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Understanding the volume–solubility dependence: the mobile order and disorder view†

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ABSTRACT: In the liquid phase, both the ephemeral character and the mobility of all intermolecular contacts and of H-bonds in particular have the result that, at constant pressure, the dissolution of a liquid or solid compound does not require the breaking of the solvent matrix. Contrary to the widely accepted idea, the observed volume–solubility relationships do not arise from the energy required to create cavities of the solute dimension in the solvents for locating the foreign molecules, but always have a hybrid origin stemming from the balance of elementary processes involved in the overall solubility phenomenon. In order to stress the quantitative solubility dependence of non-electrolytes on their molar size, the solubility of aprotic substances in solvents of varying size, polarity and hydrogen bond ability was predicted from the mobile order and disorder (MOD) theory-derived solubility model. Obtained on a strictly thermodynamic basis, the model allows reliable estimates of solubility and provides a correct understanding of the solution behavior. The analysis of the relative importance of the various processes contributing to the overall solubility demonstrates that, in water for instance, the linear decrease in solubility versus increasing size of the solute is ruled by the balance of two volume-dependent entropic contributions: the hydrophobic effect opposing solution and the mixing entropy correction factor that favors solution. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: Volume–solubility dependence; mobile order and disorder theory-derived solubility model; hydrophobic effect; mixing entropy correction factor

INTRODUCTION

Among the readily available or easily calculated structural and physico-chemical properties characterizing neutral organic solutes, the molar volume (or any other volume-related property such as the surface area or the molar refraction) is perhaps the parameter most widely used for correlating solubility data through single or multilinear regressions.[1–29] Reviews of the various pathways of predicting solubility have been published by Lyman *et al*,[30] Yalkowsky and Banerjee,[31] Grant and Higuchi[32] and Horvath.[33] Traditionally, the interpretation given to the presence of the molar volume as the main descriptor in almost popular quantitative solubility–property relationships (QSPR) and in linear solvation energy or free energy models (LSER/LFER) essentially relies on the endoergic contribution to the solution process related to the creation of a cavity of the solute dimension in the solvent. Disfavoring the solution process, the volume-related term in these models, the so-called cavity term, is generally preceded by a minus sign indicating that any increase in the size of the solute implies a lowering of solubility: the larger the size of the solute, the greater is the amount of energy required to overcome the solvent–solvent interactions for making suitable cavities to enclose the solute, and the lower is the solubility. Although they may yield good estimated solubility values in many cases, all empirical and semiempirical methods suffer from various failures. In particular, group or fragment solubility constant contribution approaches and correlative LSER/LFER or QSPR methods are often class-specific, yielding the best results when applied to simple homologous series of chemicals. Being specifically designed to estimate solubility in a particular solvent (usually in water), they are limited in their applicability. Furthermore, although all these approaches have some theoretical basis, their use in predicting solubility remains essentially empirical, and does not provide clear insights into the physical nature of the phenomena underlying the solution process (there is in fact little physical significance attached to the regression coefficients).

In contrast to the above methods, the *a priori* development of a comprehensive thermodynamic solubility model for real solutions is based on the correct understanding of all physical or chemical phenomena that determine solubility, and also on the forces that operate between molecules in solution. Such a solubility model is then applicable to predict the solubility of any liquid or

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solid substance in any apolar, polar or protic solvent including water, and may in particular shed light on the molecular origin of the empirically observed dependence of the solubility with respect to particular physicochemical properties. In fact, the general solubility model[34] based on the non-ergodic thermodynamics of the mobile order and disorder (MOD) theory for H-bonded liquids, developed by Huyskens and co-workers,[35–37] fullfils these objectives. To date, the MOD theory-derived solubility equation has been successfully applied to predict the solubility of low-polarity substances in individual and binary solvent systems,[38–49] the mutual solubility of water and hydrocarbons[50,51] and the solubility of solid and liquid proton-acceptor substances and alcohols in aprotic and protic solvents.[52–60] The MOD theory has also been used for obtaining reliable estimates of the *n*-octanol–water partition coefficients of environmentally and pharmaceutically important compounds[61,62] and to explain different ionic conductivity peculiarities observed in solution.[63–67] In all these applications, the hydrogen bond formation between like and unlike molecules is always treated by means of association constants instead of using Hansen or Hildebrand cohesion parameters, hence allowing one to take into account the entropy effects involved in H-bond formation.

The objective of the present investigation was to demonstrate, in the frame of the MOD thermodynamics, that the observed solubility dependence on the molar volume of the solute is mainly of entropic origin, and does not result from a hypothetical endoergic process associated with the breaking of solvent–solvent molecular interactions in order to create a suitably sized enclosure for the solute. The nature of the entropic effects which are at the origin of the volume–solubility dependence is, however, not always identical. Depending upon whether the solvent is self-associated or not, the solubility variation with the size of the solute arises from the balance of two opposite entropic effects (the hydrophobic effect and the correction factor for the entropy of mixing), or from the opposition between an unfavorable enthalpic contribution (the change in the non-specific cohesion forces upon mixing) and a favorable entropic contribution (the correction factor for the entropy of mixing). Accordingly, it will be shown that, although the increase in the molar volume of the solute lowers the solubility in most cases, the effect is predicted to be reversed in non-associated solvents whose modified non-specific cohesion parameter is close to that of the solute. That solubility may experimentally decrease or increase with increasing size of the solute already plays against the sole interpretation of the volume-related term involved in the QSPR or LFER/LSER solubility equations in terms of cavity effects. According to these effects only, the solubility should always be expected to decrease as the solute becomes increasingly larger regardless of the nature of the solvent.

THE MOD THEORY-DERIVED SOLUBILITY MODEL

Basically, the MOD theory for H-bonded liquids considers not the equilibrium between concentrations of self-associated polymeric species present in the liquid at a given time, but the equilibrium between fractions of the time during which the system is found in a particular state: the fraction γ of the time during which the molecule escapes from H-bonding, and the complementary fraction $(1-\gamma)$ of the time when the molecule is bonded. In the liquid state, the molecules are continuously moving, and there is accordingly a perpetual change in the partners of interaction, even when the interaction is a directional and stoichiometric hydrogen bond. In amphiphilic solvents, the associated molecules move together until the association is broken. Some molecules will then be completely free from H-bonding for a lapse of time before reforming new temporary associations with one or another neighboring partner encountered during their migration through the liquid. In contrast to what happens in H-bonded crystals, the partners of hydrogen bonds in liquids are not maintained with time, and all various self-associated aggregates (dimers, trimers, tetramers, …, *n*-mers) observed in solution at a given time are ephemeral or transient on a thermodynamic time-scale; the thermodynamic entities may differ from the spectroscopic entities.[68] Although the number of H-bonds remains constant in the course of the time, these bonds are mobile. A molecule which, at a given time, is H-bonded to another molecule can find itself completely free a few moment later and vice versa. The essential difference between non-associated and H-bonded liquids does not reside in the mobility of the molecules, but lies in the fractions of the time during which some molecular groups or molecules remain in contact with each other. When preferential or specific interactions are formed in liquids, these lead some interacting groups to remain much longer in contact with each other than if governed by random contacts. This is especially true in the case of H-bonding which requires that the H-atom of a proton-donor group follows most of the time the proton acceptor group of a neighboring molecule in its walk through the liquid, just as a dog follows its master on a leash. With respect to non-associated liquids, such behavior drastically modifies the time schedule of the molecular interactions and confer on H-bonded liquids a higher degree of order and some kind of structure. The order is, however, not static, originating from restrictions in the orientations and positions of the molecular groups, but is mobile and intermittent. The mobile character of the order refers to the fact that during small fractions of the time, this kind of order vanishes. For the time during which the molecules are bonded, the mobile order lowers the entropy of the system with respect to the situation where all amphiphilic groups would be completely free, or where the intermolecular contacts would be ruled by a

random law. Both the order introduced by the formation of preferential contacts and the mobile character of these contacts constitute the basis of the MOD theory.

The quantitative development[34] of the MOD theory is at the basis of a new thermodynamic treatment of non-associated and associated solutions. The development led in particular to a general predictive solubility model [Eqn. (1)] containing several contributions accounting for the influence of solvent–solvent, solute–solute and solvent–solute interactions on the chemical potential of the solute. Based on a correct description of the enthalpy and entropy changes accompanying the fusion and solution processes, the predictive equation for solubility in volume fraction, Φ_B, completely describes the free energy change when a solute B is dissolved in a solvent S. Depending upon the functional groups present on the solute and solvent molecules, the complete MOD theory-derived solubility expression may contain up to six different terms:

$$\ln \Phi_B = A + B + D + F + O + OH \qquad (1)$$

Characterizing an elementary physical step of the whole solubility process, each term in Eqn. (1) is thermodynamically well defined, and affects solubility favorably or unfavorably. Each term is discussed in detail below.

The term A represents the fluidization of the solute or its ideal solubility. This contribution corresponds to the suppression of the collective forces which bind the solute molecules within their crystalline state. The fluidization term is a negative solubility contribution which does not depend on the solvent. At the temperature T of interest, this term is calculated from the knowledge of the molar enthalpy of fusion, $\Delta_m H$, and from the absolute equilibrium temperature of melting, T_m, of the pure crystalline substance:

$$A = -\frac{\Delta_m H}{R}\left(\frac{1}{T} - \frac{1}{T_m}\right) \qquad (2)$$

This equation, however, is only an approximation of the ideal solubility in that it disregards the molar heat capacity difference of the liquid and solid forms of the solute. Moreover, additional similar term(s) must be included if the compound undergoes solid-state phase transition(s). In the absence of an available enthalpy of fusion, the crystallinity contribution to the solubility is calculated from the equation proposed by Yalkowsky[69] for rigid molecules, requiring only the melting-point (T_m) in Kelvin of the chemical substance:

$$A = -0.02278(T_m - T) \qquad (3)$$

The term B is a correction factor for the entropy of mixing derived from the difference in size of the molecules in solution. This term essentially depends on the ratio V_B/V_S between the solute and solvent molar volumes, and contributes positively to the solubility as long as V_B is greater than V_S. Remember that, in the MOD theory, the entropy of mixing in liquids is given by a hybrid expression[36] accounting for the nominal exchange in the positions between unlike molecules and for the expansion of the individual domains available for the motions of the molecules within solution:

$$B = 0.5\Phi_S\left(\frac{V_B}{V_S} - 1\right) + 0.5\ln\left(\Phi_B + \Phi_S\frac{V_B}{V_S}\right) \qquad (4)$$

The term D accounts for the effect on the solubility related to the changes in the solute–solute, solvent–solvent and solute–solvent non-specific interactions (induced dipole–induced dipole, induced dipole–dipole and dipole–dipole cohesion forces) accompanying the transfer of the liquid solute from its pure phase to the solvent. To a first approximation, this contribution may be evaluated in the usual way from the Scatchard–Hildebrand equation for regular solutions using the cohesion parameter. This equation, based on the geometric mean assumption,[70] states that the adhesive energy of a pair of unlike molecules is the geometric mean of the cohesive energies of the two equivalent like pairs. A direct consequence of the geometric mean assumption is that regular solutions always lead to positive deviations from Raoult's law and positive enthalpies of mixing. Although the regular solution theory is a reasonable approximation for relatively non-polar systems, it no longer holds for solutions in which specific interactions (H-bonds) occur between the solute and solvent molecules, because such interactions modify the random distribution of the molecules. For such systems, the effect of the new mode of distribution on the D term is accounted for by multiplying the Scatchard–Hildebrand expression by the fraction of the time during which the solute is not bound to the solvent, *i.e.* during which the distribution between the solvent and unbound solute molecules can still be considered to occur at random.[71] By assuming that the non-specific interactions involving the bound solute are negligible, the D contribution, expressed by Eqn. (5), brings a reduction in the solubility:

$$D = -\frac{1}{\left[1.0 + \max(K_{O_i}, K_{OH_i})\frac{\Phi_S}{V_S}\right]}\frac{\Phi_S^2 V_B}{RT}(\delta'_B - \delta'_S)^2 \qquad (5)$$

where max (K_{O_i}, K_{OH_i}) stands for the association constant governing the strongest intermolecular H-bond displayed by the molecular groups in solution.

The D contribution thus has the meaning given by Hildebrand in the method using the cohesion parameters, but refers, in the present context, only to dispersion and dipolar forces, excluding the H-bonds. Accordingly, the actual D term is calculated from corresponding new

parameters, δ', called modified non-specific cohesion parameters.

The term *F* describes the hydrophobic effect, which accounts for the reduction in solubility that results from the formation of H-bonded chains between amphiphilic solvent molecules. The MOD theory proposes a natural explanation of the hydrophobic effect,[62] and enables this effect to be expressed quantitatively by Eqn. (6). This equation is composed of two parts:[58] the first term describes the negative entropic influence of the solvent–solvent H-bond chains on the solubility of non-protic and protic substances. For the latter category of solutes, however, this first negative contribution is partially counterbalanced by the second term, which expresses the reduction in the loss of the mobile order entropy of the solvent molecules due to the participation of the amphiprotic groups of the solute to the solvent H-bond network.

$$F = -r_S \Phi_S \frac{V_B}{V_S} + \sum_i v_{OH_i} \Phi_S (r_S + b_i) \qquad (6)$$

where v_{OH_i} is the number of independent and active proton–donor sites of type *i* on the solute and b_i is a constant accounting for the primary (1.2), secondary (2.0) or tertiary (2.9) character of the proton-donor group in the case when this group is a hydroxyl group and the solubility is estimated in water; r_s represents the 'structuration factor' of the solvent which, at room temperature, is equal to 0 for non-associated solvents (hydrocarbons, esters, ethers, ketones, aldehydes, tertiary amines and amides, nitriles), to 1 for strongly associated solvents forming single H-bond chains (alcohols) and to 2 for water and diols whose molecules are involved in double H-bonded chains. More exact values for protic solvents can be calculated from particular expressions issued from the quantitative development of the MOD theory.[34,50]

The term *O* expresses the effect on solubility of the H-bonds formed between proton-acceptor sites of the solute and proton-donor solvents. Each particular H-bond interaction such as ketone–alcohol contributes to increase solubility, and is characterized by the group interaction stability constant, K_{O_i}. The overall *O* contribution is always positive, and is calculated, to a first approximation, as the sum of the partial contributions that each proton-acceptor site on the solute brings about:

$$O = \sum_i v_{O_i} \ln \left[1 + K_{O_i} \left(\frac{\Phi_S}{V_S} - v_{O_i} \frac{\Phi_B}{V_B} \right) \right] \qquad (7)$$

where *i* represents a particular type of proton-acceptor group of the solute whose interaction with the solvent is governed by K_{O_i} and v_{O_i} indicates the number of active and independent type *i* proton-acceptor sites on the solute molecule.

The term *OH* describes the effect on solubility of the amphiphilic groups on the solute [with the exception of the reduction of the hydrophobic effect already considered in Eqn. (6)]. The way in which these groups affect the solubility is twofold: (a) the insertion of the solute molecules in their own H-bonded chains by self-association in solution tends to decrease solubility; (b) with proton-acceptor and amphiphilic solvents, both the formation of single heteromolecular H-bonds and the insertion of the solute molecules in mixed H-bonded chains promote the solubility. The net result of these various specific interactions upon solubility is described by Eqn. (8):

$$OH = \sum_i v_{OH_i} \left[\ln \left(1 + K_{OH_i} \frac{\Phi_S}{V_S} + K_{BB} \frac{\Phi_B}{V_B} \right) - \ln \left(1 + \frac{K_{BB}}{V_B} \right) \right] \qquad (8)$$

where *i* represents a particular type of proton-donor group of the solute whose interaction with the solvent is governed by the association or insertion constant K_{OH_i} and v_{OH_i} indicates the number of active and independent proton-donor sites of type *i* on the solute molecule. The constant K_{BB} is the stability constant which governs the solute self-association in solution.

From the above expressions, the volume fraction solubility of any chemical substance may be predicted *a priori* in any apolar, polar, protic or aprotic solvent provided there is a knowledge of a limited number of properties characterizing both the solute and solvent molecules, and their interactions in solution. Remember that in the case of solid solutes, the molar volume to be considered is not that of the crystalline substance, but the volume of the molecule in its hypothetical subcooled liquid state. Such volumes are readily estimated from the addition of group contributions[34,52] whose values were obtained to fit best the experimental molar volumes of a large number of liquids.

Keeping in mind the overall aim, we have limited ourselves, for clarity and convenience, to study the solubility of a number of inert and proton-acceptor chemicals of increasing volume. Proton-donor solutes were not considered in this work. Indeed, in this case, the presence of one additional volume-dependent contribution (*OH* term) in the solubility predictive expression would make it more complex and more difficult to unravel the way in which the solute molar volume affects solubility. Nevertheless, to feature the different physical phenomena responsible for the correlations between solubility and the size of the solutes, we decided to analyze and compare the variations of the non-crystalline solubilities of the aforementioned solutes in solvents of varying size, polarity and self-associating ability (the non-crystalline solubility, Φ_B^L, is the liquid solubility or the hypothetical liquid subcooled solubility in the case of

a solid). For this purpose, the solubilities were predicted in two apolar and two polar aprotic solvents (*n*-hexane, benzene, butan-2-one and *n*-butyl acetate) and in three solvents of differing hydrophobic propensity capable of self-association and complexation with the solutes (ethanol, *n*-butanol and water).

RESULTS AND DISCUSSION

As noted previously, the number of terms in the predictive expression for solubility is determined by the nature of the functional groups displayed by the solute and solvent molecules. For example, as long as one is concerned with the solubility of aprotic solutes (displaying at most one type of proton-acceptor group) in solvents unable to self-associate (*n*-hexane, benzene, butan-2-one and *n*-butyl acetate), the MOD solubility model expresses the volume fraction solubility as the sum of three contributions only [Eqn. (9)], *i.e.* the ideal solubility (*A* term), the exchange entropy correction factor (*B* term), and the changes in the non-specific cohesion forces (D term):

$$\ln \Phi_B = term \cdot A + 0.5\Phi_S\left(\frac{V_B}{V_S} - 1\right) + 0.5 \ln \times \left(\Phi_B + \Phi_S \frac{V_B}{V_S}\right) - \frac{\Phi_S^2 V_B}{RT}(\delta'_B - \delta'_S)^2 \quad (9)$$

When the same aprotic solutes are dissolved in solvents able to self-associate and to interact with the solute in solution, then the corresponding terms *F* and *O* have to be added, and the solubility may be predicted by the following expression:

$$\ln \Phi_B = term \cdot A + 0.5\Phi_S\left(\frac{V_B}{V_S} - 1\right) + 0.5 \ln\left(\Phi_B + \Phi_S \frac{V_B}{V_S}\right) - \frac{\Phi_S^2 V_B}{RT}(\delta'_B - \delta'_S)^2 - r_S\Phi_S \frac{V_B}{V_S} + v_O \ln\left[1 + K_O\left(\frac{\Phi_S}{V_S} - v_O \frac{\Phi_B}{V_B}\right)\right] \quad (10)$$

Note that the non-crystalline or liquid solubility, Φ_B^L, is readily obtained from both Eqns (9) and (10) by subtracting the ideal solubility (*A* term) from the overall solubility result, $\ln \Phi_B$.

Using these two equations along with the physicochemical parameters given in Tables 1 and 2, the solubilities of a number of solid and liquid substances were calculated in the seven predetermined solvents. The calculated results and the corresponding experimental data are provided for comparison in Tables 3–5. These tables also report the values of the various contributions involved in the solubility calculation. Although the solubility data span over a 22-fold ln Φ range, the present theory provides reasonably accurate predictions, as shown by Fig. 1, illustrating the agreement between predicted and observed solubility values (the observed versus predicted standard deviation for the 271 solubility values reported in this work amounts to 0.66 ln Φ units).

In addition to its satisfactory predictive ability, the MOD solubility model also enables one to understand better the physical phenomena underlying the solubility process, and permits one to assess how and to what extent some factors, such as the molar volume, may affect the overall solubility. Such a comprehensive knowledge may particularly be gained from the analysis of the relative importance of the terms contributing to the solubility and from consideration of their variations versus the solute or solvent properties. In this context, the origin of the solubility dependence on the solute molar volume is analyzed below. For clarity, the results have been separated into three classes on the basis of the nature of the solvent considered: (a) the aprotic solvents (*n*-hexane, benzene, butan-2-one and *n*-butyl acetate), (b) the amphiprotic solvents (ethanol and *n*-butanol) with a weak hydrophobic tendency and (c) water with its very strong hydrophobic effect.

The solubility in non-associated solvents

As far as only aprotic solutes and solvents are concerned, the non-crystalline or liquid solubility involves the contribution of two terms only in the actual solubility model. One of these terms is of enthalpic nature, and represents the difference in the non-specific cohesion forces between like and unlike pairs of molecules in solution (*D* term). The other term is entropic, and corresponds to the correction of the exchange entropy related to the difference in size of the solute and solvent molecules in solution (*B* term). Although both of these contributions simultaneously increase with increasing molar volume of the solute (see Table 3), they generally affect solubility in opposite directions: the contribution *B* enhances solubility whereas the contribution *D* lowers it. As a result, two size-dependent solubility behaviors are theoretically expected to occur, and are observed experimentally (Fig. 2). On the one hand, all molecular systems whose solute and solvent modified non-specific cohesion parameters, δ'_B and δ'_S, differ widely from one another are essentially governed by the enthalpic polarizability/dipolarity effects. Their solvation process, and hence their non-crystalline solubility, is ruled by the *D* term. Being characterized by a negative value of the *B* plus *D* terms, the non-crystalline solubility of these systems will decrease as the molar volume of the solute increases. In contrast when solute and solvent molecules have close values of their modified non-specific cohesion parameters, δ'_B and δ'_S, the solution process is determined by the correction factor of the entropy of mixing (*B* term)

Table 1. Physical properties of solid solutes

Solute	T_m (K)	ΔH_m (kJ mol^{-1})	V_B (cm^3 mol^{-1})	δ_B (J$^{1/2}$ cm$^{-3/2}$)	Ref.
n-Octadecane	301.40	61.40	326.9	15.71	72
n-Nonadecane[a]	305.20	45.83	343.1	15.75	72
	296.00	13.81			
n-Eicosane	309.80	69.89	359.4	15.78	72
n-Docosane[a]	317.20	48.97	391.4	15.86	72
	316.20	28.21			
n-Tricosane[a]	320.70	53.97	410.5	15.88	72
	313.70	21.76			
n-Tetracosane[a]	323.80	54.91	423.9	15.91	72
	321.30	31.30			
n-Octacosane[a]	334.35	64.64	493.0	16.00	72
	331.15	35.44			
n-Triacontane[a]	338.60	70.90	523.2	16.03	73
	335.20	38.97			
n-Dotriacontane[a]	342.10	76.00	555.9	16.06	72
	338.90	42.70			
n-Hexatriacontane[a]	349.05	88.83	621.0	16.12	72
	345.25	40.46			
Adamantane	541.00	10.91	140.6	17.45	74
Naphthalene	353.35	19.10	130.2	19.40	74
Anthracene	489.65	29.37	150.0	20.68	74
Thianthrene	428.40	25.44	165.8	21.02	75
Phenanthrene	374.00	15.72	171.0	20.00	74
trans-Stilbene	398.15	27.40	177.0	19.69	74
Biphenyl	342.60	18.66	160.0	19.45	74
Pyrene	424.40	17.11	182.0	20.77	76
Benzil	368.35	19.76	180.0	21.72	55
Carbazole	519.20	27.00	148.2	23.04	70
Thioxanthen-9-one	487.88	35.50	161.0	20.69	41
Dinonyl ketone	330.15	67.26	338.0	17.30	55
Didecyl ketone	336.65	76.20	371.0	17.20	55
Diundecyl ketone	342.15	78.03	404.0	16.93	55
Methyl palmitate	303.75	55.65	309.0	19.24	55
Methyl stearate	312.20	64.43	342.0	17.26	55
Palmitonitrile	304.55	56.80	283.6	17.24	56
Stearonitrile	314.15	65.81	316.6	17.68	56
Testosterone formate	398.00	18.12	280.8	20.00	58
Testosterone acetate	413.15	22.51	307.1	20.00	58
Testosterone propionate	393.15	22.13	323.4	20.00	58
Testosterone butyrate	382.15	25.31	339.6	20.00	58
Testosterone valerate	380.15	30.96	355.8	20.00	58
Norethindrone acetate	480.00	27.30	311.8	20.00	58
Deoxycorticosterone acetate	430.0	29.66	330.8	20.00	58
Megestrol acetate	488.15		332.6	20.00	58
Pregnenolone acetate	423.15		341.1	20.00	58
Stanolone propionate	394.15	24.51	341.3	20.00	58
Ethynodiol diacetate	399.15		359.3	20.00	58
Dromostanolone propionate	399.15		361.2	20.00	58
Trioctadecylamine	327.15	222.66	937.5	16.47	77
N,N-Diphenylcapramide	320.65	35.16	334.0	17.93	56
N,N-Diphenyllauramide	330.15	40.77	367.0	17.54	56
N,N-Diphenylpalmitamide	342.65	52.76	433.0	17.55	78
N,N-Diphenylstearamide	345.45	57.58	466.0	17.60	78

[a] Melting (T_m and ΔH_m) and transition phase (T_{trans} and ΔH_{trans}) properties are provided.

and is not due to the enhancement of this term with respect to the previous cases, but is rather caused by the smallness of the dispersion–dipolar effects. Such molecular systems are characterized by a positive value of the *B* plus *D* terms, and their subcooled liquid solubilities will generally increase with increase in the molar volume of the solute. These very simple rules enable us to explain why, for instance, the non-crystalline solubility of aliphatic hydrocarbons of growing size increases in apolar or slightly polar solvents such as *n*-hexane and

Table 2. Group interaction standard stability constants[56–58] at 25 °C

Solute H-bond acceptor	Solvent H-bond donor	K_o ($cm^3\,mol^{-1}$)
Aliphatic ketone	— OH (alcohol)	170.0
Aliphatic ester	— OH (alcohol)	110.0
Aliphatic nitrile	— OH (alcohol)	150.0
Aliphatic tertiary amide	— OH (alcohol)	600.0
Aliphatic tertiary amine	— OH (water)	7500.0
Aliphatic ketone	— OH (water)	5000.0
Aliphatic ether	— OH (water)	3500.0
Aliphatic ester	— OH (water)	3500.0
Aliphatic aldehyde	— OH (water)	1000.0
Aromatic ring	— OH (water)	80.0

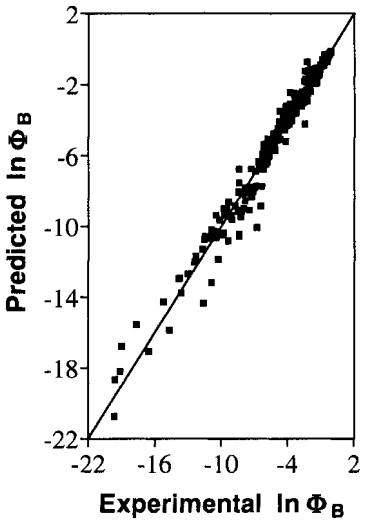

Figure 1. Predicted versus experimental volume fraction solubilities (ln Φ_B) of non-electrolyte substances

benzene, but decreases in polar solvents such as butan-2-one and *n*-butyl acetate. The reverse behavior is observed with the aromatic hydrocarbons and steroids: the larger their molar volume, the lower is their liquid solubility in *n*-hexane and the greater their liquid solubility in butan-2-one and *n*-butyl acetate. At this stage, it is important to point out that the above statements do not discuss whether the solubility of a given substance is higher or lower in different solvents, but refer to the expected or observed variations of solubility of compounds of increasing size in these solvents.

It is possible to conclude on the basis of Eqn. (9) that, in the case of non-protic solutes dissolved in non-protic solvents, the observed volume–solubility dependence results from the balance between two contributions (one enthalpic and one entropic) varying linearly but in opposite directions with the molar size of the solute. However, because these thermodynamic contributions still depend on other physico-chemical parameters (the solvent molar volume, the square difference of the solute/solvent modified non-specific cohesion parameters) than simply the molar volume of the solute, one does not observe perfect linear relationships between the solute size and the non-crystalline solubility, but only trends favoring or disfavoring solubility. The double thermodynamic origin of the solubility dependence on the solute molar volume gives a hybrid character to the volume-based term encountered in the QSPR, LFER or LSER models, and thus comes into contradiction with its traditional definition based solely on the endothermic process of an assumed cavity formation.

The solubility in alcohols

In contrast to non-amphiprotic solvents, alcohols are able to self-associate and to undergo specific heteromolecular interactions. Whereas alcohol self-association always negatively affects the solubility of all solutes through the hydrophobic effect,[62] the molecular complexation only influences the solubility of interacting solutes. These particular physical processes must therefore be considered to obtain accurate estimates of solubility in alcohols. In the frame of the MOD solubility model, and considering inert or proton-acceptor solutes only, their solubility in alcohols are reliably calculated by Eqn. (10), adding the *F* and *O* contributions to the terms *A, B* and *D* already used for aprotic solvents. Although all contributions (except the *A* term) in Eqn. (10) vary with respect to the molar volume of the solute, only the hydrophobic effect (*F* term), the exchange entropy correction factor effect (*B* term) and the dispersion–dipolarity effect (*D* term) are substantially affected by the solute size, and must be considered in studying the influence of the volume on the solubility of non-protic solutes in alcohols. In view of the relative participation of each of these terms in the overall solution process (see Table 4), it appears that the alcohol solubility is dominated by the hydrophobic contribution which, in absolute value, increases linearly with increasing size of the solute. The importance of the hydrophobic effect and of its volume dependence, added to the other unfavorable volume-related contribution, namely the *D* term, allows us to understand why the overall non-crystalline solubilities in alcohols, and in ethanol or *n*-butanol in particular, are lowered when the molar volume of the solute increases (Fig. 3). Nevertheless, for the same reasons as those mentioned for the aprotic solvents, the observed solubility decrease is not strictly linear. Furthermore, according to the extent of the *O* contribution related to the solute–solvent complexation, each chemical class of solutes is expected to present its own volume–liquid solubility behavior.

From the foregoing, it can be concluded that the experimentally observed alcohol solubility decrease with increasing size of the solute once again does not result from the need for breaking of a larger number of H-bonds

Table 3. Predicted [eqn (9)] vs observed solubilities in non-associated solvents at 25 °C and the solubility contributions

Solute	V_B	A	B	D	Ln Φ_B^{pred}	Ln Φ_B^{exp}	Ref.
Solubility in n-*hexane* (V_S = 131.6 cm^3 mol^{-1}, δ_S = 14.56 $MPa^{1/2}$)							
n-Docosane	391.4	−1.836	0.996	−0.099	−0.939	−0.956	86
n-Tetracosane	423.9	−2.975	1.438	−0.213	−1.749	−1.366	52
n-Octacosane	493.0	−4.248	1.915	−0.358	−2.691	−2.590	34
n-Triacontane	523.2	−5.154	2.119	−0.428	−3.463	−3.219	34
n-Dotriacontane	555.9	−6.010	2.302	−0.490	−4.197	−3.863	34
n-Hexatriacontane	621.3	−7.460	2.627	−0.605	−5.437	−5.404	34
Adamantane	140.6	−2.165	0.062	−0.399	−2.502	−2.582	79
Naphthalene	130.2	−1.185	−0.962	−0.009	−2.156	−2.154	80
Anthracene	150.0	−4.510	0.135	−2.259	−6.634	−6.538	80
Biphenyl	160.0	−0.977	0.177	−1.124	−1.924	−1.924	38
Thianthrene	165.8	−3.120	0.245	−2.772	−5.647	−5.514	75
Phenanthrene	171.0	−1.353	0.266	−1.825	−2.912	−2.914	80
trans-Stilbene	177.0	−2.776	0.317	−1.828	−4.287	−4.353	40
Pyrene	182.0	−2.030	0.350	−2.757	−4.438	−4.439	38
Carbazole	148.2	−4.637	0.122	−4.298	−8.813	−8.762	70
Thioxanthen-9-one	161.0	−5.569	0.212	−2.439	−7.795	−7.782	41
Benzil	180.0	−1.519	0.338	−3.670	−4.851	−4.851	55
Dinonyl ketone	338.0	−2.630	1.147	−0.831	−2.314	−2.178	55
Methyl palmitate	309.0	−0.414	0.297	−0.152	−0.269	−0.269	55
Methyl stearate	342.0	−1.170	0.713	−0.267	−0.725	−0.725	55
Palmitonitrile	283.6	−0.482	0.258	−0.046	−0.270	−0.338	81
Stearonitrile	316.6	−1.352	0.802	−0.557	−1.107	−1.110	81
Trioctadecylamine	937.5	−6.481	3.966	−1.298	−3.812	−3.609	77
Testosterone propionate	323.4	−1.300	1.156	−3.697	−3.817	−4.423	58
Stanolone propionate	341.3	−2.409	1.267	−4.028	−5.167	−4.200	58
Solubility in benzene (V_S = 89.4 cm^3 mol^{-1}, δ_S = 18.95 $MPa^{1/2}$)							
n-Octadecane (24 °C)	326.9	−0.350	0.257	−0.015	−0.108	−0.127	83
n-Nonadecane (23 °C)	343.1	−0.549	0.412	−0.036	−0.173	−0.189	83
n-Eicosane	359.4	−1.060	0.823	−0.150	−0.387	−0.321	83
n-Octacosane	493.0	−4.248	2.953	−1.532	−2.827	−2.837	38
n-Dotriacontane	555.9	−6.010	3.484	−1.825	−4.351	−4.374	84
Adamantane	140.6	−2.165	0.436	−0.090	−1.818	−2.309	79
Naphthalene	130.2	−1.185	0.260	−0.004	−0.929	−0.979	80
Anthracene	150.0	−4.510	0.589	−0.175	−4.096	−4.304	80
Biphenyl	160.0	−0.977	0.344	−0.004	−0.636	−0.630	38
Phenanthrene	171.0	−1.353	0.485	−0.027	−0.894	−1.100	80
Pyrene	182.0	−2.030	0.694	−0.145	−1.481	−2.114	38
Carbazole	148.2	−4.637	0.578	−0.987	−5.046	−4.917	70
Thioxanthen-9-one	161.0	−5.569	0.691	−0.194	−5.073	−4.679	41
Benzil	180.0	−1.519	0.615	−0.266	−1.171	−1.187	55
Dinonyl ketone	338.0	−2.630	1.550	−0.192	−1.272	−1.150	55
Didecyl ketone	371.0	−3.515	1.979	−0.327	−1.863	−1.602	55
Diundecyl ketone (30 °C)	404.0	−3.529	2.164	−0.461	−1.827	−1.745	55
Palmitonitrile	283.6	−0.482	0.318	−0.008	−0.171	−0.158	82
Stearonitrile	316.6	−1.352	0.867	−0.034	−0.518	−0.464	82
Trioctadecylamine	937.5	−6.481	5.630	−2.041	−2.892	−3.048	77
Testosterone formate	280.8	−1.067	0.653	−0.015	−0.431	−0.598	58
Testosterone acetate	307.1	−1.471	0.909	−0.027	−0.580	−0.916	58
Testosterone propionate	323.4	−1.300	0.843	−0.021	−0.478	−0.580	58
Testosterone butyrate	339.6	−1.636	1.054	−0.032	−0.616	−0.616	58
Testosterone valerate	355.8	−2.251	1.400	−0.056	−0.916	−0.799	58
Pregnenolone acetate	341.1	−2.848	1.597	−0.082	−1.347	−1.609	58
N,*N*-Diphenylcapramide (30 °C)	334.0	−0.761	0.526	−0.006	−0.242	−0.290	78
N,*N*-Diphenyllauramide (30 °C)	367.0	−1.323	0.922	−0.036	−0.438	−0.478	78
N,*N*-Diphenylpalmitamide (30 °C)	433.0	−2.413	1.678	−0.111	−0.846	−0.846	78
N,*N*-Diphenylstearamide (30 °C)	466.0	−2.797	1.954	−0.130	−0.973	−0.973	78
Solubility in butan-2-one (V_s = 90.2 cm^3 mol^{-1}, δ_s = 20.90 $MPa^{1/2}$)							
n-Eicosane	359.4	−1.060	1.908	−2.773	−1.925	−1.979	84
n-Docosane	391.4	−1.836	2.320	−3.693	−3.209	−3.242	84
n-Tricosane	410.5	−1.966	2.461	−3.901	−3.406	−3.527	84
n-Tetracosane	423.9	−2.975	2.600	−4.168	−4.543	−4.269	84
n-Octacosane	493.0	−4.248	3.075	−4.750	−5.922	−6.320	34

Table 3. Predicted [eqn (9)] vs observed solubilities in non-associated solvents at 25 °C and the solubility contributions

Solute	V_B	A	B	D	Ln Φ_B^{pred}	Ln Φ_B^{exp}	Ref.
Dinonyl ketone	338.0	−2.630	1.837	−1.392	−2.185	−2.168	55
Diundecyl ketone (30 °C)	404.0	−3.529	2.424	−2.376	−3.481	−3.461	55
Palmitonitrile	283.6	−0.482	0.339	−0.045	−0.187	−0.200	82
Stearonitrile	316.6	−1.352	1.002	−0.308	−0.658	−0.640	82
N,*N*-Diphenylcapramide (30 °C)	334.0	−0.761	0.559	−0.064	−0.265	−0.307	78
N,*N*-Diphenyllauramide (30 °C)	367.0	−1.323	1.067	−0.295	−0.551	−0.554	78
N,*N*-Diphenylpalmitamide (30 °C)	433.0	−2.413	2.110	−1.100	−1.404	−1.183	78
N,*N*-Diphenylstearamide (30 °C)	466.0	−2.797	2.441	−1.338	−1.694	−1.774	78
Trioctadecylamine	937.5	−6.481	5.865	−7.294	−7.909	−7.858	77
Solubility in n-*butyl acetate* (V_s = 132.5 $cm^3\ mol^{-1}$, δ_s = 19.66 $MPa^{1/2}$)							
n-Octadecane (24 °C)	326.9	−0.350	0.227	−0.055	−0.178	−0.148	83
n-Nonadecane (23 °C)	343.1	−0.549	0.390	−0.153	−0.312	−0.356	83
n-Eicosane	359.4	−1.060	0.933	−0.926	−1.054	−1.493	83
n-Docosane	391.4	−1.836	1.385	−1.843	−2.294	−2.319	52
n-Tricosane	410.5	−1.966	1.493	−1.974	−2.447	−2.547	52
n-Tetracosane	423.9	−2.975	1.642	−2.276	−3.609	−3.257	52
n-Octacosane	493.0	−4.204	2.004	−2.623	−4.867	−5.021	38
Anthracene	150.0	−4.510	0.127	−0.061	−4.445	−4.896	80
Pyrene	182.0	−2.030	0.292	−0.063	−1.802	−2.529	87
Thioxanthen-9-one	161.0	−5.569	0.212	−0.068	−5.426	−5.251	41
Dinonyl ketone	338.0	−2.630	1.111	−0.586	−2.105	−2.156	55
Didecyl ketone	371.0	−3.515	1.352	−0.816	−2.979	−3.302	55
Diundecyl ketone (30 °C)	404.0	−3.529	1.520	−1.091	−3.099	−3.290	55
Palmitonitrile	283.6	−0.482	0.252	−0.037	−0.267	−0.284	82
Stearonitrile	316.6	−1.352	0.681	−0.159	−0.830	−0.854	82
N,*N*-Diphenylcapramide (30 °C)	334.0	−0.761	0.429	−0.038	−0.371	−0.405	78
N,*N*-Diphenyllauramide (30 °C)	367.0	−1.323	0.776	−0.172	−0.719	−0.783	78
N,*N*-Diphenylpalmitamide (30 °C)	433.0	−2.413	1.385	−0.461	−1.489	−1.673	78
N,*N*-Diphenylstearamide (30 °C)	466.0	−2.797	1.596	−0.529	−1.730	−1.994	78
Trioctadecylamine	937.5	−6.481	4.009	−3.770	−6.242	−5.979	77

in the alcohol network to accommodate a larger foreign substance. Instead of this enthalpic interpretation, the MOD theory proposes a natural and quantitative explanation. The origin of the volume–solubility dependence of aprotic liquids or subcooled liquids in alcohols is hybrid, and arises from the balance of opposite volume-dependent physical phenomena involved in the whole solution process: the *D* and *F* contributions which disfavor solubility versus the *B* contribution favoring solubility in most cases.

The solubility in water

What essentially differentiates alcohols and water used as solvents is the relative importance of the solvophobic effect that they have on solutes. Because of both its exceptionally small molar volume and its insertion in double H-bonded chains, water has the greatest solvophobic (hydrophobic) tendency among all H-bonded solvents. In the case of alcohols and water, the difference in their hydrophobic propensity is clearly evidenced by comparing the results of the *F* contribution (Tables 4 and 5) involved in the solubility estimations of compounds of similar volumes. The very large differences in the values of the solvophobic effect opposing solution readily explain why solubilities in water are lower than those in alcohols.

Considering only non-protic solutes which are liquid at 25 °C, their solubility in water (Table 5) were calculated from Eqn. (11) by setting both the fluidization constant (*A* term) and the change in the dispersive cohesion forces upon mixing (*D* term) equal to zero in Eqn. (10). In previous studies,[38,55,58,60] the latter contribution has indeed been shown to be of no or minor importance in estimating aqueous solubility. Note that Eqn. (11) does not take into account the amount of water transferred into the organic phase during the solution process.

$$\ln \Phi_B = 0.5\Phi_S\left(\frac{V_B}{V_S} - 1\right) + 0.5\ln\left(\Phi_B + \Phi_S\frac{V_B}{V_S}\right) - r_S\Phi_S\frac{V_B}{V_S} + v_o\ln\left[1 + K_o\left(\frac{\Phi_S}{V_S} - v_o\frac{\Phi_B}{V_B}\right)\right] \quad (11)$$

The results indicates that, given a homologous series of solutes, the solubilities in water, as in alcohols, always decrease with increasing size of the solute. However, in contrast to what happens in alcohols, the observed or predicted solubility behavior appears much more regular

Table 4. Predicted [Eqn. (10)] vs observed solubilities in alcohols at 25 °C and the solubility contributions

Solute	V_B	A	B	D	F	O	$Ln\Phi_B^{pred}$	$Ln\Phi_B^{exp}$	Ref.
Solubility in ethanol (V_s = 58.7 $cm^3\ mol^{-1}$, δ_s = 17.81 $MPa^{1/2}$)									
n-Octadecane (24 °C)	326.9	−0.350	3.032	−0.537	−5.341		−3.196	−2.743	83
n-Nonadecane (23 °C)	343.1	−0.549	3.225	−0.558	−5.679		−3.562	−3.347	83
n-Eicosane	359.4	−1.060	3.425	−0.581	−6.035		−4.251	−4.063	34
n-Tricosane	410.5	−1.966	3.956	−0.612	−6.967		−5.589	−5.573	38
n-Octacosane	493.0	−4.248	4.763	−0.651	−8.397		−8.534	−7.875	38
Adamantane (20 °C)	140.6	−2.246	1.104	−0.009	−2.321		−3.473	−4.719	85
Naphthalene	130.2	−1.185	0.925	−0.109	−2.013		−2.383	−2.475	80
Anthracene	150.0	−4.510	1.245	−0.496	−2.551		−6.312	−6.194	80
Phenanthrene	171.0	−1.353	1.426	−0.298	−2.767		−2.992	−3.226	80
Pyrene	182.0	−2.030	1.593	−0.621	−3.050		−4.108	−4.629	38
trans-Stilbene	177.0	−2.776	1.544	−0.247	−2.980		−4.459	−4.644	40
Thianthrene	165.8	−3.120	1.425	−0.681	−2.809		−5.186	−5.834	75
Thioxanthen-9-one	161.0	−5.569	1.372	−0.138	−2.734	1.357	−5.712	−6.204	41
Dinonyl ketone	338.0	−2.630	3.187	−0.009	−5.620	1.339	−3.733	−3.990	55
Didecyl ketone	371.0	−3.515	3.559	−0.014	−6.273	1.353	−4.890	−4.991	55
Methyl stearate	342.0	−1.170	3.072	−0.014	−5.370	0.935	−2.547	−2.600	55
Testosterone formate	280.8	−1.067	1.503	−0.057	−2.441	1.348	−0.713	−2.302	58
Testosterone acetate	307.1	−1.471	2.183	−0.097	−3.688	1.853	−1.204	−2.489	58
Testosterone propionate	323.4	−1.300	2.197	−0.095	−3.672	1.772	−1.109	−1.966	58
Testosterone butyrate	339.6	−1.636	2.718	−0.128	−4.661	2.069	−1.661	−2.453	58
Testosterone valerate	355.8	−2.251	3.191	−0.159	−5.568	2.279	−2.513	−3.219	58
Norethindrone acetate	311.8	−4.172	2.953	−0.152	−5.233	2.391	−4.200	−2.476	58
Deoxycorticosterone acetate	330.8	−3.669	2.956	−0.147	−5.170	3.536	−2.489	−3.324	58
Megestrol acetate	332.6	−4.328	3.085	−0.156	−5.428	3.657	−3.170	−4.135	58
Pregnenolone acetate	341.1	−2.848	3.152	−0.159	−5.537	2.337	−3.058	−3.772	58
Ethynodiol diacetate	359.3	−2.301	3.318	−0.226	−5.817	2.023	−2.996	−2.830	58
Dromostanolone propionate	361.2	−2.301	3.263	−0.163	−5.700	2.292	−2.604	−3.442	58
Cholesteryl acetate	462.3	−2.050	4.434	−0.307	−7.802	1.049	−4.678	−4.976	58
Solubility in n-*butanol* (V_s = 92.0 $cm^3\ mol^{-1}$, δ_s = 17.16 $MPa^{1/2}$)									
n-Octadecane (24 °C)	326.9	−0.350	1.667	−0.202	−3.030		−1.916	−1.494	83
n-Eicosane	359.4	−1.060	2.041	−0.249	−3.707		−2.975	−2.749	83
n-Tricosane	410.5	−1.966	2.446	−0.263	−4.393		−4.176	−4.029	38
n-Octacosane	493.0	−4.248	3.016	−0.267	−5.353		−6.852	−6.908	38
Adamantane (20 °C)	140.6	−2.246	0.459	−0.003	−1.470		−3.259	−4.199	85
Naphthalene	130.2	−1.185	0.347	−0.215	−1.278		−2.331	−2.389	80
Anthracene	150.0	−4.510	0.559	−0.746	−1.628		−6.325	−6.641	80
Pyrene	182.0	−2.030	0.818	−0.923	−1.945		−4.080	−4.404	38
trans-Stilbene	177.0	−2.776	0.780	−0.445	−1.899		−4.340	−4.585	40
Thianthrene	165.8	−3.120	0.692	−0.986	−1.792		−5.206	−5.501	75
Thioxanthen-9-one	161.0	−5.569	0.653	−0.283	−1.745	1.044	−5.900	−6.218	41
Dinonyl ketone	338.0	−2.630	1.920	−0.001	−3.528	1.013	−3.226	−3.245	55
Didecyl ketone	371.0	−3.515	2.187	−0.000	−3.976	1.035	−4.269	−4.135	55
Diundecyl ketone (30 °C)	404.0	−3.529	2.410	−0.003	−4.339	1.037	−4.423	−4.474	55
Methyl palmitate	309.0	−0.414	1.768	−0.001	−3.192	0.638	−1.956	−2.058	55
Methyl stearate	342.0	−1.170	0.899	−0.056	−1.524	0.490	−0.605	−0.680	55
Palmitonitrile	283.6	−0.482	0.889	0.000	−1.564	0.449	−0.708	−0.456	82
Stearonitrile	316.6	−1.352	1.585	−0.010	−2.895	0.831	−1.841	−1.349	82
N,*N*-Diphenylcapramide (30 °C)	334.0	−0.761	0.823	−0.003	−1.338	0.819	−0.460	−0.427	78
N,*N*-Diphenyllauramide (30 °C)	367.0	−1.323	1.362	−0.001	−2.299	1.403	−0.859	−0.882	78
N,*N*-Diphenylpalmitamide (30 °C)	433.0	−2.413	2.412	−0.003	−4.258	1.912	−2.350	−1.967	78
N,*N*-Diphenylstearamide (30 °C)	466.0	−2.797	2.712	−0.005	−4.792	1.960	−2.922	−2.248	78

within each congeneric series, and the solute size dependence remains identical from one chemical group to another. Irrespective of the basic structure of the chemicals considered, the liquid solubility decreases by about 1.2–1.3 ln Φ units for each methylene group added into the hydrocarbon molecular backbone. For instance, the mean aqueous volume fraction solubility increment observed by increasing the carbon chain length by one CH_2 group (16.25 $cm^3\ mol^{-1}$) amounts to −1.24 ln Φ units on going from benzene to *n*-hexylbenzene, to −1.22 ln Φ units from propan-2-one to decan-2-one or from methyl acetate to methyl myristate and to −1.29 ln Φ units when moving up the homologous series of aldehydes from propanal to *n*-nonanal. Thermodynamically, the quasi-linear dependence of the liquid solubility on the solute molar volume is demonstrated from Eqn.

Table 5. Predicted [Eqn. (10)] vs observed solubilities of liquid chemical substances in water at 25°C and the solubility contributions

Solute	V_B	B	F	O	$\mathrm{Ln}\Phi_B^{pred}$	$\mathrm{Ln}\Phi_B^{exp}$	Ref.
Aliphatic hydrocarbons							
n-Pentane	116.1	3.636	−12.827		−9.191	−9.476	5
n-Hexane	131.6	4.127	−14.541		−10.414	−10.870	5
n-Heptane	147.5	4.624	−16.298		−11.675	−12.345	5
n-Octane	163.5	5.117	−18.066		−12.949	−13.876	5
n-Nonane	179.7	5.612	−19.056		−14.245	−15.256	10
n-Decane	195.9	6.102	−21.646		−15.544	−17.702	10
n-Undecane	211.2	6.563	−23.337		−16.774	−19.032	10
n-Dodecane	228.6	7.083	−25.260		−18.177	−19.137	10
n-Tetradecane	260.3	8.024	−28.762		−20.739	−19.675	88
Cyclopentane	94.7	2.942	−10.458		−7.516	−8.436	5
Cyclohexane	108.8	3.402	−12.020		−8.618	−9.356	5
Cycloheptane	121.7	3.814	−13.447		−9.632	−10.188	10
Cyclooctane	135.8	4.259	−15.005		−10.746	−11.552	10
Methylcyclopentane	113.1	3.540	−12.496		−8.956	−9.778	5
Methylcyclohexane	128.3	4.023	−14.176		−10.153	−10.918	5
Ethylcyclohexane	142.4	4.465	−15.735		−11.270	−11.735	9
Decalin	162.8	5.096	−17.989		−12.893	−13.766	10
Aromatic hydrocarbons							
Benzene	89.4	2.747	−9.799	1.690	−5.367	−6.194	5
Toluene	106.3	3.318	−11.732	1.690	−6.725	−7.330	5
p-Xylene	123.3	3.864	−13.620	1.690	−8.066	−8.471	5
Ethylbenzene	122.4	3.836	−13.520	1.690	−7.995	−8.479	5
n-Propylbenzene	139.4	4.371	−15.402	1.690	−9.341	−9.730	5
n-Butylbenezene	156.1	4.889	−17.248	1.690	−10.669	−11.206	5
n-Pentylbenzene	172.7	5.399	−19.083	1.690	−11.994	−12.440	5
n-Hexylbenzene	194.5	6.060	−21.492	1.690	−13.741	−13.634	5
n-Decylbenzene	255.2	7.873	−28.199	1.690	−18.636	−19.648	89
4-Ethyltoluene	136.5	4.374	−15.413	1.690	−9.349	−9.131	5
2-Isopropyltoluene	153.1	4.797	−16.917	1.690	−10.430	−10.534	88
1,4-Diethylbenzene	155.7	4.877	−17.204	1.690	−10.637	−10.495	5
1-Methylnaphthalene	139.4	4.371	−15.402	1.690	−9.341	−10.490	5
1-Ethylnaphthalene	154.9	4.852	−17.116	1.690	−10.573	−11.467	5
1,4,5-Trimethylnaphthalene	181.2	5.657	−20.022	1.690	−12.675	−13.014	90
Ketones							
Propan-2-one	74.0	2.248	−8.177	5.625	−0.304	−0.695	19
Butan-2-one	89.5	2.771	−9.889	5.625	−1.493	−1.801	3
Pentan-2-one	106.5	3.328	−11.768	5.625	−2.863	−2.690	5
Hexan-2-one	123.5	3.809	−13.391	5.603	−3.979	−3.937	5
Heptan-2-one	140.8	4.399	−15.493	5.620	−5.473	−5.231	5
Octan-2-one	156.3	4.891	−17.250	5.624	−6.736	−6.577	5
Nonan-2-one	173.3	5.415	−19.143	5.625	−8.103	−7.693	5
Decan-2-one	189.5	5.909	−20.938	5.625	−9.404	−9.262	3
Pentan-3-one	105.8	3.305	−11.691	5.625	−2.761	−2.787	14
Hexan-3-one	123.4	3.806	−13.378	5.603	−3.969	−4.007	14
Heptan-3-one	139.5	4.357	−15.342	5.620	−5.366	−5.194	91
Octan-3-one	155.9	4.878	−17.205	5.624	−6.704	−6.395	91
Nonan-3-one	171.5	5.360	−18.944	5.625	−7.959	−7.336	91
Cyclopentanone	88.7	2.745	−9.801	5.625	−1.431	−1.195	91
Cyclohexanone	103.5	3.231	−11.436	5.625	−2.580	−2.365	91
Cycloheptanone	118.0	3.595	−12.620	5.587	−3.438	−3.336	91
Carvone	155.7	4.872	−17.183	5.624	−6.688	−6.603	14
Menthone	172.3	5.385	−19.032	5.625	−8.023	−7.170	14
Esters							
Ethyl formate	80.8	2.480	−8.928	5.270	−1.178	−2.180	5
n-Propyl formate	97.3	3.029	−10.751	5.270	−2.452	−3.461	5
n-Butyl formate	115.5	3.537	−12.433	5.240	−3.656	−4.393	92
n-Pentyl formate	131.2	4.092	−14.404	5.262	−5.050	−5.831	92
n-Hexyl formate	147.7	4.623	−16.293	5.268	−6.402	−6.449	92
n-Heptyl formate	164.2	5.137	−18.136	5.269	−7.730	−6.364	92
n-Octyl formate	181.0	5.651	−19.998	5.270	−9.077	−7.475	92

Table 5. Continued

Solute	V_B	B	F	O	$\mathrm{Ln}\Phi_B^{pred}$	$\mathrm{Ln}\Phi_B^{exp}$	Ref.
n-Nonyl formate	196.7	6.126	−21.734	5.270	−10.338	−9.812	91
Methyl acetate	79.4	2.433	−8.773	5.270	−1.070	−1.353	5
Ethyl acetate	97.9	3.048	−10.818	5.270	−2.500	−2.425	5
n-Propyl acetate	115.0	3.517	−12.363	5.238	−3.607	−3.823	5
n-Butyl acetate	131.6	4.105	−14.451	5.263	−5.083	−5.183	93
n-Pentyl acetate	148.7	4.655	−16.406	5.268	−6.483	−6.258	5
n-Hexyl acetate	164.3	5.140	−18.147	5.269	−7.738	−7.470	5
n-Heptyl acetate	180.8	5.645	−19.976	5.270	−9.061	−8.312	92
n-Octyl acetate	197.9	6.163	−21.867	5.270	−10.434	−8.436	91
Methyl propionate	96.3	2.996	−10.641	5.270	−2.375	−2.691	5
Ethyl propionate	114.5	3.497	−12.291	5.236	−3.558	−3.690	5
n-Propyl propionate	131.9	4.115	−14.486	5.263	−5.108	−5.112	93
n-Butyl propionate	148.7	4.655	−16.406	5.268	−6.483	−6.212	93
n-Pentyl propionate	164.6	5.149	−18.180	5.269	−7.762	−6.985	14
n-Hexyl propionate	181.9	5.678	−20.097	5.270	−9.150	−8.497	92
Methyl butyrate	113.7	3.465	−12.175	5.233	−3.477	−3.928	92
Ethyl butyrate	132.2	4.125	−14.522	5.263	−5.134	−4.972	5
n-Propyl butyrate	149.1	4.667	−16.451	5.268	−6.516	−6.324	5
n-Butyl butyrate	165.8	5.186	−18.313	5.269	−7.858	−7.266	92
n-Pentyl butyrate	181.6	5.669	−20.064	5.270	−9.125	−8.179	92
n-Hexyl butyrate	199.1	6.199	−21.999	5.270	−10.531	−8.441	91
Methyl valerate	129.8	4.045	−14.239	5.262	−4.932	−5.174	5
Methyl caproate	147.2	4.607	−16.237	5.268	−6.362	−6.521	5
Methyl heptanoate	163.6	5.118	−18.069	5.269	−7.682	−6.867	92
Methyl caprylate	180.3	5.629	−19.920	5.270	−9.021	−9.519	5
Methyl pelargonate	195.8	6.099	−21.635	5.270	−10.266	−10.565	3
Methyl caprate	213.4	6.629	−23.580	5.270	−11.682	−12.344	3
Methyl laurate	246.3	7.609	−27.215	5.270	−14.337	−11.625	89
Methyl myristate	279.6	8.592	−30.895	5.270	−17.033	−16.587	89
Ethyl valerate	148.5	4.648	−16.383	5.268	−6.467	−5.937	5
Ethyl caproate	165.8	5.180	−18.291	5.269	−7.842	−7.117	5
Ethyl heptanoate	179.5	5.605	−19.832	5.270	−8.957	−7.958	5
Ethyl caprylate	198.2	6.172	−21.900	5.270	−10.459	−9.878	92
Ethyl pelargonate	215.2	6.683	−23.779	5.270	−11.827	−10.286	5
Ethyl caprate	231.6	7.172	−25.591	5.270	−13.149	−10.903	5
Ethyl laurate	265.0	8.162	−29.282	5.270	−15.850	−14.683	89
Cyclohexyl formate	127.4	3.965	−13.953	5.260	−4.729	−5.298	92
Cyclohexyl acetate	146.6	4.588	−16.170	5.268	−6.313	−5.844	92
Cyclohexyl propionate	166.9	5.220	−18.435	5.269	−7.946	−7.114	92
Cyclohexyl butyrate	177.9	5.556	−19.655	5.270	−8.829	−6.445	91
Ethers							
Diethyl ether	103.8	3.241	−11.470	5.270	−2.959	−2.496	5
Methyl propyl ether	100.4	3.130	−11.094	5.270	−2.694	−3.207	5
Methyl butyl ether	118.4	3.647	−12.826	5.247	−3.932	−4.416	5
Methyl isobutyl ether	120.6	3.728	−13.112	5.251	−4.133	−4.192	14
Ethyl *n*-propyl ether	119.3	3.680	−12.945	5.249	−4.016	−3.652	5
Di-*n*-propyl ether	138.8	4.340	−15.285	5.266	−5.679	−5.706	5
Diisopropyl ether	141.1	4.414	−15.547	5.267	−5.866	−5.873	14
Di-*n*-butyl ether	169.4	5.296	−18.713	5.269	−8.148	−8.154	14
Cyclopropyl ethyl ether	96.9	3.016	−10.707	5.270	−2.421	−3.811	14
Tetrahydrofuran	81.1	2.490	−8.961	5.270	−1.201	−1.434	8
Tetrahydropyran	97.7	3.042	−10.795	5.270	−2.483	−2.224	91
Aldehydes							
Propanal	72.1	2.183	−7.967	4.029	−1.755	−1.346	5
Butanal	88.3	2.535	−8.939	3.925	−2.479	−2.466	5
Isobutanal	90.8	2.668	−9.423	3.955	−2.800	−2.760	94
Pentanal	106.4	3.286	−11.597	4.014	−4.297	−4.201	5
Hexanal	123.1	3.848	−13.556	4.026	−5.682	−5.124	94
Heptanal	134.4	4.210	−14.830	4.028	−6.592	−6.338	94
Octanal	156.1	4.888	−17.244	4.030	−8.327	−7.291	5
2-Ethylhexanal	150.1	4.703	−16.579	4.030	−7.847	−7.692	94
Nonanal	172.1	5.380	−19.015	4.030	−9.606	−9.059	5

Table 5. Continued

Solute	V_B	B	F	O	$Ln\Phi_B^{pred}$	$Ln\Phi_B^{exp}$	Ref.
Diesters							
Ethyl glutarate	184.2	5.748	−20.354	10.539	−4.067	−4.757	95
Ethyl adipate	200.7	6.220	−22.068	10.528	−5.320	−5.473	95
Ethyl pimelate	217.5	6.744	−24.004	10.537	−6.723	−6.223	95
Ethyl suberate	234.7	7.263	−25.926	10.539	−8.124	−7.279	95
Ethyl azelate	251.1	7.751	−27.744	10.539	−9.454	−8.267	95
Ethyl sebacate	267.8	8.245	−29.591	10.539	−10.807	−9.397	95
Tertiary amines							
Triethylamine	118.2	3.509	−12.268	5.957	−2.802	−2.331	96
Dimethylbutylamine	119.3	3.571	−12.500	5.968	−2.961	−3.351	96
Dimethylcyclohexylamine	127.4	3.922	−13.778	6.005	−3.852	−4.241	97
Diisopropylethylamine	152.4	4.765	−16.798	6.026	−6.007	−5.682	96
Triallylamine	144.2	4.502	−15.857	6.024	−5.331	−5.905	96
Tripropylamine	161.2	5.041	−17.791	6.028	−6.722	−8.430	96
Diethylcyclohexylamine	161.5	5.050	−17.824	6.028	−6.746	−6.203	97
Diethyloctylamine	174.8	5.461	−19.307	6.029	−7.818	−7.824	96
Tributylamine	202.7	6.307	−22.397	6.029	−10.061	−6.816	96

(11) which, for dilute solutions ($\Phi_S \gg \Phi_B$), can be rewritten as

$$\ln \Phi_B = C_1 - 0.08287 V_B + 0.50 \ln V_B \qquad (12)$$

or converted into the molar solubility scale ($S_B \approx 1000\ \Phi_B/V_B$):

$$\log S_B = C_2 - 0.0360 V_B - 0.2174 \ln V_B \qquad (13)$$

with

$$C_1 = -1.948 + v_o \ln\left(1 + \frac{K_o}{18.1}\right)$$

and

$$C_2 = 2.154 + \frac{v_o}{2.302} \ln\left(1 + \frac{K_o}{18.1}\right)$$

The constants C_1 and C_2 include all factors of Eqn. (11) which do not depend on the solute molar volume and contain, in particular, the solvation effects (O term) due to solute–solvent specific interactions. Depending on both the type and the number of proton-acceptor groups on the solute, [ketone, ether, ester, diester ($v_o = 2$), aromatic ring, etc.] and on the strength (K_o) of their interaction with water, Eqns (12) and (13) give rise to a set of nearly linear thermodynamic relationships relating, for each congeneric series, the liquid aqueous solubility to the molar volume of the congeners (Fig. 4). Within each chemical series, the aqueous solubility is governed by the same factors, and shows the same theoretical dependence on the solute size as shown by the parallel character of the equations. These relationships only differ from one another by the values of the intercept (C_1 or C_2). Being explicitly issued from the quantitative development of the MOD non-ergodic thermodynamics, Eqn. (12) or (13) could be considered as the fundamental theoretical basis of the various empirical volume–solubility straight lines reported by McAuliffe,[25] Lande and Banerjee,[22] Gert-Jan de Maagd *et al.*[99] and Huibers and Katritzky.[100] Indeed, the present thermodynamic treatment not only provides explanations for why all the empirically derived straight lines are characterized by very similar slopes ranging from −0.03 to −0.04 [compared with −0.036 for Eqn. (13)], but also enables one to explain the great variations observed in the values of the intercept which encode, among other, the specific solvation effects associated with the functionality and the degree of unsaturation and of cyclization relevant to each chemical series of compounds. However, if Eqns (12) and (13) closely resemble the regression equations obtained from experimental data, they have a completely different origin, and differ totally in essence. The use of the molar volume as a key descriptor in several approaches to solubility prediction, such as linear solvation energy relationships (LSER), and various group contribution methods including UNIFAC, always relies on the enthalpic interpretation of the solution process reflecting the need to create a cavity in water to accommodate the solute: the larger the solute, the greater is the number of H-bonds that are to be broken, the higher is the energy to supply for this breaking and the lower is the solubility. In contrast, the presence of the solute size in Eqns (12) and (13) has once again a hybrid origin stemming from two entropic effects with opposite signs, *i.e.* the hydrophobic effect (F term) opposing solution and the mixing entropy correction factor (B term) favoring solution. Although the absolute values of both of these effects increase with increasing molar volume of the solute, the hydrophobic effect increases much faster, and the corresponding mobile order entropy decrease of the water molecules upon introduction of the solute becomes rapidly the

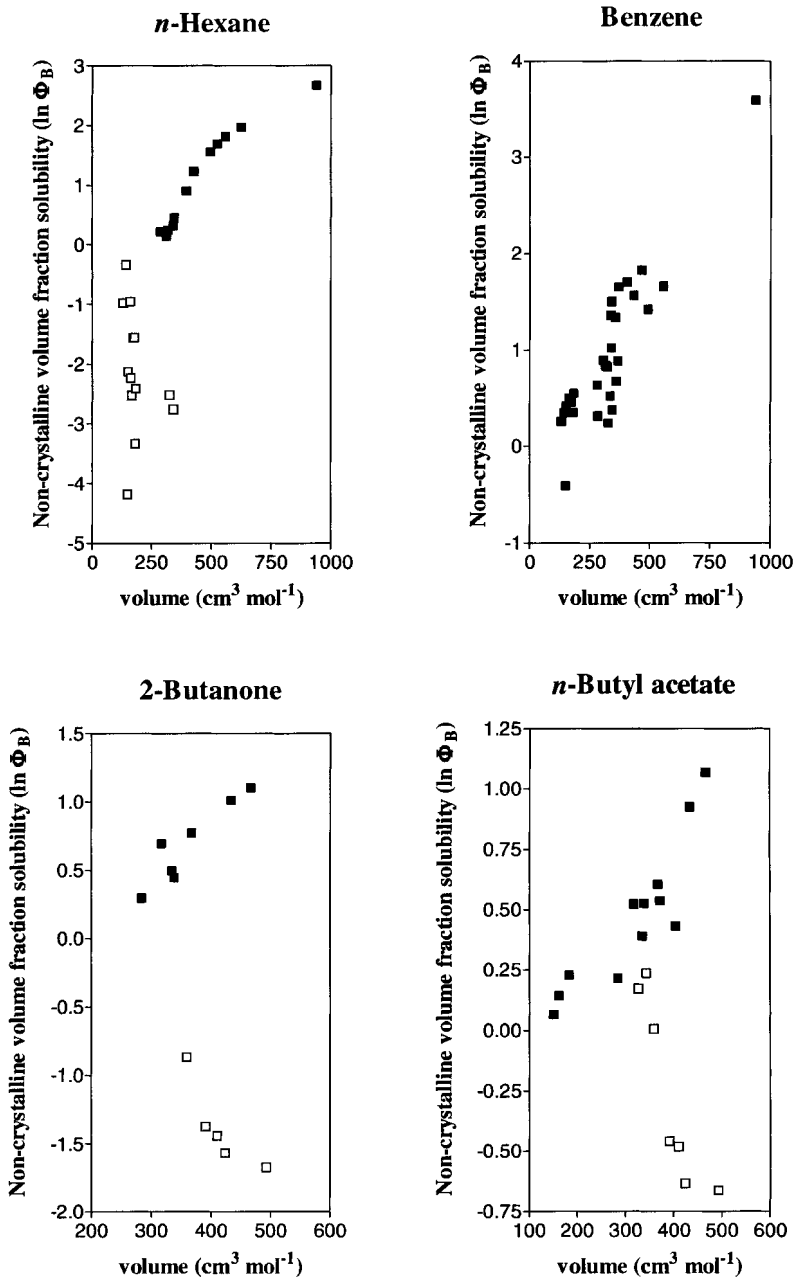

Figure 2. Napierian logarithm of the non-crystalline volume fraction solubility (ln Φ_B^L) versus the molar volume (V_B) of the solute in aprotic solvents

leading term responsible for the observed quasi-linear solubility lowering as the solute size increases. Figure 5 illustrates the variation of the relative contributions encoded in the overall liquid solubility values in the case of the *n*-alkyl acetate and 2-alkyl ketone chemical series. Clearly, the results reveal that the aqueous solubility dependence of aprotic substances upon their molar volume is essentially governed by the hydrophobic effect (*F* term) which increases more rapidly than the correction factor for the entropy of mixing (*B* term), whereas the solvation effect (*O* term) remains constant within a particular homologous chemical series.

CONCLUSION

The general solubility equation for real solutions, derived from the MOD theory, has been successfully applied to predict the solubility of a number of aprotic substances in solvents of varying volume, polarity and H-bonding ability. In addition to its reasonably accurate predictive ability, the MOD solubility model enables one to assess the relative importance of the various physico-chemical processes involved in the overall solubility phenomenon. Being derived on a strictly thermodynamic basis, it also provides natural explanations concerning the origin of the

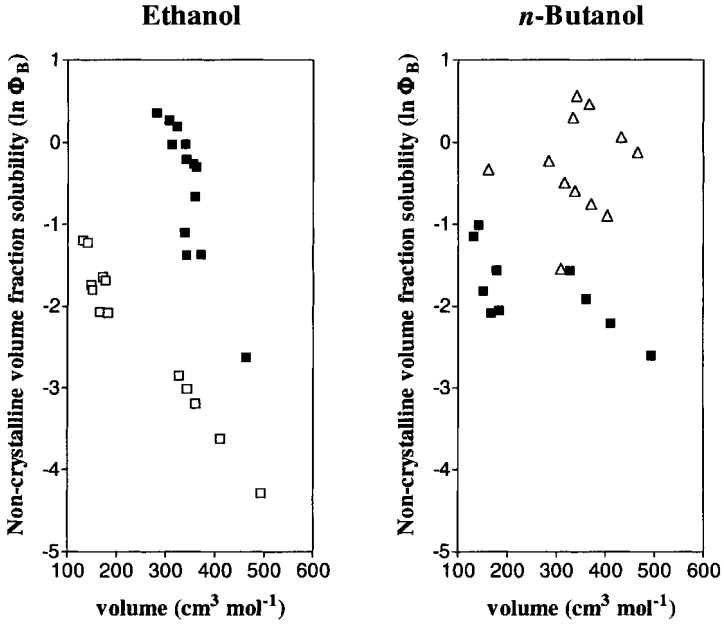

Figure 3. Napierian logarithm of the non-crystalline volume fraction solubility ($\ln \Phi_B^L$) versus the molar volume (V_B) of the solute in alcohols

experimentally observed dependence between solubility and some molecular properties such as the molar volume of the solute. The traditional interpretations of the volume–solubility relationships generally start from the fact that, to dissolve a substance, a cavity of suitable size must first be created within the solvent for locating the foreign molecules, and that this particular process requires breaking of the solvent matrix or destruction of the net of H-bonds linking associated solvent molecules like water.

These phenomenological theories are questionable, however, because they do not adequately take into account the specific nature of the liquid state. Most theories in their quantitative development ignore the continuous motions of the molecules, and are mainly static regarding solutions more like deformed lattices of molecules, rather than as collections of individual entities in continuous rapid motion with respect to each other. At constant pressure, there is no practical need to create a cavity to dissolve a solid or a liquid substance in water or

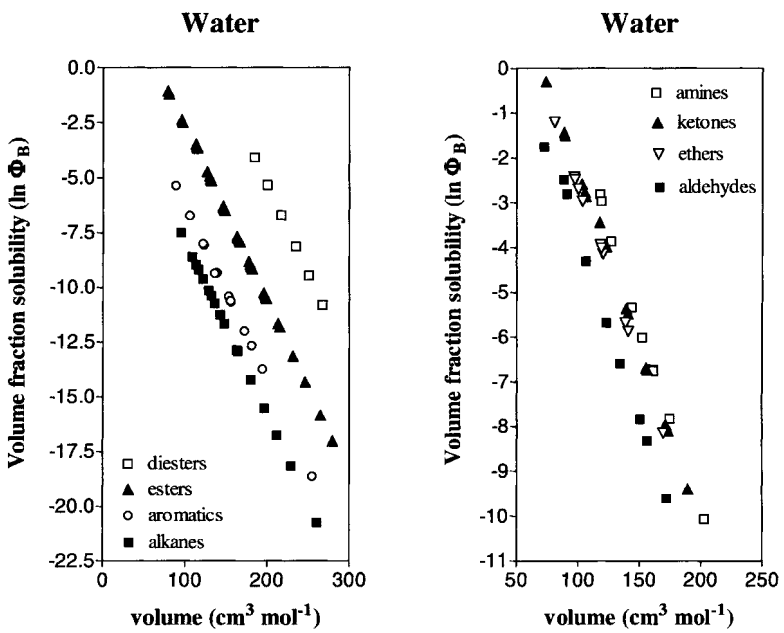

Figure 4. Napierian logarithm of the volume fraction solubility ($\ln \Phi_B$) versus the molar volume (V_B) of liquid solutes in water

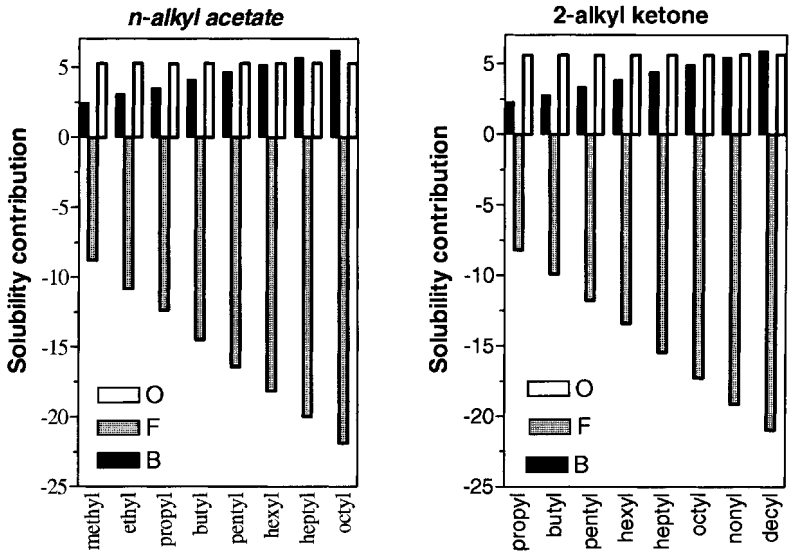

Figure 5. Contributions of the mixing entropy correction factor (*B*), the hydrophobic effect (*F*) and the solute–water H-bond formation (*O*) to the aqueous volume fraction solubility (ln Φ_B) of some liquid *n*-alkyl acetates and 2-alkyl ketones at 25 °C

in any other liquid. When a solute molecule enters the solvent, the mobile solvent molecules adapt themselves to the presence of the moving volume of the foreign substance, and both volumes are simply added unless unlike molecules differing in size and shape, when mixed, will rearrange themselves so that the final volume is not exactly the sum of the volumes added. In particular, the introduction of a substance into liquid alcohol or water does not prevent a hydroxyl group following another hydroxyl group in its walk through the liquid. Both simply move together around the obstacle created by the new neighbor.

The H-bonded chains in water or in alcohols are moreover not affected by the introduction of a chemical because, in the perpetual motions of the water (alcohol) molecules, the H-bonds are transient species which are continuously broken and then formed again with another partner on a very short time-scale. Both the negative enthalpy of solution for most organic liquids of eight carbons or less[101,102] and the very weak alkane solubility dependence on temperature [103,104] unambiguously demonstrate that the introduction of inert substances in water does not require an appreciable breaking of water–water H-bonds. Moreover, the small value (2.3 ± 0.3 KJ mol^{-1}) of the energy of transfer of an alkane methylene group from its own phase to water obtained from calorimetric measurements,[105] *i.e.* only one tenth of the energy of a hydrogen bond, can be explained by simply considering the changes in the nonspecific forces upon mixing.

Finally, the traditional interpretation of the volume–solubility dependence assuming that the larger the solute molecule the greater is the energy required for breaking a greater number of molecular contacts (dispersive, dipolar or H-bonds) would imply that, whatever the solvent considered, the solubility of aprotic compounds should always be lowered upon increasing their molar volume. Such general behavior is, however, not observed experimentally and, as demonstrated in this work, the solubility may either increase or decrease according to the relative importance of the various contributions involved in the overall solubility process. All these observations thus really question the necessity for creating cavities which is universally considered at the basis of the dependence observed between the solubility and the molar volume.

Taking proper account of the essential characteristics of the liquid state, the MOD theory-derived solubility model proposes an alternative thermodynamic explanation concerning the origin of the experimentally observed volume–solubility relationships. The variation of the liquid (subcooled liquid) solubility with respect to the molar volume of the solute always has a hybrid origin, and results from the balance of elementary processes affecting solubility in opposite directions. On the one hand, the liquid solubility of aprotic compounds in apolar or polar aprotic solvents may either increase or decrease depending upon whether the change in the non-specific cohesion forces (*D* term) is smaller or greater than the correction factor for the entropy of mixing (*B* term). In these cases, the observed behavior results from two thermodynamic processes of different nature, enthalpic and entropic. On the other hand, in protic solvents, the behavior of liquid solubility versus solute molar volume is essentially governed by two opposite elementary processes which are both of entropic nature: the hydrophobic effect (*F* term) opposing solution and the correction factor for the mixing entropy (*B* term) favoring solution. Because, in the case of aprotic solutes, the former effect always overcomes the latter, one always observes a solubility decrease as the size of the solute increases. That the solubility decrease in water is more

pronounced than that in alcohols is furthermore explained by the stronger hydrophobic propensity of water with respect to that of alcohols. In conclusion, the formation of a cavity is definitely not a necessary step in the solution process of a substance in a liquid.

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