41.05	33.43	20.53	I,Y,Y,Y
2-BUTANOL	0.0536	68.81	87.87	16.68	S,N,N,N
2-METHYL-1-PROPANOL	0.03186	105.21	100.70	48.42	I,Y,Y,Y
2-METHYL-2-PROPANOL	0.06844	89.17	40.95	22.62	S,N,N,N
BUTYL ACETATE	0.03345	58.37	32.10	14.97	I,Y,Y,Y
DIETHYL ETHER	0.03529	116.78	2.92	13.85	I,Y,N,N
METHYL ACETATE	0.05287	52.25	-10.30	-24.84	S,N,Y,Y
PROPYLENE GLYCOL	0.017 (22.55 C)	177.80	164.15	48.19	I,Y,Y,Y
PYRIDINE	0.5348	16.40	-104.56	-114.73	S,Y,Y,Y
Limited Radius of Solubility (squared) or Solvation Limit		40	32	14.8	
Successful Predictions		14/23	16/23	16/23	

*As in Table 4.

Table 6 Evaluation of the solubility of benzoic acid in various solvents (solubility limit $X_{\text{benz. acid}} = 0.178$)

Solvent	Solubility ⁴⁴ (Mole fraction of Benzoic acid, 25 °C)	R ² HSP	Δs	Δs,2	Results
METHANOL	0.1632	273.77	184.60	208.25	I,Y,Y,Y*
ETHANOL	0.1789	148.13	66.00	49.97	S,N,N,Y
ISOPROPANOL	0.1937	102.56	-10.69	25.49	S,N,Y,Y
1-BUTANOL	0.2016	90.44	12.48	24.47	S,Y,Y,Y
1-PENTANOL	0.1839	77.85	8.98	32.00	S,Y,Y,Y
1-HEXANOL	0.1905	71.34	2.99	32.94	S,Y,Y,Y
1-HEPTANOL	0.1946	67.37	7.06	33.33	S,Y,Y,Y
1-OCTANOL	0.1987	67.77	7.41	37.24	S,Y,Y,Y
ACETONE	0.1857	107.69	-39.35	-41.07	S,N,Y,Y
TETRAHYDROFURAN	0.0734	50.24	-137.39	-105.59	I,N,N,N
ETHYL ACETATE	0.1649	86.08	-35.37	3.41	I,N,N,N
ACETONITRILE	0.0539	233.66	153.46	132.82	I,Y,Y,Y
CHLOROFORM	0.1283	59.81	52.78	82.31	I,N,Y,Y
2-METHYL-1-PROPANOL	0.1524	123.49	49.25	67.43	I,Y,Y,Y
BUTYL ACETATE	0.1699	101.05	5.28	45.62	I,Y,N,N
DIETHYL ETHER	0.1837	175.44	-33.15	47.76	S,N,Y,Y
1,4-DIOXANE	0.2853	54.25	-112.90	-109.72	S,Y,Y,Y
ACETIC ACID	0.1675	129.5	60.59	161.73	I,Y,Y,Y
ACETOPHENONE	0.1878	53.94	-13.92	-25.14	S,Y,Y,Y
BENZYL ALCOHOL	0.1441	19.01	-19.88	-13.17	I,N,N,N
N,N-DIMETHYLFORMAMIDE	0.4909	73.53	-70.16	-162.74	S,Y,Y,Y
DIMETHYL SULFOXIDE	0.5102	100.85	-206.09	-238.38	S,N,Y,Y
ETHYLENE GLYCOL	0.0884	289.05	101.19	99.14	I,Y,Y,Y
FORMAMIDE	0.1525	471.09	526.13	586.65	I,Y,Y,Y
GLYCEROL	0.0164	315.36	-3.41	29.30	I,Y,N,N
N-METHYL-2-PYRROLIDONE	0.1562 (23.8 °C)	58.12	-150.35	-171.43	I,N,N,N
PROPIONIC ACID	0.1887	117.48	46.97	129.02	S,N,Y,N
N,N-DIMETHYLACETAMIDE	0.5254	64.08	-142.66	-164.61	S,Y,Y,Y
METHYL FORMATE	0.3428	90.97	-16.04	25.66	S,Y,Y,Y
Limited Radius of Solubility (squared) or Solvation Limit		100	47	60	
Successful Predictions		18/29	22/29	22/29	

*As in Table 4.

and *n*-methyl-2-pyrrolidone (14.56) which excessively overrun the positive contribution of the “similarity” matching terms. The plain Hansen criterion (eqn (10)) also fails in these two cases.

Let us now examine the solubility of two representative polymers in a number of solvents of varying polarity. In thermodynamic terms, the function or quantity that dictates solubility is the free energy change on mixing rather than the plain energy exchange. Thus, for a binary mixture of a solvent 1 with a polymeric solute 2, the classical Flory–Huggins theory⁴⁵

gives the following expression for the molar Gibbs free energy of mixing:

$$\frac{\Delta G^M}{RT} = x_1 \ln \varphi_1 + x_2 \ln \varphi_2 + x_1 \varphi_2 \chi_{12} \quad (14)$$

where, x_i and φ_i are the mole fraction and volume fraction, respectively, of component i in the mixture. The Flory–Huggins χ_{12} parameter is the key characteristic parameter of the 1–2 system and dictates its miscibility. Miscibility requires low or negative χ_{12} values, the critical value being 0.5.

Table 7 Evaluation of the solubility of salicylic acid in various solvents (solubility limit $X_{\text{salic. acid}} = 0.100$)

Solvent	Solubility ⁴⁴ (Mole fraction of Salicylic acid, 25 C)	R ² HSP	Δs	Δs,2	Results
METHANOL	0.1321	158.81	151.50	136.51	S,N,N,N*
ETHANOL	0.1100	73.49	30.78	-3.00	S,Y,Y,Y
1-PENTANOL	0.1547	48.09	-19.19	-7.86	S,Y,Y,Y
1-OCTANOL	0.1549	58.25	-19.51	0.78	S,Y,Y,Y
ACETONE	0.1792	95.85	-98.02	-127.49	S,N,Y,Y
ETHYL ACETATE	0.1223	96.90	-84.53	-55.19	S,N,Y,Y
ACETONITRILE	0.0294	193.52	95.10	16.31	I,Y,Y,Y
CHLOROFORM	0.0015	104.57	51.74	86.10	I,Y,Y,Y
DIETHYL ETHER	0.1521	201.02	-84.04	-12.37	S,N,Y,Y
1,4-DIOXANE	0.2979	82.93	-155.73	-145.65	S,N,Y,Y
ACETIC ACID	0.0549	82.04	57.14	125.26	I,Y,Y,Y
ACETOPHENONE	0.1527	101.60	-50.13	-64.67	S,N,Y,Y
N,N-DIMETHYLFORMAMIDE	0.3840	38.09	-138.37	-254.10	S,Y,Y,Y
ETHYLENE GLYCOL	0.0851	174.82	75.33	51.22	I,Y,Y,Y
FORMAMIDE	0.0426	336.89	496.98	484.70	I,Y,Y,Y
GLYCEROL	0.0746	197.78	-26.97	-20.47	I,Y,N,N
PROPIONIC ACID	0.0661	89.34	38.08	101.51	I,Y,Y,Y
ETHYL FORMATE	0.0076	77.45	-54.39	-41.69	I,N,N,N
PROPYLENE GLYCOL	0.1136	79.08	59.77	-12.66	S,Y,N,Y
Limited Radius of Solubility (squared) or Solvation Limit		81	31	1	
Successful Predictions		13/19	15/19	16/19	

*As in Table 4.

So far, the relation of this parameter to the solubility parameters was given, almost invariably, by the following equation¹⁴

$$\begin{aligned}\chi_{12} &= \frac{V_1}{4RT} [4(\delta_{d1} - \delta_{d2})^2 + (\delta_{p1} - \delta_{p2})^2 + (\delta_{hb1} - \delta_{hb2})^2] \\ &= \frac{V_1}{4RT} R^2\end{aligned}\quad (15)$$

where, V_1 is the molar volume of the solvent. It is clear that, regardless of the strength of intermolecular interactions, this equation is calculating χ_{12} as being always positive. With our solvation criteria of eqn (12) and (13), eqn (15) becomes

$$\begin{aligned}\chi_{12} &= \frac{V_1}{4RT} [4(s_{d1} - s_{d2})^2 + (s_{p1} - s_{p2})^2 + 2(s_{a1} - s_{a2})(s_{b1} - s_{b2})] \\ &= \frac{V_1}{4RT} \Delta s\end{aligned}\quad (16)$$

and

$$\begin{aligned}\chi_{12} &= \frac{V_1}{4RT} [4(\delta_{d1} - \delta_{d2})^2 + (\delta_{p1} - \delta_{p2})^2 + 2(s_{a1} - s_{a2})(s_{b1} - s_{b2})] \\ &= \frac{V_1}{4RT} \Delta s, 2\end{aligned}\quad (17)$$

Eqn (16) and (17) do allow for negative values of the χ_{12} parameter (higher miscibility) in cases of strong specific intermolecular interactions such as the strong acid–base or hydrogen-bonding cross-associations. It should be pointed out that, for simplicity, we disregard here free-volume effects on the non-combinatorial part of the free energy of mixing, as was done in the original Flory–Huggins theory.⁴⁵ By differentiating between heats of mixing and non-combinatorial free energies of mixing in eqn (14), Patterson *et al.*⁴⁶ were able to calculate negative heats of mixing even with the original Scatchard–Hildebrand¹⁰ simple form of eqn (15) with the total solubility parameters. A more comprehensive equation-of-state treatment of HSPs was given earlier.³¹

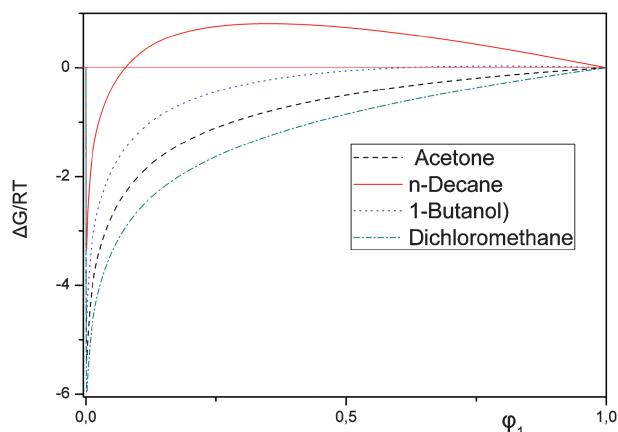


Fig. 3 The Gibbs free energy of mixing (eqn (13)) PMMA with acetone, *n*-decane, 1-butanol and dichloromethane at 298.15 K.

Before proceeding to the solubility calculations, it is interesting to see what eqn (14), in connection with eqn (16), predicts for the miscibility of polymer–solvent systems. In Fig. 3 is shown the variation of free energy change with solvent volume fraction in PMMA–solvent systems. As observed, there is an abrupt deep negative peak at very low solvent volume fractions for all four solvents shown. In other words, the sorption of even minute amounts of these solvents by the pure polymer is a favorable process. On the contrary, the dissolution of even minute amounts of the polymer may not be a favorable process for some solvents. In this work we have chosen a standard composition of $\varphi_1 = 0.95$ (dissolution of 5% of polymer, which is close to typical practical tests) in which the free energy change is calculated. If it is negative, the polymer is considered to be soluble in this particular solvent.

In Tables 8 and 9 are compared the predictions of solubility of poly(methyl methacrylate) (PMMA) and poly(vinyl acetate) (PVAc), respectively, in various solvents with the experimental data.¹⁴ The basic assumption has been made here that the relation of acidic to basic character of a polymer is the same as that of its oligomeric or monomeric analog. In our case, this implies that both tested polymers have basic character only. The degree of solubility is reported on the basis of a scale from 1 (highly soluble) to 6 (insoluble). With some degree of arbitrariness, we consider that the degrees 1 to 3 should exhibit a negative ΔG while the degrees 4 to 6 a zero or positive one. With this criterion we judge our predictions. If ΔG is negative and the system was found experimentally to be miscible, our prediction is successful. The calculations in Tables 8 and 9 have been done with the three alternative equations (15)–(17) for χ_{12} . As observed, both, the *PSP* and the *Combined* criterion (eqn (16) and (17)) present an improvement over the *Hansen* criterion (eqn (15)) for the prediction of polymer solubility. For both polymers the *PSP* criterion (eqn (16)) shows a success rate near 80% or more.

Steric or orientation factors may play an important role in the miscibility of polymer/solvent systems. This is a factor that is not taken into account by this approach and this might be in part an explanation for the cases of failure. A noticeable example is the case of acetic acid which dissolves the “easily accessible” PVAc but fails in the case of the more sterically

hindered PMMA (the carbonyl closer to the main chain). As observed, the PSP criterion successfully predicts the dissolution of PVAc but fails to predict the insolubility of PMMA since it does not incorporate the orientation factor in a direct manner. The other two criteria fail for both polymers.

Both tested polymers have basic character only. Although we could extract the needed information for the polymers from their metafiles and cosmo fragments (module COSMOfrag),³⁶ we have preferred in this work to use directly their Hansen solubility parameters¹⁴ and have interchanged them with the corresponding solvation parameters. The above results indicate that this is a rather good approximation of polymer PSPs. Of course, there may be better sets of PSPs for the polymers and their search is worthy. As an example, if we change the s_d of PMMA to 12.52 MPa^{1/2}, the successful predictions with the PSP criterion would increase from 27 to 29/33. Similarly, by changing s_d of PVAc from 20.93 to 19.93 and s_p from 11.27 to 9.27, the successful prediction with the PSP criterion in Table 9 would increase from 26 to 28/33. Thus, there is room for refinement of polymer PSPs and no new experimental solubility data are needed for their determination but a systematic examination of the already available experimental information.

A last test regards the effect of solvent composition (in the case of mixed solvents) on the solubility of polymers. A case of interest is the solubility of PMMA (3) in the mixed solvent acetone (1) + *n*-hexane (2). In Fig. 4 is shown the variation of $\chi_{12,3}$ with the composition of the solvent (on a solute-free basis) for this system at 298 K. By using the classical criterion of $\chi < 0.5$ for solubility, this particular system is predicted by the current PSP approach (eqn (16)) to be miscible when the volume fraction of acetone in the mixed solvent is bigger than 0.53 and that there is a minimum in χ at a volume fraction near 0.85. This information is in agreement with the experimental information for this system.⁴⁷ No special mixing and combining rules were needed in this example for the hydrogen bonding solvation parameters, but this possibility could be explored in cases of solvent pairs both of which have non-zero acid/base parameters.

4. Discussion

It is widely recognized that the concept of solubility parameter had a remarkable impact on the advancement of solubility theories and prediction strategies for the selection of solvents in numerous processes. The pioneering work of Hansen¹¹ and his introduction of Hansen solubility parameters have enhanced very much the capacity and practical usefulness of the original concept as introduced by Hildebrand and Scott¹⁰ and of an early division of solubility parameters into dispersion and polar components, proposed by Blanks and Prausnitz.⁴⁶ Hansen's handbook¹⁴ and the continuing updates of ref. 30, with tabulations of the three partial solubility parameters (HSP), incorporate a large amount of knowledge and valuable practical experience from the broader field of solubility. The present work attempts to further enhance the strength and capacity of this concept by removing some unnecessary restrictions that accompany it. In order to do this, we had to reconsider the very foundations of the concept and propose the solvation rather than the cohesion as the basis of our

Table 8 Prediction of PMMA solubility in various solvents with eqn (14)–(16). For PMMA, $s_d = 18.64$, $s_p = 10.52$, $s_a = 0$, $s_b = 7.51$. Data from Hansen¹⁴

Solvent	Extent of Solubility	Calculations with Partial Solvation Parameters			Calculations with HSPs		Calculations with δ_d , δ_p , s_a , and s_b				
		Equation 15	χ	ΔG	Solubil. Predict.	Equation 14	χ	Solubil. Predict.	Equation 16	χ	Solubil. Predict.
ACETIC ACID	6*	0.68	-0.017	N**	0.64	N	1.00	N			
ACETONE	1	0.40	-0.031	Y	0.30	Y	0.29	Y			
ACETONITRILE	6	0.74	-0.014	N	0.55	N	0.54	N			
ACETOPHENONE	1	0.05	-0.049	Y	0.26	Y	0.09	Y			
BENZENE	5	1.00	-0.002	N	1.51	Y	1.00	N			
1-BUTANOL	6	1.30	0.014	Y	1.11	Y	1.14	Y			
BUTYL ACETATE	1	0.79	-0.012	Y	1.07	N	1.05	Y			
CARBON TETRACHLORIDE	5	1.08	0.003	Y	1.67	Y	1.11	Y			
CHLOROFORM	1	-0.80	-0.091	Y	0.50	Y	-0.60	Y			
CYCLOHEXANE	6	1.36	0.017	Y	1.98	Y	1.36	Y			
DICHLOROMETHANE	1	-0.33	-0.068	Y	0.50	Y	-0.26	Y			
DIETHYL ETHER	6	0.87	-0.008	N	1.43	Y	1.34	Y			
DIETHYLAMINE	6	1.15	0.006	Y	1.32	Y	1.36	Y			
DIMETHYL SULFOXIDE	1	0.51	-0.026	Y	0.30	Y	0.33	Y			
1,4-DIOXANE	1	0.97	-0.003	Y	0.72	Y	0.70	Y			
ETHANOL	6	1.53	0.025	Y	1.04	Y	1.23	Y			
ETHYL ACETATE	1	0.42	-0.031	Y	0.59	Y	0.59	Y			
ETHYLENE GLYCOL	6	1.73	0.035	Y	2.01	Y	1.58	Y			
GLYCEROL	6	1.57	0.027	Y	2.92	Y	1.39	Y			
n-HEXANE	5	1.18	0.008	Y	2.96	Y	2.21	Y			
METHANOL	6	0.85	-0.009	Y	1.16	Y	0.70	Y			
METHYL ETHYL KETONE	1	0.51	-0.026	Y	0.79	Y	0.27	Y			
METHYL ISOBUTYL KETONE	1	0.38	-0.032	Y	0.96	Y	0.81	Y			
MONOCHLOROBENZENE	1	0.23	-0.040	Y	0.99	Y	0.40	Y			
N,N-DIMETHYLFORMAMIDE	1	1.25	0.011	N	0.24	Y	0.13	N			
1-PENTANOL	6	1.43	0.020	Y	1.01	N	1.22	Y			
1-PROPANOL	6	1.43	0.020	Y	0.74	N	1.14	Y			
1,2 PROPYLENE GLYCOL	6	1.70	0.034	Y	1.93	Y	1.31	Y			
PYRIDINE	1	0.01	-0.051	Y	0.04	Y	0.03	Y			
STYRENE	2	1.13	0.005	N	1.19	N	1.06	N			
TETRAHYDROFURAN	1	0.12	-0.045	Y	0.31	Y	0.30	Y			
TOLUENE	2	0.89	-0.007	Y	1.52	N	0.91	Y			
m-XYLENE	4	1.14	0.006	Y	2.09	Y	1.39	Y			
Successful Predictions					27/33		26/33		28/33		

*1: soluble; 2: almost soluble; 3: strongly swollen, slight solubility; 4: swollen; 5: little swelling; 6: no visible effect. **Y, successful prediction; N, unsuccessful prediction.

Table 9 Prediction of PVAc solubility in various solvents with eqn (14)–(16). For PVAc, $s_d = 20.93$, $s_p = 11.27$, $s_a = 0$, $s_b = 9.66$. Data from Hansen¹⁴

Solvent	Extent of Solubility	Calculations with Partial Solvation Parameters			Calculations with HSPs		Calculations with δ_d , δ_p , s_a , and s_b	
		χ	ΔG	Solubil. Predict.	χ	Solubil. Predict.	χ	Solubil. Predict.
ACETIC ACID	1*	0.60	-0.021	Y**	1.11	N	1.15	N
ACETONE	1	0.67	-0.018	Y	0.94	Y	0.88	Y
ACETONITRILE	1	0.91	-0.006	Y	0.99	Y	0.92	Y
ACETOPHENONE	1	0.00	-0.051	Y	0.59	Y	0.17	Y
BENZENE	1	1.04	0.001	N	2.22	N	1.38	N
1-BUTANOL	5	1.85	0.041	Y	1.54	Y	1.49	Y
BUTYL ACETATE	1	1.26	0.012	N	2.33	N	2.18	N
CARBON TETRACHLORIDE	1	1.14	0.006	N	2.54	N	1.63	N
CHLOROFORM	1	-0.60	-0.081	Y	0.99	Y	-0.52	Y
CYCLOHEXANE	4	1.62	0.030	Y	3.17	Y	2.14	Y
DICHLOROMETHANE	1	-0.18	-0.060	Y	1.11	N	0.00	Y
DIETHYL ETHER	4	1.30	0.013	Y	2.76	Y	2.49	Y
DIETHYLAMINE	5	1.62	0.030	Y	2.51	Y	2.40	Y
DIMETHYL SULFOXIDE	1	0.58	-0.023	Y	0.38	Y	0.44	Y
1,4-DIOXANE	1	1.07	0.002	N	1.19	N	1.18	N
ETHANOL	4	1.98	0.047	Y	1.22	Y	1.39	Y
ETHYL ACETATE	1	0.74	-0.014	Y	1.46	N	1.40	N
ETHYLENE GLYCOL	6	2.12	0.055	Y	1.89	Y	1.53	Y
GLYCEROL	6	1.94	0.045	Y	2.65	Y	1.33	Y
n-HEXANE	6	1.73	0.035	Y	4.85	Y	3.61	Y
METHANOL	1	1.16	0.007	N	1.29	N	0.89	Y
METHYL ETHYL KETONE	1	0.88	-0.007	Y	1.78	N	0.93	Y
METHYL ISOBUTYL KETONE	1	0.60	-0.021	Y	2.34	N	1.95	N
MONOCHLOROBENZENE	1	0.24	-0.040	Y	1.62	N	0.66	Y
N,N-DIMETHYLFORMAMIDE	1	1.56	0.027	N	0.46	Y	0.44	Y
1-PENTANOL	2	2.04	0.051	N	1.62	N	1.66	N
1-PROPANOL	4	1.94	0.046	Y	1.60	Y	1.39	Y
1,2 PROPYLENE GLYCOL	6	2.19	0.058	Y	1.88	Y	1.35	Y
PYRIDINE	1	0.04	-0.050	Y	0.26	Y	0.15	Y
STYRENE	1	1.16	0.006	N	1.85	N	1.48	N
TETRAHYDROFURAN	1	0.29	-0.037	Y	0.84	Y	0.82	Y
TOLUENE	1	0.98	-0.002	Y	2.42	N	1.42	N
m-XYLENE	4	1.27	0.012	Y	3.11	Y	1.95	Y
Successful Predictions					26/33		19/33	
								23/33

*As in Table 8. **As in Table 8.

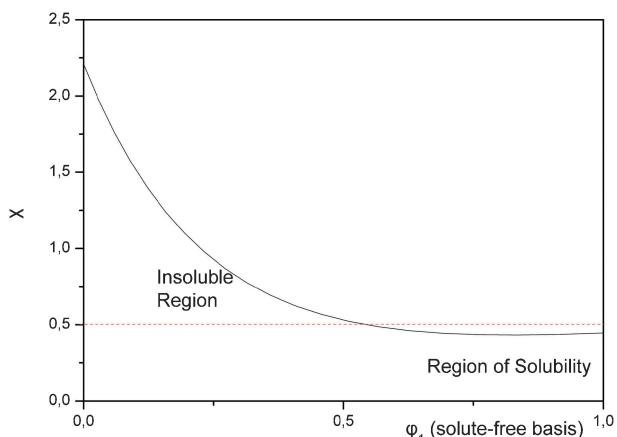


Fig. 4 The variation with solvent composition of the Flory–Huggins interaction parameter, χ , for the system PMMA–mixed solvent (acetone (1) + *n*-hexane (2)) at 298 K. The dashed line is the base line of the critical $\chi = 0.5$. The minimum is near $\varphi_1 = 0.85$.

development. In this respect, the various chemical compounds are separated conveniently into two major classes, the *homosolvated* and the *hetero-solvated*. If all compounds were homosolvated, the identification of total solubility parameter with the square root of cohesive energy density would have been fully justified. The “similarity matching” strategy of solubility would have been also rather legitimate. The intermolecular interactions are, however, much more complex than this “cohesion” picture implies. The recognition of the class of hetero-solvated compounds appears to be a useful step towards a systematic and sound improvement of the original solubility parameter concept. In order to avoid any confusion with HSP and in order to underline this broadening of the concept, we have coined the name of *Partial Solvation Parameters* (PSP) s_d , s_p , s_a and s_b , for the dispersive, polar, acidic and basic, respectively, character of the compounds. The first two are used for expressing the “similarity matching” criterion of solubility while the last two are used to primarily express the “complementarity matching” criterion. Since the “similarity matching” criterion was the basis of HSPs, the new solvation parameters s_d and s_p are closely similar to the corresponding δ_d and δ_p HSP parameters, as shown in Tables 1 and 3. The new s_a and s_b parameters do not have their counterpart HSP parameters but there are various sets of δ_a and δ_b that have been proposed in the literature.^{18,19,26–30,35}

Three entirely independent routes are proposed in this work for the calculation of PSPs. Besides independence, the three calculation routes do not require any experimental data, not even the prior synthesis of the compound. All needed information comes from quantum-mechanics-based computations in the frame of COSMO-RS theory³⁶ even for oligomers of relatively large molar mass. Although the homomorph concept was already existing in the literature,^{14,43,47} there is a crucial new element in the calculation of s_d through which the compound of interest and its homomorph are brought into the corresponding solvation cavity volumes (eqn (3)). Since the homomorph is exclusively a hydrocarbon molecule, it is easy to find its solubility parameter δ_d either directly in current compilations^{14,42} or through a robust group-contribution

scheme.^{30,32,35} An inspection in Table 1 shows that s_d and δ_d are indeed closely comparable parameters. Noticeable differences are observed in the first members of the homologous series. As we have seen from the applications of the previous section, the pairs s_d , s_p and δ_d , δ_p are essentially interchangeable. A definite answer to the question, which pair gives better results, can be given after an extensive comparison comprising large varieties of solutes and processes. The fact, however, that the proposed calculation routes are entirely independent, permits the refinement of solvation parameters s_d and/or s_p for homo-solvated compounds since for them an additional source of information, eqn (2), is valid. Care should be exercised, of course, in this step of meeting eqn (2) in order to avoid overestimations or underestimations of PSPs. In this work we have not done this but plan to do it after we acquire sufficient feedback from more extensive applications. Analogous challenges and dangers exist in the case of hetero-solvation and need to be addressed in future iterations of the PSP approach.

The solvation parameter s_p is proposed to be calculated in a most simple manner for the very simple reason that it is the least well understood. It is not only the difficulty in fixing the borderlines in a COSMO σ -profile, which determine the region of polar interactions. It is the very dipole moment itself which causes much ambiguity since it has different values depending on whether it is calculated in gas phase, in polar or in apolar solvents. Since the solvation environment does affect the dipole moment of the compound, the parameter s_p has elements that could be parts of the “complementarity matching” criterion or be characteristics of hetero-solvated compounds. This is probably the reason for the scattered values observed in Fig. 5 for the corresponding solubility parameter δ_p . The straight line for s_p shown in Fig. 5 is definitely an oversimplified compromise but we should keep in mind that a significant part of the scattered data was obtained from subtraction or from fitting data to the constraining eqn (2).

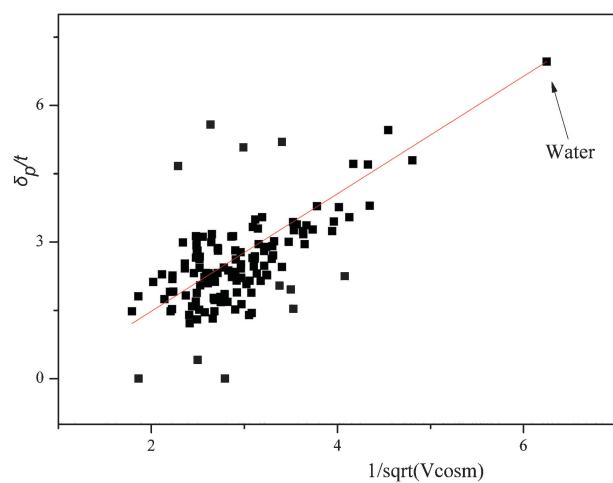


Fig. 5 The variation of the ratio of “experimental” δ_p^{14} over the dipole moment t^{36} with the inverse of the square root of V_{cosm} . The “polar” straight line is calculated from eqn (8) for s_p . It starts from water, our reference compound which stands alone in the right upper corner, and descends through the rest of the data as a least-squares line.

As already mentioned, the new solvation parameters s_a and s_b do not have counterpart HSPs to compare with, although one might split the solubility parameter δ_{hb} into its acidic and basic components,^{18,19,26–30,35} but this is already a restriction in their absolute values. In addition to this restriction, the key problem is the reference scale of acidity and basicity. Since our main objective was to develop an easy-to-apply scheme, even for not synthesized compounds, the quantum-mechanics computation of molecular descriptors was the preferred route. The COSMO σ -profiles offer a reliable description of the molecular surface charge density distribution and the third σ -moments HB_acc3 and HB_don3 are a good basis for the development of such reference scales. Obviously, the use of additional σ -moments would represent more accurately the acidic and basic character of the compound but the third moments seem to have captured the bulk of it. This is the picture that emerges from the alternative calculations shown in the Appendix and which are based on the widely tested and used Abraham's acid/base descriptors.⁷ Our selection of water as the reference neutral compound may be judged as arbitrary but it is convenient and easy to match with the common chemistry experience of acidity and basicity and it gives the very simple defining eqn (6). Abraham's acid/base descriptors⁷ also indicate that the selection of water as the reference neutral compound is a rather good choice. Above all, however, a change in the reference neutral compound may change the absolute values of s_a or s_b but will not change their relative magnitude when comparing two compounds. Although a comparison of s_a and s_b with the corresponding solubility parameters cannot be made on a common scale, we may compare s_{hb} with δ_{hb} . As mentioned earlier, these two parameters may differ substantially, especially, in hetero-solvated compounds (*cf.* Table 2). It is this difference that makes *solvation* and *solubility* parameters distinctly different.

The comparisons that have been made in the previous section are heavily based on existing criteria developed for the partial solubility parameters. Doubtless, eqn (11)–(13) must be refined in order to reliably encompass all solute–solvent cases. Nevertheless, the overall picture that emerges from the comparisons made in Tables 4–9 is that the partial solvation parameters offer a significant improvement over the corresponding HSPs in predicting solubilities. The major part of this improvement is due to the new solvation parameters s_a and s_b . This has been verified by interchanging the “similarity matching” parameters s_d and s_p with the corresponding δ_d and δ_p . As already mentioned, there is some degree of arbitrariness in the selection of the solubility limits in Tables 4–9 but the above overall picture does not change by reasonably changing these limits.

In view of the expansion of the concept of solubility parameter, other criteria of solubility may be applied with PSPs. In a general manner, such a criterion could have a form like the following:

$$\Delta s = a_1(s_{d1} - s_{d2})^2 + a_2(s_{p1} - s_{p2})^2 + a_3 s_{p1} s_{p2} + \Delta s_{hb} \quad (18)$$

where, Δs_{hb} is given by eqn (11) and the factors a_i are to be determined for each class of applications. Preliminary trials have shown that the set of factors, $a_1 = 2$, $a_2 = 2$, $a_3 = -1$,

$c_1 = c_3 = 0$, $c_2 = 2$, is a promising one. If a constant volumetric term or an “entropic” composition-dependent term were added in eqn (18) as suggested by eqn (14), it would constitute a QSPR/LSER-type equation for various properties, including solubility. The molecular descriptors in such a case would have been simple combinations of the four PSPs. Obviously, many more tests should be performed before deciding on the form of the working equation (18).

A most convenient feature of the methodology of Hansen solubility parameters is the solubility sphere¹⁴ of a solute, which is mathematically expressed by eqn (14). Solvents with coordinates δ_d , δ_p , and δ_{hb} falling within the sphere of radius R are most likely to be good solvents for this solute. With the PSP criterion—eqn (16), the solubility sphere is no longer useful and must be replaced by an alternative visualization scheme. Such a scheme could be constructed as follows: first, we create the *solubility circle* in the plane of s_d and s_p with the first two terms of the rhs of eqn (16). An axis through the center of the solubility circle and perpendicular to its plane represents the third term of eqn (16), or the general complementarity matching term. At various heights along the axis, the radius of the solubility circle also varies. The more negative the axis coordinate, the bigger the radius of the solubility circle can be (larger differences in dispersion and polar components of solute and solvent are tolerable). In this way, one could visualize the solubility region as a *solubility cone* rather than a *solubility sphere*. Alternatively, the original¹⁴ sphere visualization scheme could be retained for the similarity matching terms while the complementarity matching terms could be used to calculate the radius of a penetrating sphere around each solvent point. In this way, good solvents located outside the central *similarity* sphere may enter it and bad solvents located inside the *similarity* sphere may exit it.

In this work, we have tried to avoid involved equations and complex thermodynamic analysis, respecting the simplicity of the concept of solubility parameter which is also transferred as an integral feature to PSPs and a source of their strength. This simplicity, along with the strong quantum chemical basis of PSPs, warrants an expansion of the approach to an equation of state framework, as we have shown recently.^{31,38} Such a framework would securely expand the range of applicability of the PSP methodology over an extended range of external conditions of temperature, pressure and composition. Systems of ionic liquids, supercritical fluids or swollen polymers could, then, be handled in a straightforward manner and their properties predicted, and this is a subject of future work.

5. Conclusions

In this work, an effort has been made to enhance the capacity and strength of the solubility parameter approach by reconsidering its foundation. The validity of eqn (2)—the cornerstone of the current solubility parameter methodology—has been reexamined in the light of modern quantum-mechanics calculations. The chemical compounds are divided into two major classes, the homo-solvated and the hetero-solvated ones, depending on whether they obey eqn (2) or not. Eqn (2) is not valid for hetero-solvated compounds because the cohesive forces in their pure state do not show up the full potential of

their intermolecular interactions originated from their molecular surface charge distribution. To account for this, the partial solvation parameters (PSP) have been introduced. The new PSPs depict in a consistent manner the capacity of the compound to interact with dispersive, polar, Lewis-acidic and Lewis-basic interactions. Water has been chosen as the reference neutral homo-solvated compound for the acidity and basicity scales. The acidic and basic PSPs obtained from COSMOments are in good agreement with the ones obtained from Abraham's acid/base descriptors. PSP methodology present a significant improvement over the classical Hansen solubility parameter (HSP) methodology¹⁴ for the prediction of solubility of various solutes in a variety of solvents. PSPs preserve the conceptual simplicity of HSPs and are calculated, entirely independently, by simple equations even for compounds not synthesized yet. Because of their sound foundation, it is hoped that PSPs will contribute in the design of new materials, at least for a first screening, as molecular descriptors in QSPR/LSER-type schemes. Ionic interactions have not been considered in this work but the PSP methodology can be easily extended at least to systems of ionic liquids and to systems for which the cosmo-files of the COSMO-RS theory³⁶ are either available or can be obtained in reasonable computation time.

Appendix: calculation of the hydrogen bonding solvation parameters using Abraham's acid/base descriptors

There are similarities between Abraham's⁷ molecular descriptors and partial solvation parameters (PSP) but there are, also, fundamental structural differences. Thus, the mapping of one

set onto the other is not a trivial issue and will be treated in detail in a separate forthcoming publication. However, for the purposes of this Appendix, it suffices to state that Abraham's acidity/basicity is a "combined" one. It combines a weak or residual acidity/basicity, which is almost omnipresent and is exhibited even by saturated hydrocarbons, with a strong acidity/basicity, which is exhibited by compounds interacting with strong specific forces such as the hydrogen bonding interactions. On the other hand, the hydrogen bonding PSPs, as the name implies, reflect only the strong acid/base character of the compounds.

A simple way to separate weak and strong components of Abraham's acidity/basicity descriptors is through the homomorph concept exposed in the main text. As an example, methanol may be considered to possess the weak acidity/basicity of its homomorph ethane and a strong acidity/basicity component due to its OH \cdots OH hydrogen bonding interaction. Thus, Abraham's A and B descriptors may be analysed into their components as follows:

$$A = A_{\text{weak}} + A_{\text{strong}} = A_{\text{hom}} + \text{HB}_a \quad (\text{A-1})$$

and

$$B = B_{\text{weak}} + B_{\text{strong}} = B_{\text{hom}} + \text{HB}_b \quad (\text{A-2})$$

In the above equations, subscript hom stands for homomorph.

Columns 2 and 3 of Table A below contain Abraham's acid/base descriptors for a number of common solvents as obtained from the COSMObase.³⁹ The next two columns report the acid/base descriptors of the corresponding homomorph of each solvent. The next columns 6 and 7 report the strong

Table A Abraham's acid/base descriptors and calculated hydrogen-bonding PSPs

Solvent	B	A	B _{hom}	A _{hom}	HB _b	HB _a	s _{hb}	s _b	s _a
Water	0.663	0.676	-0.042	0.026	0.705	0.651	42.30	29.91	29.91
Methanol	0.527	0.360	-0.033	0.0227	0.5596	0.3373	24.91	19.38	15.66
Ethanol	0.5182	0.2942	-0.019	0.0201	0.5376	0.2741	19.68	15.79	11.74
1-Propanol	0.5157	0.2954	-0.006	0.0175	0.5221	0.2779	17.07	13.59	10.32
1-Butanol	0.5231	0.2872	0.0064	0.0151	0.5167	0.2721	15.21	12.14	9.17
1-Pentanol	0.5491	0.3302	0.0197	0.0125	0.5294	0.3177	14.47	11.26	9.08
1-Hexanol	0.5642	0.33	0.0328	0.01	0.5314	0.320	13.44	10.46	8.45
1-Heptanol	0.5748	0.325	0.0454	0.0075	0.5294	0.3175	12.57	9.79	7.89
1-Octanol	0.5871	0.3223	0.0587	0.005	0.5284	0.3173	11.86	9.23	7.45
1-Nonanol	0.6002	0.3201	0.0716	0.0025	0.5286	0.3176	11.26	8.76	7.07
1-Decanol	0.6179	0.3182	0.0845	0.0	0.5334	0.3182	10.79	8.41	6.76
1-Undecanol	0.627	0.3148	0.0977	-0.003	0.5293	0.3173	10.30	8.02	6.46
1-Dodecanol	0.6435	0.3133	0.1105	-0.005	0.533	0.3183	9.94	7.74	6.23
1-Tridecanol	0.6522	0.31	0.1237	-0.008	0.5285	0.3175	9.54	7.42	5.99
1-Tetradecanol	0.6654	0.3072	0.1365	-0.01	0.5289	0.3172	9.22	7.18	5.79
1-Pentadecanol	0.678	0.3048	0.1494	-0.013	0.5286	0.3173	8.93	6.95	5.61
1-Hexadecanol	0.6916	0.3022	0.1626	-0.015	0.529	0.3173	8.67	6.75	5.44
1-Heptadecanol	0.704	0.2998	0.1755	-0.018	0.5285	0.3174	8.42	6.56	5.29
1-Octadecanol	0.7215	0.298	0.1885	-0.020	0.533	0.3181	8.24	6.42	5.16
1-Nonadecanol	0.7307	0.2947	0.2015	-0.023	0.5292	0.3173	8.00	6.23	5.02
1-Eicosanol	0.7431	0.2922	0.2145	-0.025	0.5286	0.3173	7.81	6.08	4.90
Phenol	0.2727	0.5636	0.135	0.0124	0.1377	0.5512	14.06	6.09	12.68
Benzyl alcohol	0.5229	0.307	0.148	0.0092	0.3749	0.2978	12.59	9.23	8.56
m-Cresol	0.3002	0.5404	0.135	0.0124	0.1652	0.528	12.98	6.14	11.43
<i>o</i> -Cresol	0.2736	0.5299	0.148	0.0092	0.1256	0.5207	12.55	5.36	11.35
Formic acid	0.3342	0.7297	0.067	0.0139	0.2672	0.7158	25.18	12.75	21.72
Acetic acid	0.4608	0.593	0.0859	0.01	0.3749	0.583	20.98	12.80	16.62
Propionic acid	0.4594	0.5728	0.0924	0.0082	0.367	0.5646	18.25	11.18	14.43
<i>n</i> -Butyric acid	0.4665	0.567	0.1067	0.0051	0.3598	0.5619	16.36	9.97	12.97
<i>n</i> -Pentanoic acid	0.4798	0.5636	0.1177	0.0031	0.3621	0.5605	15.01	9.17	11.88

Table A (continued)

Solvent	B	A	B_{hom}	A_{hom}	HB_b	HB_a	s_{hb}	s_b	s_a
n-Hexanoic acid	0.4906	0.5598	0.1314	0.0004	0.3592	0.5594	13.94	8.50	11.04
Ethyl acetate	0.5521	0.0146	0.1067	0.0051	0.4454	0.0095	11.23	11.10	1.69
Ethyl propionate	0.5531	0.0095	0.1108	0.0038	0.4423	0.0057	10.22	10.15	1.20
Dimethyl ether	0.3815	0.0398	-0.019	0.0201	0.4009	0.0197	13.83	13.47	3.11
Diethyl ether	0.3975	0.0339	0.0064	0.0151	0.3911	0.0188	10.85	10.58	2.42
Methyl-n-propyl ether	0.3945	0.0335	0.0064	0.0151	0.3881	0.0184	10.76	10.50	2.38
Di-n-butyl ether	0.4503	0.0248	0.0328	0.01	0.4175	0.0148	8.39	8.23	1.61
Di-n-octyl ether	0.5509	0.004	0.1626	-0.015	0.3883	0.0191	5.95	5.79	1.34
Dinonyl ether	0.5764	-0.001	0.1885	-0.020	0.3879	0.019	5.62	5.48	1.26
Methylamine	0.7229	0.0884	-0.033	0.0227	0.7555	0.0657	22.53	21.54	6.61
Ethylamine	0.7178	0.081	-0.019	0.0201	0.7372	0.0609	18.64	17.85	5.34
n-Propylamine	0.7185	0.0784	-0.006	0.0175	0.7249	0.0609	16.29	15.59	4.71
n-Butylamine	0.728	0.0754	0.0064	0.0151	0.7216	0.0603	14.68	14.06	4.23
n-Pentylamine	0.7396	0.073	0.0197	0.0125	0.7199	0.0605	13.47	12.90	3.89
n-Hexylamine	0.7522	0.0703	0.0328	0.01	0.7194	0.0603	12.53	12.00	3.62
n-Heptylamine	0.7461	0.0691	0.0454	0.0075	0.7007	0.0616	11.64	11.12	3.43
n-Octylamine	0.7586	0.0668	0.0587	0.005	0.6999	0.0618	11.00	10.51	3.25
n-Nonylamine	0.7696	0.0644	0.0716	0.0025	0.698	0.0619	10.44	9.97	3.09
n-Decylamine	0.7822	0.062	0.0845	0.0	0.6977	0.062	9.97	9.53	2.96
Undecylamine	0.795	0.0594	0.0977	-0.003	0.6973	0.0619	9.56	9.13	2.83
n-Dodecylamine	0.8074	0.057	0.1105	-0.005	0.6969	0.062	9.20	8.78	2.73
Dimethylamine	0.5515	0.0758	-0.019	0.0201	0.5709	0.0557	16.46	15.65	5.09
Trimethylamine	0.4004	0.0461	-0.004	0.0177	0.4045	0.0284	12.00	11.57	3.19
Diethylamine	0.5136	0.0557	0.0064	0.0151	0.5072	0.0406	12.28	11.78	3.47
Di-n-propylamine	0.5298	0.0505	0.0328	0.01	0.497	0.0405	10.41	9.98	2.97
Triethylamine	0.4417	0.0224	0.0278	0.0118	0.4139	0.0106	9.29	9.16	1.53

components of the acid/base descriptors, which are of direct interest to us here. These components HB_b and HB_a may be considered as constituting Abraham's proper hydrogen-bonding acceptor and donor scales, respectively. They may be used in the very same way COSMOments $\text{HB}_{\text{acc}3}$ and $\text{HB}_{\text{don}3}$ were used in the main text.

According to Abraham's combined acidity/basicity scale, water is an almost neutral or slightly acidic compound, as shown in Table A. This neutrality is retained in its strong acid/base components, though now water appears slightly basic. As in the main text, water will be selected here as our reference neutral compound. The hydrogen bonding PSPs are, then, obtained in a straightforward manner by following the procedure exposed in the main text and are shown in the last three columns of Table A.

A comparison of the hydrogen bonding PSPs obtained from Abraham's HB_b and HB_a acid/base descriptors with the corresponding PSPs obtained from COSMOments $\text{HB}_{\text{acc}3}$ and $\text{HB}_{\text{don}3}$ in the main text shows that the two sets are very similar. This may be taken as a double check of the validity of our PSP method. What is, however, much more important is the insight gained from this exercise. It proves that Abraham's descriptors are a powerful source of reliable information for solute–solvent interactions. It should be mentioned in this regard that Abraham's descriptors obtained from COSMObase³⁹ are close to but not identical with the original “experimental” data. The essence of the calculations, of course, will not change by using the original data but the use of COSMObase-type compilations is often advantageous when having process and product simulators in mind.

I am thankful to one of the (unknown) Reviewers of this work, who brought into my attention one chapter in the latest version of ref. 30, where Abraham's descriptors were also used for splitting Hansen's δ_{hb} into its acidic and basic components

and an interesting alternative to eqn (11) was proposed. There are major differences between the present approach and that of ref. 30. First, in ref. 30, Abraham's combined acidity/basicity, rather than the proper hydrogen-bonding one, is mapped onto hydrogen-bonding δ_a and δ_b . Second, this method³⁰ has as a prerequisite the knowledge of δ_{hb} , that is, it is not a predictive method. Third, this method³⁰ cannot handle appropriately hetero-solvation since it is restricted by δ_{hb} . As a consequence, the calculations by the two methods are substantially different and their deviations may be often larger than 100%.

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