New General Models for Evaluating Interactions in Non-Regular Solutions and Adsorption Energies Based on Both Hansen's and Drago's Parameters

Michel Buchmann[a,#], Nam-Tran Ho[a,#], Roger Lamartine[b] and Isabelle Bonnamour[b,*]

[a]*Institute of Pharmaceutical Analysis, School of Pharmacy, University of Lausanne, B. E. P., CH-1015 Lausanne, Switzerland (closed in 2004)*

[b]*ICBMS UMR CNRS 5246, Equipe Chimie Supramoléculaire Appliquée, Université de Lyon, Université Lyon 1, 43 Boulevard du 11 Novembre 1918, F-69622, Villeurbanne, France*

Abstract: This study aims at providing a model for the internal mixing energy of two liquids. The concerned variables are the solute molar volume V (cm^3/mol.), the cohesion parameters and the Drago's parameters. The model is based on the following fundamental novelties:

The fragmentation of molar cohesive energy ΔE_{coh} (kJ/mol) into two distinct categories. Indeed, the dispersive and polar cohesion energies are magnetic and electrical in nature, and the cohesive energy of the chemical bonds (Hydrogen Bond) is due to charge transfer and orbital overlap. The origins of these two categories of energy are different, requiring two different treatments in use.

For the first time, a relationship has been established between the cohesive energy from chemical bonds ΔE_h (kJ/mol) and Drago's parameters E_a, E_b, C_a, and C_b ($KJ^{1/2}mol^{-1/2}$).

A simple equation has been proposed for the salvation energy of a gaseous solute in a liquid solvent. This equation contains a term for the perturbation energy of the solvent in the presence of the solute, namely the cavity formation energy, and different types of interaction energies between the solvent and the solute at infinite dilution.

Based on calorimetric data published, the proposed model is compared with the classic model in terms of the mixing energy. The result shows a clear advantage of the new model over the old or conventional one.

Clearly, this new model should provide a new method to determine the interaction parameters or interaction capacities of complex pharmaceutical molecules using a series of simple and well-chosen solvents.

Keywords: Internal energy, molecular interaction, Drago's parameters, solubility parameters, solvent, magnetic field, electric field.

1. THEORETICAL BASIS

Conventionally, the three solubility parameters [1, 2] ∂_d, ∂_p, and ∂_h, which are extracted from the three components of the cohesive energy, namely, the vaporization energy, have been considered as three different parameters related to molecular capacity interactions. As per convention [2], these three parameters, in addition to the molar volume, *V,* are the sole variables used for the internal interaction energy function. The last is split into the dispersive, polar, and chemical bonding energy Components. It is used in chemical evaluations related to industrial applications [3-13] and furthermore it is known to play a prominent role in investigations of pharmaceutical and biological systems [14-30]. Herein, we propose a new equation for the molar mixing internal energy [31], $\Delta E_{mix\ 2,1}$, volume, *V,* and Hansen's solubility parameters, ∂_d (dispersive), ∂_p (polar), and ∂^2_h (chemical bonding) but also Drago's parameters, *E* and *C,* [32] in the expression for chemical bonding:

$$\Delta E_{mix\ 2,1} = \text{Function}\ (V, \partial_d, \partial^2_d, \partial p, \partial^2_p, \partial^2_h, E_a, C_a, E_b, C_b)$$

According to Maxwell, the movement of a charge creates a magnetic field. As a result, a chemical molecule, with its many electrons moving in their orbits, has its own molecular volume magnetic field. There are two kinds of molecules: non-polar and polar, the latter having permanent dipoles. These dipoles produce an electric field, E, on the molecule and this can polarize other surrounding molecules. This polarization creates an induced dipole moment on a surrounding molecule equal to the electric field E multiplied with a coefficient of polarizability α".

In a molecule composed of different atoms, charge polarization occurs. Therefore, such a molecule has its own molecular volume electric field or, in other words, its own dipole. It is also known that the atoms within

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*Correspondence Address to this author at the ICBMS UMR CNRS 5246, Equipe Chimie Supramoléculaire Appliquée, Université de Lyon, Université Lyon 1, 43 Boulevard du 11 Novembre 1918 F-69622, Villeurbanne, France; Tel: +33-4-26234405, +33-6-78531164;
E-mail: isabelle.bonnamour@univ-lyon1.fr
[#]Present Address: Grand-Rue 14, CH-1680 Romont, Switzerland.

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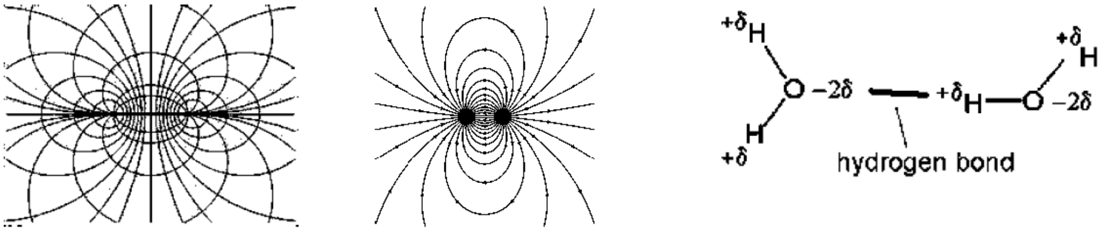


1a **1b** **1c**

Figure 1: 1a represents molecular magnetic field, **1b** represents the molecular electric field, and **1c** represents the cohesive inter-molecular chemical bonding by charge transfer and orbital overlap.

molecules are able to form intermolecular chemical bonds. Schematics of these molecular properties are shown in Figure **1a**, **1b**, **1c**.

As a working hypothesis, it is assumed that all the molecules of a liquid mass except one are fixed in place. The single free molecule is then removed from the liquid mass. In this isolated state, the free molecule has its own magnetic field volume. The two poles of the magnetic field, however, do not have determined positions, owing to the very rapid fluctuations of the electrons in their orbits. Furthermore, this magnetic field must be stabilized, as shown in Figure **1a**.

In addition, the molecules surrounding the empty volume within the body of the liquid from which the single molecule has been removed create a magnetic field similar to the one they would have formed, if the molecule had not been removed. Therefore, this field must also be stabilized in order for the entire system to be stable, as shown in Figure **2a**.

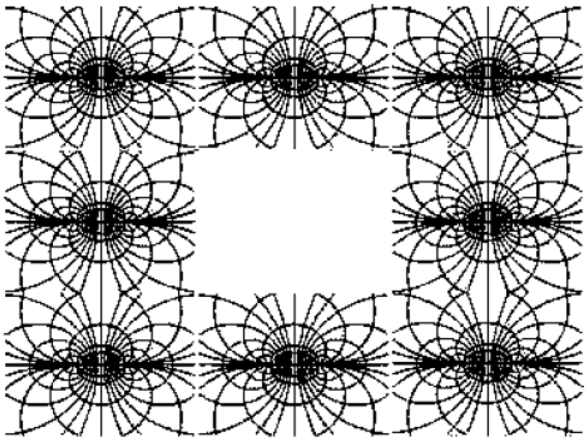


Figure 2a: Magnetic field created by molecules surrounding the volume left vacant after the removal of a single molecule.

The isolated molecule is then returned to its former position within the liquid bulk. As a result, the mass of the liquid becomes stable once again.

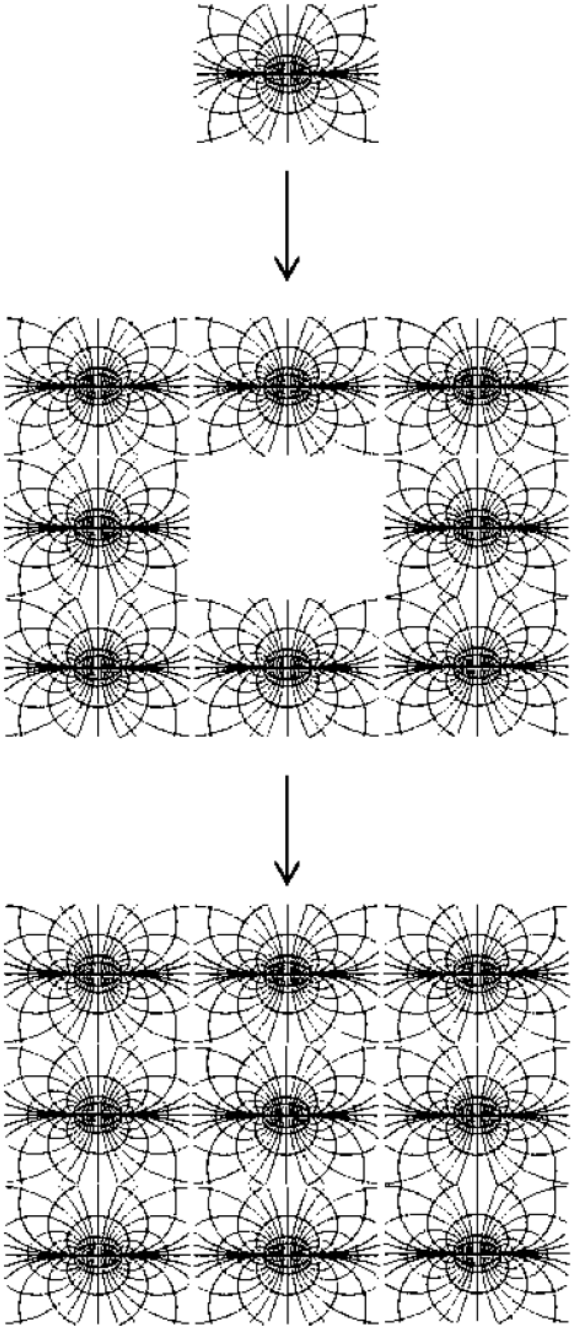


Figure 2b: Dispersive interactions in the bulk material.

Therefore, there occurs a magnetic interaction, referred to as the dispersive interaction, in bulk materials, as shown in Figure **2b**. The volume of the magnetic field of an isolated molecule will occupy the same volume as the magnetic field of the molecule at the center of liquid. That is to say the volumes of these two magnetic fields would be the same. Therefore, the energy must be derived from molecules with equivalent contributions, and consequently, the square root of this energy retains the properties of the molecule.

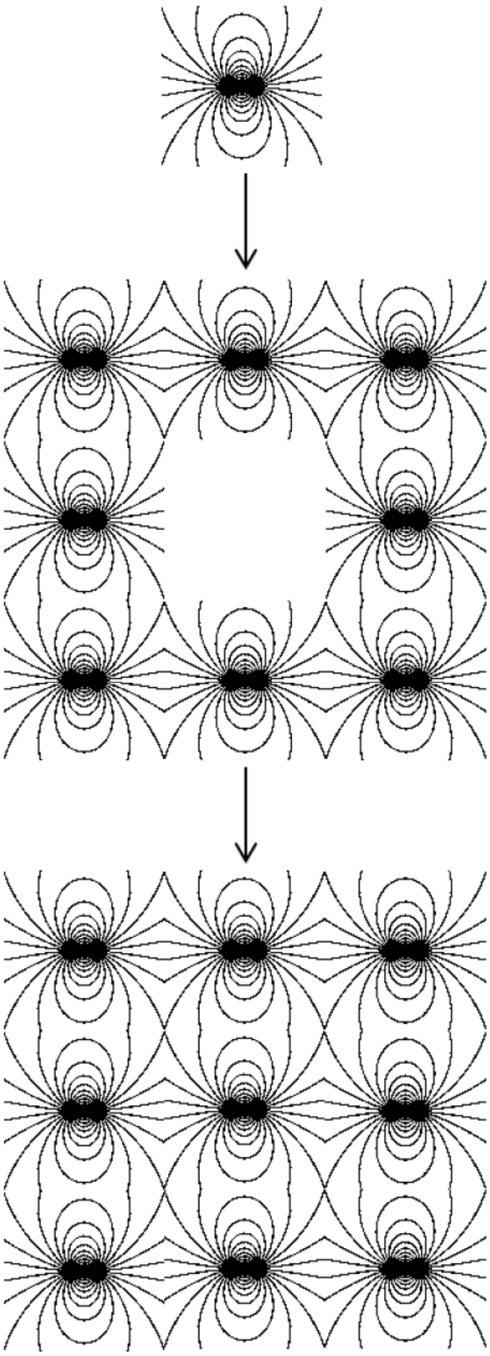


Figure 3: Dipolar interactions in the bulk material.

The same reasoning also holds for the molecular electric field. In this case, however, the positions of the two electric poles are more or less determined, and electric interactions, referred to as dipolar interactions, occur; these are shown schematically in Figure **3**.

For a pure substance in the liquid state, the molar cohesive energy is determined by these three types of interactions and is thus equivalent to the energy of vaporization of the substance. Therefore, the energy of vaporization, ΔE_{vap}, is the same as the cohesive energy and has three components: the magnetic (ΔE_{d}) component, the electrical or polar (ΔE_{p}) component, and the chemical bond (ΔE_{h}) components.

With respect to chemical bond interactions, in a chemical bond, there is orbital overlap and charge transfer between the two atoms involved, as shown in Figure **4**.

$$\Delta E_{vap} = \Delta E_{d} + \Delta E_{p} + \Delta E_{h}$$

According to Hansen or to the School of Regular Solutions [1, 2], the expressions for these components are as follows:

$$\Delta E_{d} = V\partial^{2}_{d} = \text{cohesive dispersive energy}$$

$$\Delta E_{p} = V\partial^{2}_{p} = \text{cohesive polar or dipolar energy}$$

$$\Delta E_{h} = V\partial^{2}_{h} = \text{cohesive chemical bond energy} \qquad (1)$$

The terms ∂^{2}_{d}, ∂^{2}_{p}, and ∂^{2}_{h} represent three types of cohesive density energies, while V is the molar volume of the liquid.

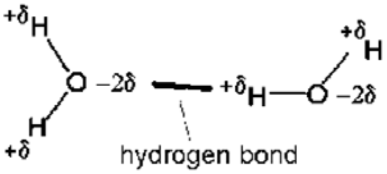


Figure 4: Cohesive inter-molecular chemical bonding by charge transfer and orbital overlap between the oxygen and hydrogen atoms of water.

According to convention [2], this idea can be exploited to generate parameters characterizing the interaction capacities of molecules, Further on the basis of these three types of energies, the following parameters can be calculated:

$$\partial_{d} = (\Delta E_{d} / V)^{1/2} = \text{dispersive parameter}$$

$$\partial_{p} = (\Delta E_{p} / V)^{1/2} = \text{polar parameter}$$

$$\partial_{h} = (\Delta E_{h} / V)^{1/2} = \text{chemical bond parameter} \qquad (2)$$

However, the energy of a chemical bond depends on the capacity for orbital overlap, C, and the charge transfer, *E,* of each atom, and each atom exhibits different capacities for both. Therefore, Drago [32] introduced the notion of donor–acceptor pairs to account for the electrons, and assigned to the atom that is the electron donor the parameters E_a and C_a and to the atom that is the electron acceptor the parameters E_b and C_b. Using these definitions, the expression for the cohesive energy of a mole of a chemical bond can be written as follows:

$$\Delta E_h = V\,\partial^2_h$$

And

$$V\,\partial^2_h = n\,(E_a\,E_b + C_aC_b) \qquad (3)$$

Then

$$\partial_h = (n(E_a\,E_b + C_aC_b)/V)^{1/2} \qquad (4)$$

Where, *n* is the number of chemical bonds that a molecule can form with its own environment. Note that the parameter ∂_h is, in fact, a function of the parameters of the two atoms that form the chemical bond. Therefore, it is actually the square root of the energy and not a parameter that can be used in the same manner as the molecular parameters ∂_d and ∂_p. Based on this analysis, the parameters V, ∂_d, ∂^2_d, ∂_p, ∂^2_p, ∂^2_h, E, and C were selected to formulate the equation for the mixing energy.

2. DERIVATION OF EQUATIONS

Next, the mathematical equation for the internal mixing energy, $\Delta E_{mix\ 2,1,}$ was derived. For this purpose, the sketch shown in Figure **5**, which is based on the principle of energy conservation, was used to describe the relationships between the internal mixing energy of solute (2) in solvent (1) at infinite dilution on one hand, and those between the molar volumes V_1 and V_2 and Hansen's solubility and Drago's donor–acceptor parameters on the other hand.

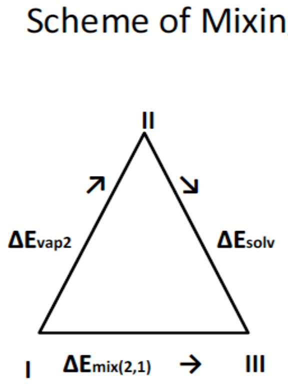


Figure 5: Shows the three states I, II, and III of a solute according to Hess cycles.

For this purpose, we will proceed in two different ways. In the indirect way, we will build a three-step Hess cycle. Firstly, the solute is evaporated; this step requires the vaporization energy ΔE_{vap}. Then the solute vapor is introduced in the solvent mass, inducing a reorganization of the solvent around the solute, as described by Fuch [34]; this involves the salvation energy ΔE_{solv}. The final step is designed according to [35-40] involving the cavity-forming energy ΔE_{cav} in the solvent or the solvent perturbation energy ΔE_{pert1} in the presence of the solute in the solvent and different interaction energies between the solvent and the solute. In the other way, we directly mix the liquid solute in the liquid solvent. This step gives us the mixing energy $\Delta E_{mix1,2}$.

Based on this scheme, where I, II, and III represent the three states of the solute, the following statements can be made:

Direct path from I to III →
$\Delta Emix_{(2,1)}$ = Energy of mixing 2 in 1

Path from I to II →
ΔE_{vap2} = Energy of vaporization of solute 2

Path from II to III →
ΔE_{salv} = Energy of salvation for 2 in the gaseous state in liquid

solvent 1.

In addition, some authors [33-35] proposed the following relation for energy of salvation:

$$\Delta E_{salv} = \Delta E_{pert1} + \Delta E_{inter2,1} \qquad (5)$$

Or

$$\Delta E_{salv} = \Delta E_{cav} + \Delta E_{inter2,1} \qquad (5a)$$

where

ΔE_{pert1} = Perturbation Energy for solvent 1

ΔE_{cav} = Cavity formation Energy in solvent 1

$\Delta E_{inter2,1}$ = Energy of interaction between solute 2 and solvent 1

V_i = molar volume with i = 1 or 2

Applying the principle of energy conservation, we get the following:

$$\Delta E_{mix\ (2,1)} = \Delta E_{vap2} + \Delta E_{salv} \tag{6}$$

Using Eq. (5), the following equation is obtained:

$$\Delta E_{mix\ (2,1)} = \Delta E_{vap2} + \Delta E_{pert1} + \Delta E_{inter2,1} \tag{7}$$

The concept of solvent perturbation or the creation of a cavity [36-39] and of the interactions [40] has been introduced.

By using a different set of different Hansen's solubility parameters and Drago's parameters, we get the following:

$$\Delta E_{vap2} = V_2\ (\partial^2_{d2} + \partial^2_{p2} + \partial^2_{h2}) \tag{8}$$

When one mole of a gas solute with a molar volume V_2 enters into a large solvent mass, it must overcome the magnetic and electric energies of cohesion in the solvent mass. In addition, the chemical bonds between the molecules in the solvent must be broken for the formation of chemical bonds between the solvent and solute molecules.

Thus, when one mole of a solute with a molar volume V_2 is added to a large solvent mass with a cohesive magnetic energy density equal to ∂^2_{d1} per cm^3, the energy of the magnetic perturbation for the volume V_2 in that solvent mass must be equal to

$$\Delta E_{pert\ 1,d} = V_2\ \partial^2_{d1} \tag{9}$$

With respect to the electrical disturbance energy, the problem is slightly different from that for the magnetic disturbance, because the interactions are electrical in nature, owing to the presence of dipoles (Figure **6**).

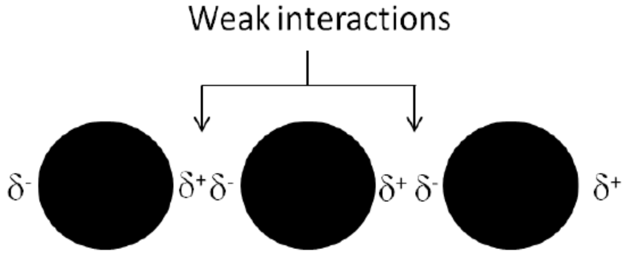


Figure 6: Dipolar interactions that must be considered when determining the electrical disturbance energy.

According to the definition of the cohesive energy due to the electric field of a solvent mass, the energy density of electrical cohesion equals ∂^2_{p1} per cm^3. When a solute molecule approaches a polar solvent, it seeks the path of least energy. Therefore, only one of the two existing poles is disturbed. Consequently, the energy of the electric disturbance of solvent for a molar volume V_2 of solute must be equal to:

$$\Delta E_{pert\ 1,p} = V_2\ \partial^2_{p1}/2 \tag{10}$$

After considering both the electric and the magnetic disturbances caused by the presence of a solute in the solvent, the disturbance of the chemical bonds between two solvent molecules was evaluated.

Note that for any solvent with non-zero energy $V_1\partial^2_{h1}$, chemical bonds must exist between the solvent molecules.

Thus, to obtain the desired equation, several typical solvents were considered as examples.

In the case of water, each water molecule in the liquid state can form three chemical bonds with its environment (Figure **7**).

In an alcohol, each alcohol molecule in the liquid state can form two chemical bonds with its environment (Figure **8**).

In the case of a ketone, each ketone molecule in the liquid state can also form two chemical bonds with its environment (Figure **9**).

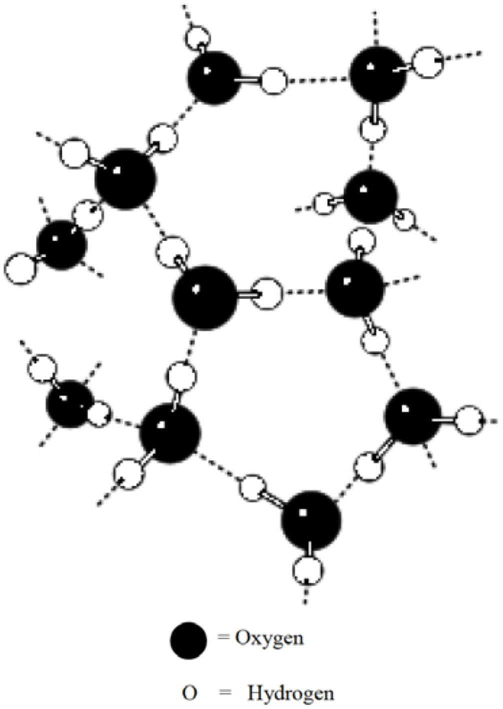


Figure 7: Each molecule of liquid water can form three bonds with other liquid water molecules.

Let *n* be the number of chemical bonds that a solvent molecule can form with its surroundings. Then,

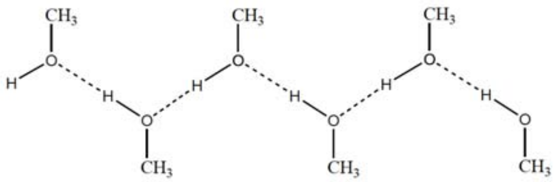


Figure 8: Each liquid alcohol molecule can form two bonds with other liquid alcohol molecules.

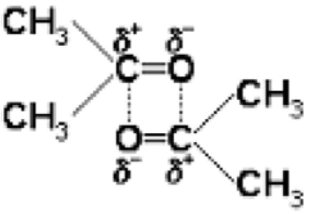


Figure 9: Represents two cohesive inter-molecular chemical bonds formed by charge transfer and orbital overlap between the carbon and oxygen atoms of two acetone molecules in liquid state.

if (V_1 ∂^2_{h1}) is the cohesive energy of the chemical bonds, the energy required to break one mole of the bonds of the solvent will be

$$\Delta E_{pert\ 1,h} = (V_1\partial^2_{h1})/n, \tag{11}$$

Where, n = 3 for water, n = 2 for an alcohol, and n = 2 for acetone.

Therefore, the total energy of the magnetic, electrical, and chemical disturbances in the solvent can be written as

$$\Delta E_{pert1} = V_2\,(\partial^2_{d1} + \partial^2_{p1}/2) + V_1\partial^2_{h1}/n. \tag{12}$$

Then, the energies corresponding to interactions between the solute and the solvent, $\Delta E_{inter2,1}$, can be written as follows:

For the magnetic part, $\Delta E_{inter2,1,m}$ is given as following [41]

$$\Delta E_{inter2,1,m} = 2V_2\partial_{d2}\,\partial_{d1}. \tag{13}$$

For the electrical part, $\Delta E_{inter1,2,e}$ is given by:

$$\Delta E_{inter2,1,e} = 2V_2\partial_{p2}\partial_{p1}. \tag{14}$$

The chemical part, $\Delta E_{inter1,2,c,}$ must be expressed in a different manner.

During the mixing process, the solute binds chemically to the solvent. The energy of this chemical bond depends on the capacities for orbital overlap, *C,* and charge transfer, *E,* of each atom. Further, the atoms do not have the same capacities for either interaction.

Therefore, Drago introduced the notion of the donor–acceptor pair to explain electron interactions and assigned the parameters E_a and C_a to the electron donor atom and E_b and C_b to the electron acceptor atom in each pair. Using these definitions, the expression for the energy of a mole of a chemical bond can be written as follows, according to Drago [32]:

$$\Delta E_{bond} = E_a\,E_b + C_aC_b \tag{15}$$

According to the donor–acceptor pair concept, for any substance for which ∂^2_h is not equal to zero, there must be two sets of parameters:

(E_{ai}, C_{ai}) and (E_{bj}, C_{bj}) with i, j = 1, 2

Thus, for a solvent molecule, we have,

(E_{a1}, C_{a1}) and (E_{b1}, C_{b1}),

and for the solute molecule we have,

(E_{a2}, C_{a2}) and (E_{b2}, C_{b2}).

Consider now a mixture of ethanol in water:

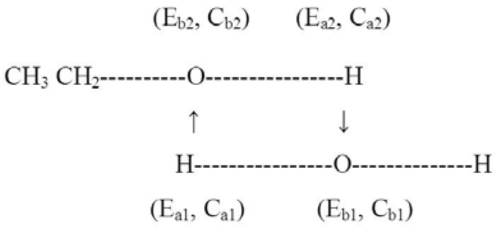


Figure 10: Interactions between ethanol and water in a liquid mixture.

Thus, the expression for the energy of chemical bonding interactions for any solute in any solvent is given by:

$$\Delta E_{inter2,1,c} = (E_{a1}\,E_{b2} + C_{a1}\,C_{b2}) + (E_{a2}\,E_{b1} + C_{a2}\,C_{b1}). \tag{17}$$

3. CONTRACTION AND DILATION OF VOLUME DURING MIXING

These phenomena arise because of the internal pressure of the solvent P_{int1}, since the system has to perform work. This work, ΔE_{contr}, can be expressed as follows:

$$\Delta E_{contr} = \Delta V_2\,P_{int1}.$$

$$\Delta V_2 = {}^{p}V_2 - V_2$$

${}^{p}V_2$ = Partial molar volume of solute 2

Now according to Bagley [42]

$$P_{int1} = \partial^2_{d1} + (3/2\ RT)/V_1,$$

Thus,

$$\Delta E_{contr} = \Delta V_2\ (\partial^2_{d1} + (3/2\ RT)/V_1). \tag{18}$$

Adding this term to all the contributions mentioned above and on the basis of the energy conservation principle (the sign is always positive), the final equation can be written as follows:

$$\Delta E_{mix\ (2,1)} = \Delta E_{vap2} + \Delta E_{pert1} + \Delta E_{inter\ 2,1}$$

$$\Delta E_{mix\ (2,1)} = \Delta E_{vap2} + V_2(\partial^2_{d1} + \partial^2_{p1}/2) + V_1\partial^2_{h1}/n + 2V_2\partial_{d2}\ \partial_{d1} + 2V_2\partial_{p2}\ \partial_{p1} + (E_{a1}\ E_{b2} + C_{a1}\ C_{b2}) + (E_{a2}\ E_{b1} + C_{a2}\ C_{b1}) + \Delta V_2(\partial^2_{d1} + (3/2\ RT)/V_1). \tag{19}$$

For numerical applications, the appropriate signs must be added for the different terms.

If the system receives energy, the sign is +.

If the system produces energy, the sign is −.

$\Delta E_{mix\ (2,1)}$ could be negative or positive. For this reason, it was decided to not give it any sign.

$\Delta E_{vap2} + V_2(\partial^2_{d1} + \partial^2_{p1}/2) + V_1\partial^2_{h1}/n$ is the energy that the system receives.

The sign must be +.

$2V_2\partial_{d2}\ \partial_{d1} + 2V_2\partial_{p2}\ \partial_{p1} + (E_{a1}\ E_{b2} + C_{a1}\ C_{b2}) + (E_{a2}\ E_{b1} + C_{a2}\ C_{b1})$ is the energy that is liberated by the system.

The sign must be −.

$\Delta V_2(\partial^2_{d1} + (3/2\ RT)/V_1)$ is the work done by the system.

The sign must be − .

Then, Eq. (19) becomes:

$$\Delta E_{mix\ (2,1)} = \Delta E_{vap2} + V_2(\partial^2_{d1} + \partial^2_{p1}/2) + V_1\partial^2_{h1}/n - 2V_2\partial_{d2}\ \partial_{d1} - 2V_2\partial_{p2}\ \partial_{p1} - (E_{a1}\ E_{b2} + C_{a1}\ C_{b2}) - (E_{a2}\ E_{b1} + C_{a2}\ C_{b1}) - \Delta V_2(\partial^2_{d1} + (3/2\ RT)/V_1).$$

This is the equation for the newly proposed model for the internal mixing energy, $\Delta E_{mix\ (2,1)}$.

Finally, the separation of the different terms yields two expressions for the interaction energy on both sides of the equation:

$$-\ \Delta E_{mix\ (2,1)} + \Delta E_{vap2} + V_2(\partial^2_{d1} + \partial^2_{p1}/2) + V_1\partial^2_{h1}/n - \Delta V_2(\partial^2_{d1} + (3/2\ RT)/\ V_1) = 2V_2\partial_{d2}\ \partial_{d1} + 2V_2\partial_{p2}\ \partial_{p1} + (E_{a1}\ E_{b2} + C_{a1}\ C_{b2}) + (E_{a2}\ E_{b1} + C_{a2}\ C_{b1}) \tag{20}$$

4. PARTICULAR CASES

1. For a mixture of two absolutely non-polar substances, the expression is as follows:

$$-\Delta E_{mix\ (2,1)} + \Delta E_{vap2} + V_2\ \partial^2_{d1} = 2V_2\partial_{d2}\ \partial_{d1} + \Delta V_2\ (\partial^2_{d1} + (3/2\ RT)/V_1),$$

with

$$\Delta E_{vap2} = V_2\ \partial^2_{d2.}$$

Then,

$$\Delta E_{mix\ (2,1)} = V_2\ \partial^2_{d2} + V_2\ \partial^2_{d1} - 2V_2\partial_{d2}\ \partial_{d1} - \Delta V_2\ (\partial^2_{d1} + (3/2\ RT)/V_1).$$

2. If neither dilation nor contraction occurs, that is, $\Delta V_2 = 0$, then we have

$$\Delta E_{mix\ (2,1)} = V_2\ (\partial_{d1} - \partial_{d2})^2. \tag{21}$$

3. If $\partial_{d1} = \partial_{d2}$,

$$\Delta E_{mix\ (2,1)} = -\ \Delta V_2\ (\partial^2_{d1} + (3/2\ RT)/V_1). \tag{22}$$

Here, $\Delta E_{mix\ (2,1)}$ may be negative or positive, depending on the sign for ΔV_2, as has been observed in the cases where two nonp-olar substances are mixed.

4. If we consider the particular case of the adsorption of solute 2 on solid 1,

$$\Delta E_{ads\ (2,1)} = V_2\partial_{d2}\ \partial_{d1} + V_2\partial_{p2}\ \partial_{p1} + E_{a1}\ E_{b2} + C_{a1}\ C_{b2} + E_{a2}\ E_{b1} + C_{a2}\ C_{b1} \tag{23}$$

The adsorption energy $\Delta E_{ads\ (2,1)}$ is a function of seven parameters corresponding to the solvent used (liquid injected into the column) : V_2, ∂_{d2}, ∂_{p2}, E_{a2}, C_{a2}, E_{b2}, and $C_{b2.}$ Further, it allows one to determine the six parameters for the solid in question: ∂_{d1}, ∂_{p1}, E_{a1}, C_{a1}, E_{b1}, and C_{b1}.

For a set of used solvents, the matrix form can be written as follows:

Matrix ($\Delta E_{ads\ (2,1)}$) = Expérience matrix (X) × matrix (S)

Matrix ($\Delta E_{ads\ (2,1)}$) is a column matrix containing a set of measured adsorption energies.

The experience matrix (X) is a rectangular matrix that contains the following values ($V_2\partial_{d2}$, $V_2\partial_{p2}$, E_{a2}, C_{a2}, E_{b2}, C_{b2}).

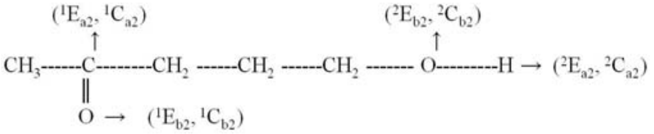
The matrix (S) is a column matrix containing the six unknowns ∂_{d1}, ∂_{p1}, E_{a1}, C_{a1}, E_{b1}, C_{b1} to be determined.

Given the need for multiple regressions, an orthogonal experience matrix (X) is required to account for these six parameters, which are independent of each other.

5. When the solute has n_1 functional groups, because of the repetition of the four variables E_{a1}, C_{a1}, E_{b1}, and C_{b1} of the solvent, Eq. (21) becomes:

$$-\Delta E_{mix\ (2,1)} + \Delta E_{vap2} + V_2\ (\partial^2_{d1} + \partial^2_{p1}/2) + n_1 V_1 \partial^2_{h1}/n - \Delta V_2\ (\partial^2_{d1} + (3/2\ RT)/V_1) = 2V_2\partial_{d2}\ \partial_{d1} + 2V_2\partial_{p2}\ \partial_{p1} + (\sum E_{b2})\ E_{a1} + (\sum C_{b2})\ C_{a1} + (\sum E_{a2})\ E_{b1} + (\sum C_{a2})\ C_{b1} \qquad (24)$$

As an example, consider the following solute molecule with two functional groups, namely, a ketone and an alcohol.



$$\begin{array}{l} \quad (^1E_{a2},\ ^1C_{a2}) \qquad\qquad\qquad\qquad\qquad\qquad\qquad (^2E_{b2},\ ^2C_{b2}) \\ \qquad\quad \uparrow \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \uparrow \\ CH_3\text{------}C\text{--------}CH_2\text{ ------}CH_2\text{ ------}CH_2\text{ ------- }O\text{---------}H \rightarrow (^2E_{a2},\ ^2C_{a2}) \\ \qquad\quad \| \\ \qquad\quad O \rightarrow \ (^1E_{b2},\ ^1C_{b2}) \end{array}$$

$\sum E_{b2} = {}^1E_{b2} + {}^2E_{b2}$ for the two oxygen atoms.

$\sum C_{b2} = {}^1C_{b2} + {}^2C_{b2}$ for the two oxygen atoms.

$\sum E_{a2} = {}^1E_{a2} + {}^2E_{a2}$ for the hydrogen and carbon atoms,

$\sum C_{a2} = {}^1C_{a2} + {}^2C_{a2}$ for the hydrogen and carbon atoms.

These equations indicate that the parameters E_a, E_b, C_a, and C_b exhibit the additive property and represent the transfer of molecular ownership of the charge and orbital overlap.

To summarize, the new model for evaluating the internal mixing energy is as follows:

$$\Delta E_{mix\ (2,1)} = \Delta E_{vap2} + V_2\ (\partial^2_{d1} + \partial^2_{p1}/2) + V_1\partial^2_{h1}/n - \Delta V_2\ (\partial^2_{d1} + (3/2\ RT)/\ V_1) - 2V_2\partial_{d2}\ \partial_{d1} - 2V_2\partial_{p2}\ \partial_{p1} - (E_{a1}\ E_{b2} + C_{a1}\ C_{b2}) - (E_{a2}\ E_{b1} + C_{a2}\ C_{b1}) \qquad (25)$$

Further, the interaction energy, $\Delta E_{inter\ (2,1)}$, has the two following forms:

$$\Delta E_{inter\ x\ (2,1)} = -\ \Delta E_{mix\ (2,1)} + \Delta E_{vap2} + V_2\ (\partial^2_{d1} + \partial^2_{p1}/2) + V_1\partial^2_{h1}/n - \Delta V_2\ (\partial^2_{d1} + (3/2\ RT)/\ V_1) = 2V_2\partial_{d2}\ \partial_{d1} + 2V_2\partial_{p2}\ \partial_{p1} + (E_{a1}\ E_{b2} + C_{a1}\ C_{b2}) + (E_{a2}\ E_{b1} + C_{a2}\ C_{b1})$$

The equation derived from the conventional concepts is as follows [43-44]:

$$\Delta E_{mix\ (2,1)} = V_2(\partial_{d2} - \partial_{d1})^2 + V_2(\partial_{p2} - \partial_{p1})^2 + V_2\ (\partial_{h2} - \partial_{h1})^2$$

Thus,

$$\Delta E_{mix\ (2,1)} = \Delta E_{vap2} + V_2\ (\partial^2_{d1} + \partial^2_{p1} + \partial^2_{h1}) - 2V_2\partial_{d2}\ \partial_{d1} - 2V_2\partial_{p2}\ \partial_{p1} - 2V_2\partial_{h2}\ \partial_{h1} \qquad (26)$$

The interaction energy, as determined when using the the conventional concepts, has the two following forms:

$$\Delta E_{inter\ x\ (2,1)} = -\ \Delta E_{mix\ (2,1)} + \Delta E_{vap2} + V_2\ (\partial^2_{d1} + \partial^2_{p1} + \partial^2_{h1}) = 2V_2\partial_{d2}\ \partial_{d1} + 2V_2\partial_{p2}\ \partial_{p1} + 2V_2\partial_{h2}\ \partial_{h1}$$

In the next step, for the purpose of comparison, these two models, namely, the new model and the conventional one are verified using experimental data.

5. EXPERIMENTAL VERIFICATION OF THE ACCURACY OF THE NEW MODEL

Tertio-butanol (0) was selected as the solute, while the following mono-functional substances were used as the solvent:

Diethyl ether (1), iso-propyl ether (2), N-butylether (3), trimethylamine (4), pyridine (5), diethylformamide (6), dimethylacetamide (7), and acetonitrile (8). Tables **1** and **2** list the published values used to verify the model.

If we simultaneously look at the new mixing model and Tables **1** and **2**, we see that the necessary values of the parameters E_{a1} and C_{a1} for the different solvents are not given by Drago. What causes a difference in the values of the term (E_{a1} E_{b2} + C_{a1} C_{b2}) for the different solvents used remains unknown!

Thus, it is essential to first estimate the missing values in Table **2**, in order to be able to verify the new proposed model.

For this purpose, we first calculate the energy of the chemical cohesion of the solvents used, that is, $V_1\partial^2_{h1}/n$, and enter the calculated value into the equation, which relates it to the parameters given by Drago:

Table 1: **Published values of the mixing energy [31], ΔE_{mix} (2,1), of the solute tertio-butanol in different solvents (diethyl ether, i-propyl ether, n-butyl ether, triethylamine, pyridine, dimethylformamide, dimethylacetamide, acetonitrile) and published values of the contraction or dilatation work [31], $\Delta V_2\ P_{int1}$, of the volume of the solute tertio-butanol the in solvents**

Name of Solvent	$\Delta E_{mix\ (2,1)}$ / kJ mol^{-1}	$\Delta V_2\ P_{int1}$/ J mol^{-1}
Diethyl ether	4.92	−24.19
i-Propyl ether	7.46	−10.67
n-Butyl ether	8.58	382.39
Triethylamine	0.80	−842.42
Pyridine	2.56	113.76
Dimethylformamide	3.17	328.48
Dimethylacetamide	2.10	54.54
Acetonitrile	9.05	382.39

Table 2: **Published values of Drago's parameters [32] E_{a2} (kJ$^{1/2}$ mol$^{-1/2}$), C_{a2} (kJ$^{1/2}$ mol$^{-1/2}$), E_{b2} (kJ$^{1/2}$ mol$^{-1/2}$), and C_{b2} (kJ$^{1/2}$ mol$^{-1/2}$) of the solute and the E_{a1} (kJ$^{1/2}$ mol$^{-1/2}$), C_{a1} (kJ$^{1/2}$ mol$^{-1/2}$), E_{b1} (kJ$^{1/2}$ mol$^{-1/2}$), and C_{b1} (kJ$^{1/2}$ mol$^{-1/2}$); values of the volume V (cm^3 mol^{-1}), solubility parameters [44] , ∂_d (MPa$^{1/2}$), ∂_p (MPa$^{1/2}$), and ∂_h (MPa$^{1/2}$), and of the solvents**

Solute	V	∂_d	∂_p	∂_h	E_{a2}	C_{a2}	E_{b2}	C_{b2}
0	94.8	15.23	5.10	14.92	2.19	1.41	3.42	2.54
Solvent	**V**	∂_d	∂_p	∂_h	E_{a1}	C_{a1}	E_{b1}	C_{b1}
1	104.8	14.50	2.89	5.10			3.69	3.34
2	142.2	13.60	4.7	1.50			4.00	3.40
3	170.4	14.60	4.30	4.51			3.87	3.42
4	140.0	14.62	3.70	1.90			2.70	11.75
5	80.87	17.60	10.10	7.70			4.69	4.70
6	77.40	17.43	13.7	11.32			4.49	2.69
7	92.50	16.83	11.52	10.21			4.82	2.69
8	52.60	15.31	18.00	6.11			3.30	1.46

The numbers in the first column have the following meaning: 0= tertio-butanol, 1 = diethyl ether, 2 = iso-propyl ether, 3 = N-butyl ether, 4 = trimethylamine, 5 = pyridine, 6 = diethylformamide, 7 = dimethylacetamide, and 8 = acetonitrile.

$$V_1\partial^2_{h1}/n = E_{a1}\,E_{b1} + C_{a1}\,C_{b1}. \tag{27}$$

Table **3** lists the different values of E_{b1}, C_{b1}, and $V_1\partial^2_{h1}/2$ for the considered solvents, which should be used in Eq. (27).

It is now possible to construct a system of equations on the basis of Eq. (27), every equation may be attributed to one of the solvents considered. Table **4** lists the results obtained.

Table 3: **Values [32] of Drago's parameters E_{b1} (kJ$^{1/2}$ mol$^{-1/2}$) and C_{b1} (kJ$^{1/2}$ mol$^{-1/2}$) for volume V_1(cm^3 mol^{-1}), Hansen's solubility parameter [44], ∂_h(MPa$^{1/2}$) and the expression $V_1\partial^2_{h1}/2$ (kJ mol $^{-1/2}$) for the solvents considered**

Name of Solvent	V_1/cm^3 mol^{-1}	∂_h/ MPa$^{1/2}$	$V_1\partial^2_{h1}/2$/ kJ mol $^{-1/2}$	E_{b1}/kJ$^{1/2}$ mol$^{-1/2}$	C_{b1}/kJ$^{1/2}$ mol$^{-1/2}$
Diethyl ether	104.8	5.10	1.36	3.69	3.34
i-Propyl ether	142.2	1.50	0.48	4.00	3.40
n-Butyl ether	170.4	4.51	1.73	3.87	3.42
Triethylamine	140.0	1.90	0.16	2.70	11.75
Pyridine	80.87	7.70	2.4	4.69	4.70
Dimethylformamide	77.40	11.32	4.9	4.49	2.69
Dimethylacetamide	92.50	10.21	4.82	4.82	2.69
Acetonitrile	52.60	6.11	0.98	3.30	1.46

Table 4: Equations for the molar chemical cohesion energy, $V_1\partial^2_{h1}/2$ (kJ $mol^{-1/2}$) of the solvents under consideration as per Drago's parameters, E_{a1}(kJ$^{1/2}$ mol$^{-1/2}$) and C_{a1}(kJ$^{1/2}$ mol$^{-1/2}$)

Name of Solvent	Equation
Diethyl ether	$1.36 = 3.69\ E_{a1} + 3.34\ C_{a1}$
i-Propyl ether	$0.48 = 4.0\ E_{a1} + 3.4\ C_{a1}$
n-Butyl ether	$1.73 = 3.87\ E_{a1} + 3.42\ C_{a1}$
Triethylamine	$0.16 = 2.7\ E_{a1} + 11.75\ C_{a1}$
Pyridine	$2.4 = 4.69\ E_{a1} + 4.7\ C_{a1}$
Dimethylformamide	$4.9 = 4.49\ E_{a1} + 2.69\ C_{a1}$
Dimethylacetamide	$4.82 = 4.82\ E_{a1} + 2.69\ C_{a1}$
Acetonitrile	$0.98 = 3.3\ E_{a1} + 1.45\ C_{a1}$

Looking at Table **4**, we can see that for every solvent, there is only one equation with two unknown variables. In order to resolve the relevant equation, we must use the graphical method. For this purpose, for every equation in Table **4**, we must construct two new equations for every solvent. After doing so, we can obtain the following equations for the eight solvents.

When using the graphical method, if the vertical axis is $E_{a1,}$ then the horizontal axis is C_{a1}, and vice versa. Thus, it is possible to calculate the values for E_{a1} and $C_{a1.}$ Therefore, Table **2** could be completed, as shown in Table **6**.

Next, to compare the conventional approach with the new theoretical model, we first evaluated the equation based on traditional concepts [43, 44]:

$$-\Delta E_{mix\ (2,1)} + \Delta E_{vap2} + V_2\ (\partial^2_{d1} + \partial^2_{p1} + \partial^2_{h1}) = 2V_2\partial_{d2}\partial_{d1} + 2V_2\partial_{p2}\partial_{p1} + 2V_2\partial_{h2}\partial_{h1,}$$

For this purpose, *A* and *B* are defined as follows:

$$A: = -\ \Delta E_{mix\ (2,1)} + \Delta E_{vap2} + V_2(\partial^2_{d1} + \partial^2_{p1} + \partial^2_{h1})$$

$$B: = 2V_2\partial_{d2}\partial_{d1} + 2V_2\partial_{p2}\partial_{p1} + 2V_2\partial_{h2}\partial_{h1}$$

In fact, *A* and *B* are the two forms of the interaction energy $\Delta E_{inter\ (2,1).}$

We then calculated the relative error between *A* and *B*, that is, the error corresponding to the classic model, using the following expression:

$$\text{Relative error \%} = ((A - B)/A) \times 100.$$

The results are given in Table **7**.

The same approach was used for the new model:

$$-\Delta E_{mix\ (2,1)} + \Delta E_{vap2} + V_2\ (\partial^2_{d1} + \partial^2_{p1}/2) + V_1\partial^2_{h1}/n - \Delta V_2\ (\partial^2_{d1} + (3/2\ RT)/\ V_1) = 2V_2\partial_{d2}\ \partial_{d1} + 2V_2\partial_{p2}\ \partial_{p1} + (E_{a1}\ E_{b2} + C_{a1}\ C_{b2}) + (E_{a2}\ E_{b1} + C_{a2}\ C_{b1})$$

These results are given in Table **8**.

6. DISCUSSION

We have proposed a new model for the internal energy of mixing, $\Delta E_{mix,2,1}$, at infinite dilution as a function of different molecular and atomic capacity interaction parameters for chemical bonding.

The parameters derived for molecular interactions, namely, ∂_d and ∂_p, have their origins in the magnetic and electric fields, with each molecule always having two of these fields, which are independent of one another.

The parameters derived for the atoms, *E* and *C,* have their origins in their capacities for chemical

Table 5: Equations for Drago's parameter E_{a1} (kJ$^{1/2}$ mol$^{-1/2}$) based on the parameter C_{a1} (kJ$^{1/2}$ mol$^{-1/2}$) and for Drago's parameter C_{a1}(kJ$^{1/2}$ mol$^{-1/2}$) based on the parameter E_{a1} (kJ$^{1/2}$mol$^{-1/2}$)

Name of Solvent	Equation for E_{a1}	Equation for C_{a1}
Diethyl ether	$E_{a1} = -0.91\ C_{a1} + 0.37$	$C_{a1} = -1.10\ E_{a1} + 0.41$
i-Propyl ether	$E_{a1} = -0.85\ C_{a1} + 0.12$	$C_{a1} = -1.18\ E_{a1} + 0.14$
n-Butyl ether	$E_{a1} = -0.88\ C_{a1} + 0.45$	$C_{a1} = -1.13\ E_{a1} + 0.51$
Triethylamine	$E_{a1} = -4.35\ C_{a1} + 0.06$	$C_{a1} = -0.23\ E_{a1} + 0.01$
Pyridine	$E_{a1} = -1.00\ C_{a1} + 0.51$	$C_{a1} = -0.99\ E_{a1} + 0.51$
Dimethylformamide	$E_{a1} = -0.60\ C_{a1} + 1.09$	$C_{a1} = -1.67\ E_{a1} + 1.82$
Dimethylacetamide	$E_{a1} = -0.56\ C_{a1} + 1.0$	$C_{a1} = -1.8\ E_{a1} + 1.80$
Acetonitrile	$E_{a1} = -0.44\ C_{a1} + 0.30$	$C_{a1} = -2.3\ E_{a1} + 0.66$

bonding *via* orbital overlapping and charge transfer. These parameters are specific to each individual atom and are different from one another. Furthermore, if a molecule has many functional groups, these parameters are additive.

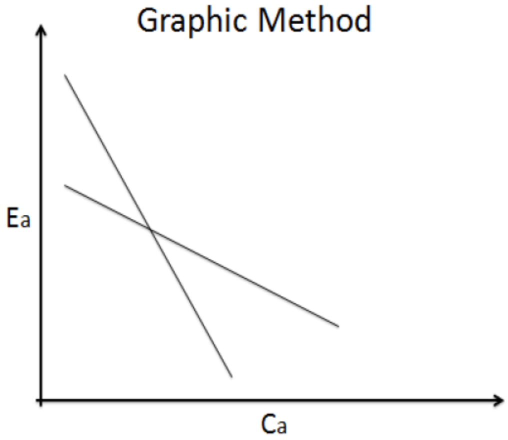


Figure 11: Graphical representation of two of the simultaneous equations listed in Table **5**.

Therefore, during the development of the new model, we treated the molecular and atomic properties separately.

As a result, the new model for the internal energy of mixing, $\Delta E_{mix2,1}$, differs from that based on conventional wisdom, because in the traditional models, these properties are not separated. The effect of this difference was clear when we compared the relative errors generated by the two models.

Indeed, after testing a given model by comparing selected calculated values with those determined experimentally, the differences observed can typically be attributed to two sources: an error in the design of the model and errors in the values of the parameters used in the model. Of these two types of errors, the error in the model structure is much more serious than the errors in the parameter values.

If an error exists in the structural model, it will probably be very large and systematic. Consequently, the differences will not be distributed around zero but will lie above or below zero in a systematic way. On the other hand, if the differences are due to incorrect parameter values, they will probably be smaller and will be distributed randomly around zero (sometimes positive and sometimes negative).

From the data in Table **7**, which shows the results obtained using the conventional model, it can be seen that the errors resulting from the use of this model were always positive, suggesting that the error lay on the left-hand side of the model structure, as it is the dominant one. Thus, the error was in the structure of the conventional model and not in the parameter values.

In contrast, a comparison of the results obtained using the new model (Table **8**) and those obtained using the conventional ones (Table **7**) revealed that the new model generally caused fewer errors. In addition, the errors resulting from the proposed model were distributed on both sides of zero. Therefore, we can conclude that there is no structural error in the new model and that the random errors must be due to inaccuracies in the parameter values used.

Table 6: Values [32] of Drago's parameters E_{b2} (kJ$^{1/2}$ mol$^{-1/2}$) and C_{b2} (kJ$^{1/2}$ mol$^{-1/2}$), obtained using the values of Drago's parameters E_{a1}(kJ$^{1/2}$ mol$^{-1/2}$)and C_{a1}(kJ$^{1/2}$ mol$^{-1/2}$); Values [44] of the volume, V(cm^3 mol^{-1}); Hansen's cohesion parameters [44], ∂_d (MPa$^{1/2}$), ∂_p (MPa$^{1/2}$), and ∂_h (MPa$^{1/2}$); using Eq. (27)

Solute	V/ cm^3 mol^{-1}	∂_d/ MPa$^{1/2}$	∂_p/ MPa$^{1/2}$	∂_h/ MPa$^{1/2}$	E_{a2}/ kJ$^{1/2}$ mol$^{-1/2}$	C_{a2}/ kJ$^{1/2}$ mol$^{-1/2}$	E_{b2}/ kJ$^{1/2}$ mol$^{-1/2}$	C_{b2}/ kJ$^{1/2}$ mol$^{-1/2}$
0	94.8	15.23	5.10	14.92	2.19	1.41	3.42	2.54
Solvent	**V**	∂_d	∂_p	∂_h	E_{a1}	C_{a1}	E_{b1}	C_{b1}
1	104.8	14.50	2.89	5.10	0.20	0.19	3.69	3.34
2	142.2	13.60	4.7	1.50	0.07	0,05	4.00	3.40
3	170.4	14.60	4.30	4.51	0.43	0.02	3.87	3.42
4	140.0	14.62	3.70	1.90	0.05	0.004	2.70	11.75
5	80.87	17.60	10.10	7.70	0.25	0.26	4.69	4.70
6	77.40	17.43	13.71	11.32	0.95	0.20	4.49	2.69
7	92.50	16.83	11.52	10.21	0.28	1.28	4.82	2.69
8	52.60	15.31	18.00	6.11	0.08	0.5	3.30	1.46

Table 7: Values of the measured interaction energy $A := -\Delta E_{mix\ (2,1)} + \Delta E_{vap2} + V_2(\partial^2_{d1} + \partial^2_{p1} + \partial^2_{h1})$ between the solute tertio-butanol and the different solvents compared to the values of the calculated interaction energy, obtained using the conventional approach, $B: = 2V_2\partial_{d2}\partial_{d1} + 2v_2\partial_{p2}\partial_{p1} + 2v_2\partial_{h2}\partial_{h1})$

Name of Solvent	A/kJ mol^{-1}	B/kJ mol^{-1}	Relative error % =(($A - B$)/A) × 100
Diethyl ether	71.11	65.75	7.5
i-Propyl ether	90.36	73.37	18.8
n-Butyl ether	116.40	107.23	7.9
Triethylamine	98.95	76.01	23.2
Pyridine	74.67	68.98	7.6
Dimethylformamide	81.66	78.77	3.5
Dimethylacetamide	90.53	87.98	2.8
Acetonitrile	47.09	44.37	5.8

Table 8: Values of the measured energy $A := -\Delta E_{mix\ (2,1)} + \Delta E_{vap2} + V_2\ (\partial^2_{d1} + \partial^2_{p1}/2) + V_1\partial^2_{h1}/n - \Delta V_2\ (\partial^2_{d1} + (3/2\ RT)/\ V_1))$ of interaction between the solute tertio-butanol and the different solvents compared to the calculated values of the energy, obtained using the new approach, $B := 2V_2\partial_{d2}\ \partial_{d1} + 2V_2\partial_{p2}\ \partial_{p1} + (E_{a1}\ E_{b2} + C_{a1}\ C_{b2}) + (E_{a2}\ E_{b1} + C_{a2}\ C_{b1}))$ of interaction between the solute tertio-butanol and the different solvents

Solvent	A/ kJ mol^{-1}	B/ kJ mol^{-1}	Relative error % = (($A - B$)/A) × 100
Diethyl ether	61.76	58.62	5
i-Propyl ether	56.46	57.73	−2
n-Butyl ether	58.72	61.09	−4
Triethylamine	65.96	68.46	−3
Pyridine	78.85	79.00	0
Dimethylformamide	83.96	80.95	3
Dimethylacetamide	80.61	78.08	1
Acetonitrile	73.52	72.44	1

Furthermore, in the proposed model, for any chemical molecule with a non-zero molar cohesive energy, $V\partial^2_h$, two sets of parameters, (E_a, C_a) and (E_b, C_b), must be known. This is unlike the case for older models, which considered only purely acidic or alkaline substances and used one of the two pairs: (E_b, C_b) or (E_a, C_a).

However, if the introduction of Drago's parameters, *E* and *C,* can resolve the chemical or hydrogen bonds, the values for these parameters must be determined. This is because, for a simple group of functions present in a molecule, two atoms are always involved in a chemical or hydrogen bridge. Thus, two parameters, namely, *E* and *C*, are required for each atom. All four parameters related to the donor-acceptor pairs are then used in one equation, with there being four unknowns for determining the cohesive energy of a chemical bond or a hydrogen bridge:

$$V\ \partial^2_h = n\ (E_a\ E_b + C_a\ C_b)$$

The problem with this model is that the values for Drago's parameters are still very rare. However, if only the energies of the chemical bonds are needed, then the new model can be used without knowing the values of E_a, E_b, C_a, and C_b for a substance during the mixing process.

However, with the data provided by Drago in his book [22] (pp 53-58) on acid and base parameters, it is possible to estimate the values of E_{b1} and C_{b1} as well as those of E_{a1} and C_{a1} using the following expression:

$$V\ \partial^2_h = n\ (E_a\ E_b + C_a\ C_b)$$

Therefore, a sufficient number of solvents should be available for determining the values of the four parameters for any substance using the new model.

7. CONCLUSIONS

The originality of this paper lies in fact that we separated the energies of cohesion into two different parts: those resulting from the interactions between the magnetic and electric fields and those resulting from charge transfer and orbital overlap.

The former are related to the molar volume, while the latter are independent of the molar volume and are related instead to molar interactions.

In addition, we have highlighted the irrelevancy of the parameter ∂_h. Its use creates structural errors in all models; we refer to this as the "chameleon phenomenon". However, many researchers in this field are not yet aware of this issue and continue to employ this parameter.

Finally, we have outlined the need of six parameters to describe globally the interactions in a chemical system. These parameters include two for the interactions between the magnetic and electric fields, namely, ∂_d and ∂_p, and four others, namely, E_a, E_b, C_a, and C_b, to determine the chemical bonding interactions.

Drago's parameters are atomic parameters and exhibit additive properties. For this reason, they can become molecular parameters for complex molecules. That should be used to determine the capacity interactions of complexe pharmaceutical molecules or pharmaceutical active ingredients.

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