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How to Resolve the Problem of Drago's Four Parameters in the Context of Molecular Interactions

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Abstract: This study aims to provide a new thermodynamic method for determining the value of Drago's four interaction parameters, namely E_a, E_b, C_a, and C_b (kcal$^{1/2}$ mol$^{-1/2}$). The method is based on the following fundamental novelties:

The values of the parameters E_a, E_b, C_a, and C_b are simultaneously determined for seven amphoteric substances. Thus, there are a total of 28 values to be determined, with each set consisting of seven substances. For the seven selected amphoteric substances, there are seven equations of the type:

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

Next, all possible 2-to-2 combinations of these seven substances are generated. For each 2-to-2 combination, one of the two is selected as a solute (2) and the other as a solvent (1), or vice versa. By measuring the mixing energy, $\Delta E_{mix\ (2.1)}$, of these combinations, the 21 measurements available to extract the energy, ΔE_{int}, of chemical bonds, according to the enclosed Buchmann paper:

$\Delta E_{mix\ (2.1)\ =} (E_{a1} E_{b2} + C_{a1} C_{b2}) + (E_{a2} E_{b1} + C_{a2} C_{b1})$

Next, the seven equalities of the type $V\partial^2_h / n_j = (E_{aj} E_{bj} + C_{aj} C_{bj})$ (kJ / mol) with j = 1,7 are put together with 21 equalities of the type $\Delta E_{int} = (E_{aj} E_{bj+1} + C_{aj} C_{bj+1}) + (E_{aj+1} E_{bj} + C_{aj+1} C_{bj})$. This will generate a system comprising 28 equations for 28 unknown parameters. The resolution of this system will afford the 28 sought values of Drago's four parameters E_a, E_b, C_a, C_b for the seven selected substances.

Keywords: Mixing energy, chemical interaction energy, Hansen's solubility parameters, Drago's interaction parameters, orthogonal matrix of experiments.

1. THEORETICAL BASIS

The interaction capacity of an active ingredient is quantified by 6 interaction parameters ∂_d, ∂_p, E_a, E_b, C_a, C_b, of which the first two ∂_d, ∂_p come from Hansen [1-2] and the last four E_a, E_b, C_a, C_b are from Drago [3-4].

It is a big mistake to want to characterize the interaction capacity by chemical bonds of an active principle or a chemical molecule by a single pair of parameters (E_a, C_a) or (E_b, C_b). On the other hand, these two couples are needed for a substance or an active ingredient. The reason is in the fact that, between a solute and a solvent, in the mixing frame, there is the breaking of a bond between a solvent molecule with its environment to form two new bonds between a solute molecule and two solvent molecules, for example for the case of mixing alcohol with water.

In the body of water, each molecule of water makes 3 chemical bonds with other molecules:

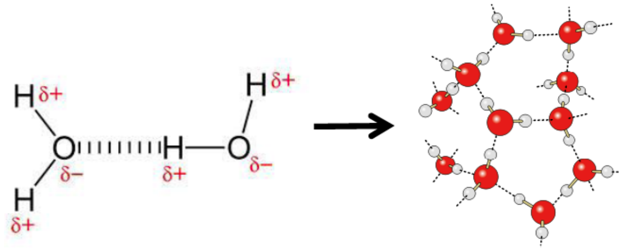
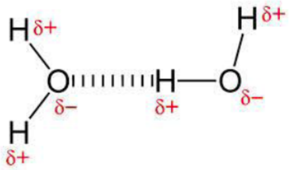


Figure 1:

For alcohol, wanting to come into contact with water, it is necessary that this bond between two molecules of water is broken down.



The energy of this chemical bond is written according to Drago and Hansen: In the mass of pure water, every molecule has three cohesive bonds with others. Therefore, the number 3 must be present in the following equation.

$$V\,\partial^2_h /3= E_aE_b + C_a\,C_b \tag{1}$$

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From the point of view of interaction parameters, in the case of the methyl alcohol and of tow molecules of water, we have:

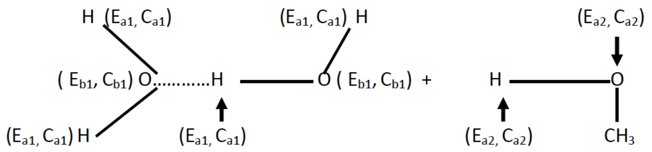

Figure 2:

For a mixture of methyl alcohol in water, we have:

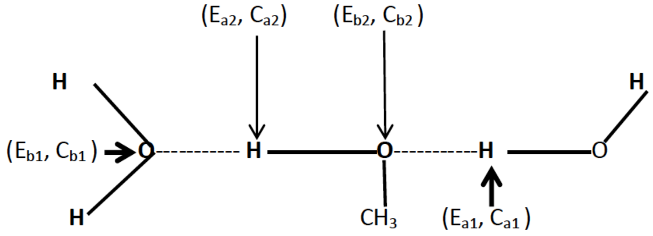

Figure 3:

Therefore, for one mole of methyl alcohol in water, the total energy ΔE_{int} of chemical bond is written as, group (E_{a1}, C_{a1}) combines with a group (E_{b2}, C_{b2}), and group (E_{a2}, C_{a2}) with (E_{b1}, C_{b1}) to form two bonds.

$$\Delta E_{int} = (E_{a2}E_{b1} + C_{a2}\, C_{b1}) + (E_{a1}E_{b2} + C_{a1}\, C_{b2}) \qquad (2)$$

This example demonstrates the need for 4 parameters: E_a, E_b, C_a, C_b for any molecule. For a mono-functional molecule, the parameters: E_a, E_b, C_a, C_b are atomic parameters. For a poly-functional molecule, the parameters: E_a, E_b, C_a, C_b are molecular parameters because they have additive properties.

Up to date, they are the best and unique description of the interactive capacity of active ingredients, whether liquid or solid. As a result, they have become very powerful tools for studying active principles and their interactions with receptor sites. However, to be able to determine the interaction parameters of the active ingredients, whether solid or liquid, one must have the following sine qua non-conditions:

A mathematical model, able to describe well the phenomenon of a mixture of the substances or adsorption of a gas on a solid built on the variables ∂_d, ∂_p, E_a, E_b, C_a, C_b.

It is necessary to have a sufficient number of solvents with the values of the 6 parameters available for probes. The multilinear regression permits finally to have access to the 6 values ∂_d, ∂_p, E_a, E_b, C_a, C_b.

2. CURRENT SITUATION

According to the work of Michel Buchmann [5] *et al.*, for the case, where the active ingredient is a liquid, and the calorimeter are used, the following equation must be exploited:

$-\Delta E_{mix\ (i,j)} + \Delta E_{vapi} + V_i\ (\ \partial^2_{dj} + (\ \partial^2_{pj}/2)) + n_i\ V_j\ \partial^2_{hj}/n_j - \Delta V_i(\partial^2_{dj} + 3/2\ RT\ /V_j) = 2\ Vi\ \partial_{dj}\ \partial_{di} + 2\ V_i\ \partial_{pj}\ \partial_{pi} + (E_{aj}\ E_{bi} + C_{aj}\ C_{bi}) + (E_{ai}\ E_{bj} + C_{ai}\ C_{bj}\ )$. For solute i and solvents j with j = 1, n,

Let's be:

$Y_{ij} = -\Delta E_{mix\ (i,j)} + \Delta E_{vapi} + V_i\ (\ \partial^2_{dj} + (\ \partial^2_{pj}/2) + n_i\ V_j\ \partial^2_{hj}/n_j - \Delta V_i(\partial^2_{dj} + 3/2\ RT\ /V_j)$.

In the form of a matrix, when j goes from 1 to n, we have the following matrix system:

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \\ Y_{i3} \\ . \\ . \\ Y_{in} \end{pmatrix} = \begin{pmatrix} 2\,V_i\,\partial_{d1} & 2\,V_i\,\partial_{p1} & E_{a1} & C_{a1} & E_{b1} & C_{b1} \\ 2\,V_i\,\partial_{d2} & 2\,V_i\,\partial_{p2} & E_{a2} & C_{a2} & E_{b2} & C_{b2} \\ 2\,V_i\,\partial_{d3} & 2\,V_i\,\partial_{p3} & E_{a3} & C_{a3} & E_{b3} & C_{b3} \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ 2\,V_i\,\partial_{dn} & 2\,V_i\,\partial_{pn} & E_{an} & C_{an} & E_{bn} & C_{bn} \end{pmatrix} \begin{pmatrix} \partial_{di} \\ \partial_{pi} \\ E_{bi} \\ C_{bi} \\ E_{ai} \\ C_{ai} \end{pmatrix} \qquad (3)$$

The following matrix:

$$\begin{pmatrix} 2\,V_i\,\partial_{d1} & 2\,V_i\,\partial_{p1} & E_{a1} & C_{a1} & E_{b1} & C_{b1} \\ 2\,V_i\,\partial_{d2} & 2\,V_i\,\partial_{p2} & E_{a2} & C_{a2} & E_{b2} & C_{b2} \\ 2\,V_i\,\partial_{d1} & 2\,V_i\,\partial_{p3} & E_{a3} & C_{a3} & E_{b3} & C_{b3} \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ 2\,V_i\,\partial_{dn} & 2\,V_i\,\partial_{pn} & E_{an} & C_{an} & E_{bn} & C_{bn} \end{pmatrix} \qquad (4)$$

Is the matrix of experiments? According to this same work, when the active ingredient i is a solid, equation (2) is modified as follows and GC (gas chromatography) must be used. Let's be:

$$\Delta E_{ads\ (i,j)} = V_i\partial_{dj}\partial_{di} + V_i\ \partial_{pj}\partial_{pi} + (E_{aj}\ E_{bi} + C_{a1}\ C_{b2}) + (E_{a2}\ E_{b1} + C_{a2}\, C_{b1}\ ) \qquad (5)$$

And in matrix form, when j goes from 1 to n, we have the three following matrices for solid i:

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \\ Y_{i3} \\ . \\ . \\ Y_{in} \end{pmatrix} = \begin{pmatrix} V_1\,\partial_{d1} & V_i\,\partial_{p1} & E_{a1} & C_{a1} & E_{b1} & C_{b1} \\ V_2\,\partial_{d2} & V_i\,\partial_{p2} & E_{a2} & C_{a2} & E_{b2} & C_{b2} \\ V_3\,\partial_{d3} & V_i\,\partial_{p3} & E_{a3} & C_{a3} & E_{b3} & C_{b3} \\ \cdots & & & & & \\ \cdots & & & & & \\ V_n\,\partial_{dn} & V_i\,\partial_{pn} & E_{an} & C_{an} & E_{bn} & C_{bn} \end{pmatrix} \times \begin{pmatrix} \partial_{di} \\ \partial_{pi} \\ E_{bi} \\ C_{bi} \\ E_{ai} \\ C_{ai} \end{pmatrix} \quad (6)$$

The values of ∂_{dj}, ∂_{pj} of Hansen where j = 1,n can be found in the literature [6]. However the Drago's value of E_{aj}, C_{aj}, E_{bj}, C_{bj} do not exist or there are only some and partial values. They will have to be determined.

3. NEW METHOD FOR DETERMINATIONS OF THE VALUE OF DRAGO'S PARAMETERS E_a, C_a, E_b, C_b FOR PURE AMPHOTERIC SOLVENTS

Take a number of amphoteric solvents, n, and form pairs of 2-to-2. Moreover, it is necessary, for each pair chosen, that one can be mixed with the other, or vice versa, to determine mixing energy.

The number of pairs 2-to-2 for n solvents will be:

$$N = n\,!/2!\,(n-2)! = (n-1)\,n/2 \quad (7)$$

If n= 7, then there are 21 pairs or 21 combinations 2-to-2. Hence, 21 values of mixing energy available: ΔE_{mix} (j, j + 1) with j = 1, 7. From mixing energy, we can extract chemical interaction energy, $\Delta E_{intj,j+1}$ energy, then we have 21 equations of type:

$$\Delta E_{intj,\,j+1} = (E_{aj}\,E_{bj+1} + C_{aj}\,C_{bj+1}) + (E_{aj+1}\,E_{bj} + C_{aj+1}\,C_{bj}) \quad (8)$$

At the same time, we have 7 equations of the type:

$$V_j\,\partial^2_{hj}/n_j = E_{aj}\,E_{bj} + C_{aj}\,C_{bj} \quad (8a)$$

In total, we have a system of 28 nonlinear equations.

As each substance have four chemical bonding interaction parameters to be determined. So seven substances present 28 unknown. For this case, the number of equations is equal to the number of unknowns.

Table 1: E_a, E_b, C_a, C_b ($kcal^{1/2}mol^{-1/2}$) of these Seven Substances to be Determined

Substance	E_{aj} j=1,8	E_{bj} j=1,8	C_{aj} j=1,8	C_{bj} j=1,8
1	E_{a1}	E_{b1}	C_{a1}	C_{b1}
2	E_{a2}	E_{b2}	C_{a2}	C_{b2}
3	E_{a3}	E_{b3}	C_{a3}	C_{b3}
4	E_{a4}	E_{b4}	C_{a4}	C_{b4}
5	E_{a5}	E_{b5}	C_{a5}	C_{b5}
6	E_{a6}	E_{b6}	C_{a6}	C_{b6}
7	E_{a7}	E_{b7}	C_{a7}	C_{b7}

Table 2: Seven Equations of Type $V\partial_{hj}^2/n_j = (E_{aj}\,E_{bj} + C_{aj}\,C_{bj})$ (kcal/mol)

No	$V\partial_{hj}^2/n_j$ j=1,8	$E_{aj}\,E_{bj} + C_{aj}\,C_{bj}$ j=1,8
1	Y_1	$E_{a1}\,E_{b1} + C_{a1}\,C_{b1}$
2	Y_2	$E_{a2}\,E_{b2} + C_{a2}\,C_{b2}$
3	Y_3	$E_{a3}\,E_{b3} + C_{a3}\,C_{b3}$
4	Y_4	$E_{a4}\,E_{b4} + C_{a4}\,C_{b4}$
5	Y_5	$E_{a5}\,E_{b5} + C_{a5}\,C_{b5}$
6	Y_6	$E_{a6}\,E_{b6} + C_{a6}\,C_{b6}$
7	Y_7	$E_{a7}\,E_{b7} + C_{a7}\,C_{b7}$

Table 3: 21 equations du type $\Delta E_{intj,\, j+1} = (E_{aj}\, E_{bj+1} + C_{aj}\, C_{bj+1}) + (E_{aj+1}\, E_{bj} + C_{aj+1}\, C_{bj})$ (kcal/mol)

No	$\Delta E_{int\ j,\ j+1}$ j= 1,8	$(E_{aj}\, E_{bj+1} + C_{aj}\, C_{bj+1}) + (E_{aj+1}\, E_{bj} + C_{aj+1}\, C_{bj})$ j= 1,8
8	$Y_{1,2}$	$(E_{a1}\, E_{b2} + C_{a1}\, C_{b2}) + (E_{a2}\, E_{b1} + C_{a2}\, C_{b1})$
9	$Y_{1,3}$	$(E_{a1}\, E_{b3} + C_{a1}\, C_{b3}) + (E_{a3}\, E_{b1} + C_{a3}\, C_{b1})$
10	$Y_{1,4}$	$(E_{a1}\, E_{b4} + C_{a1}\, C_{b4}) + (E_{a4}\, E_{b1} + C_{a4}\, C_{b1})$
11	$Y_{1,5}$	$(E_{a1}\, E_{b5} + C_{a1}\, C_{b5}) + (E_{a5}\, E_{b1} + C_{a5}\, C_{b1})$
12	$Y_{1,6}$	$(E_{a1}\, E_{b6} + C_{a1}\, C_{b6}) + (E_{a6}\, E_{b1} + C_{a6}\, C_{b1})$
13	$Y_{1,7}$	$(E_{a1}\, E_{b7} + C_{a1}\, C_{b7}) + (E_{a7}\, E_{b1} + C_{a7}\, C_{b1})$
14	$Y_{2,3}$	$(E_{a2}\, E_{b3} + C_{a2}\, C_{b3}) + (E_{a3}\, E_{b2} + C_{a3}\, C_{b2})$
15	$Y_{2,4}$	$(E_{a2}\, E_{b4} + C_{a2}\, C_{b4}) + (E_{a4}\, E_{b2} + C_{a4}\, C_{b2})$
16	$Y_{2,5}$	$(E_{a2}\, E_{b5} + C_{a2}\, C_{b5}) + (E_{a5}\, E_{b2} + C_{a5}\, C_{b2})$
17	$Y_{2,6}$	$(E_{a2}\, E_{b6} + C_{a2}\, C_{b6}) + (E_{a6}\, E_{b2} + C_{a6}\, C_{b2})$
18	$Y_{2,7}$	$(E_{a2}\, E_{b7} + C_{a2}\, C_{b7}) + (E_{a7}\, E_{b2} + C_{a7}\, C_{b2})$
19	$Y_{3,4}$	$(E_{a3}\, E_{b4} + C_{a3}\, C_{b4}) + (E_{a4}\, E_{b2} + C_{a4}\, C_{b3})$
20	$Y_{3,5}$	$(E_{a3}\, E_{b5} + C_{a3}\, C_{b5}) + (E_{a5}\, E_{b3} + C_{a5}\, C_{b3})$
21	$Y_{3,6}$	$(E_{a3}\, E_{b6} + C_{a3}\, C_{b6}) + (E_{a6}\, E_{b3} + C_{a6}\, C_{b3})$
22	$Y_{3,7}$	$(E_{a3}\, E_{b7} + C_{a3}\, C_{b7}) + (E_{a7}\, E_{b3} + C_{a7}\, C_{b3})$
23	$Y_{4,5}$	$(E_{a4}\, E_{b5} + C_{a4}\, C_{b5}) + (E_{a5}\, E_{b4} + C_{a5}\, C_{b4})$
24	$Y_{4,6}$	$(E_{a4}\, E_{b6} + C_{a4}\, C_{b6}) + (E_{a6}\, E_{b4} + C_{a6}\, C_{b4})$
25	$Y_{4,7}$	$(E_{a4}\, E_{b7} + C_{a4}\, C_{b7}) + (E_{a7}\, E_{b4} + C_{a7}\, C_{b4})$
26	$Y_{5,6}$	$(E_{a5}\, E_{b6} + C_{a5}\, C_{b6}) + (E_{a6}\, E_{b5} + C_{a6}\, C_{b5})$
27	$Y_{5,7}$	$(E_{a5}\, E_{b7} + C_{a5}\, C_{b7}) + (E_{a7}\, E_{b5} + C_{a7}\, C_{b5})$
28	$Y_{6,7}$	$(E_{a6}\, E_{b7} + C_{a6}\, C_{b7}) + (E_{a7}\, E_{b6} + C_{a7}\, C_{b6})$

As mixing energy $\Delta E_{mix\ j,j+1}$ with j = 1, 7 is an experimental value. It is not exact. So it is better to have an over-determined system of equations. It means that the number of equations must be greater than the number of unknowns. This is the case if we take eight substances

When n = 8, we will then have 28 pairs or 28 combinations 2-to-2, so 28 values of the mixing energy ΔE mix (j, j + 1) with j = 1, 8. Additionally, we have 8 more equations like equation (8). Now there are 36 equations for 32 unknowns

4. SOLVING A SYSTEM OF NONLINEAR EQUATIONS

In both cases, it is a system of nonlinear equations. In the case of seven substances, the number of equations is equal to the number of unknowns. In the case of eight substances, the number of equations is greater than the number of unknowns. This difference imposes two different resolution methods, with the constraint that all values must be positive.

In the case of seven substances, the system can be solved in a unique way. In the second case, we must solve it in the least squares sense and the 36 equations cannot be exactly satisfied.

From this point of view, the choice became clear: We must accept the experimental values mixing energy as accurate and without worrying about the problem of precision to solve it uniquely. That is to say, we must choose the case of seven amphoteric substances.

5. ILLUSTRATION PART

In the framework of an illustration of the capacity of hydrogen-bonding or chemical bonding in general (charge transfer and overlap orbital) of the substances of different classes: alkoxylates, alkoxy alcohols, ethers, alkyl acetates, Table **4** gives an overview of the magnitude of the expression $V\partial^2_h / n = (E_aE_b + C_aC_b)$, taken from chemical cohesion energy [6].

Indeed, the class of alcohols and alkoxy alcohols, amphoteric substances, shows a stable chemical

Table 4: V(cm^3 $mol^{-1)[}$, $V\partial^2_h$ ($kcal^{1/2}mol^{-1/2}$), ∂_h ($cal^{1/2}cm^{-3/2}$), E_a, E_b, C_a, C_b ($kcal^{1/2}mol^{-1/2}$)

Substance	V	$V\partial^2_h$	n	∂_h	E_a E_b + C_a C_b	Drago's average class value
Alcohols						
Methanol	40.7	4.84	2	10.93	2.42	
tert-butanol	94.8	5.02	2	7.28	2.51	
1- butanol	91.5	5.48	2	7.74	2.74	
Water	18	7.73	3	20.73	2.57	
cyclohexanol	106.0	4.63	2	6.61	2.31	
1-decanol	191.8	4.60	2	4.9	2.30	
						2.47
Alkoxyalcohol						
3-methoxybutanol	104.2	5.1	2	7.0	**2.55**	**2.55**
Ethers						
furan	72.5	0.49	2	2.59	0.25	**small**
diethylether	104.8	0.68	2	2.55	0.34	**small**
dibenzyl ether	192.7	2.63	2	3.7	2.63	**great**
Alkylacetats						
ethyl acetate	98.5	1.27	2	3.6	0.63	
butyl acetate	132.5	1.31	2	3.15	0.66	
isaobutyl acetate.	133.5	1.32	2	3.15	0.66	
						0.65

cohesive energy of about 2.45 kcal/mol. This means that the value of Drago's four chemical interaction parameter is great and of the same magnitude.

For the class of ethers, the value of the expression E_a E_b + C_a C_b depends on the nature of alkyl groups. This means that the value of E_a and C_a could be very small. Finally, for the class of alkyl acetates, the value of the expression E_a E_b + C_a C_b is very small. This comes from the very small value of E_a, C_a, without that the value of E_b and C_b being small. Their magnitude is very different.

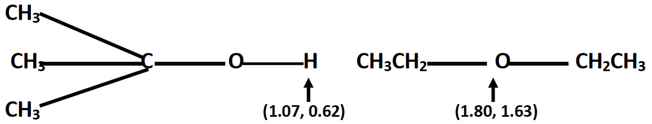

Figure 4:

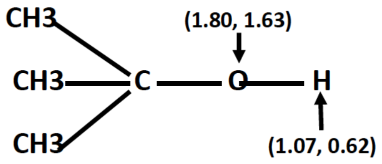

Figure 5:

Take the example of tert-butanol and diethyl ether. For tert-butanol, Drago gives:

E_a = 1.07, C_a = 0.63 (Figure **4**). For diethyl ether, Drago gives: E_b = 1.80, C_b = 1.63 (Figure **4**). Let us try to take the values E_b = 1.80, C_b = 1.63 for the oxygen of tert-butanol and calculate the value of the expression: E_a E_b + C_a C_b and compare with the magnitude of the expression: $V\partial^2_h$. According to Table **4**:

E_a E_b + C_a C_b = 1.07 x 1.80 + 062 x 1.63 = 2.90 ($kcal^{1/2}mol^{-1/2}$)

$V\partial^2_h$ / 2 = 2.51 ($kcal^{1/2}mol^{-1/2}$)

This means that the value of the parameters E_a, E_b, C_a, C_b given by Drago is a bit overestimated. It seems that these values are specific to the atoms of the functional groups of the molecule which carries them. Besides, the difference between 2.90 and 2.51 is not huge. The ratio between the values = 2.51 / 2.90 = 0.86. The factor of correction is 0.93.

6. DISCUSSION

Molecular interactions can be studied using several approaches depending on the final objective. Our interaction parameter approach required tools that were difficult to manufacture. However, once these tools were available, sequencing was conducted smoothly.

These tools consisted of a model of interaction energy (ΔE_{inter}) and probe molecules, six interaction parameters. The six interaction parameters included overlap orbital and charge transfer. The interaction parameters were grouped into the following two pairs: (E_a and C_a) and (E_b and C_b). Generally, these two pairs do not have the same importance from the point of view of ΔE_{inter} value.

For an acid, the pair, (E_a and C_a), is overwhelming compared to the pair, (E_b and C_b), and in the case of a base, it is the opposite.

1. The probes chosen must be amphoteric. In this case, the two pairs may be equivalent.
2. In the case of a mixture of body 1, in body 2, the values of the ΔE_{inter} in the pair (E_{a1}, E_{b2} + C_{a1}, C_{b2}) or the pair (E_{a2}, E_{b1} + C_{a2}, C_{b1}) do not fall into the domain of random errors of the other members of the mixture model.
3. To release the four values of the parameters, E_a, E_b, C_a, and C_b in solvents, the number of solvents makes it possible to have a system of nonlinear equations, of which the number of equations is equal to the number of unknowns. Consequently, we can solve the system uniquely.
4. When this difficult step is solved, the next step is to use these probe molecules to identify the six interaction parameters as well as the importance of the interaction components between the probe and a new substance or the nature of interaction sites.
5. Before experimenting, it is necessary to control the quality of the matrix of experiments so that the six parameters released by the regression are not biased, i.e., they are independent.

Starting from the mixing model, we arrived at the interaction model in the following manner:

$$-\Delta E_{mix\ (i,j)} + \Delta E_{vapi} + V_i\ (\ \partial^2_{dj} + (\ \partial^2_{pj}/2)) + n_i\ V_j\ \partial^2_{hj}/n_j - \Delta V_i(\partial^2_{dj} + 3/2\ RT\ /V_j) = 2\ Vi\ \partial_{dj}\ \partial_{di} + 2\ V_i\ \partial_{pj}\ \partial_{pi} + (E_{aj}\ E_{bi} + C_{aj}\ C_{bi}) + (E_{ai}\ E_{bj} + C_{ai}\ C_{bj}\ ).$$

For solute i and solvents j with j = 1, n,

Let's be:

$$Y_{ij} = -\Delta E_{mix\ (i,j)} + \Delta E_{vapi} + V_i\ (\ \partial^2_{dj} + (\ \partial^2_{pj}/2) + n_i\ V_j\ \partial^2_{hj}/n_j - \Delta V_i(\partial^2_{dj} + 3/2\ RT\ /V_j).$$

In the form of a matrix, when j goes from 1 to n, we have the following matrix system:

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \\ Y_{i3} \\ . \\ . \\ Y_{in} \end{pmatrix} = \begin{pmatrix} 2\ V_1\ \partial_{d1} & 2\ V_1\ \partial_{p1} & E_{a1} & C_{a1} & E_{b1} & C_{b1} \\ 2\ V_2\ \partial_{d2} & 2\ V_2\ \partial_{p2} & E_{a2} & C_{a2} & E_{b2} & C_{b2} \\ 2\ V_3\ \partial_{d3} & 2\ V_3\partial_{p3} & E_{a3} & C_{a3} & E_{b3} & C_{b3} \\ \dots & \dots & \dots & \dots & \dots & \dots \\ \dots & \dots & \dots & \dots & \dots & \dots \\ 2\ V_n\ \partial_{dn} & 2\ V_n\ \partial_{pn} & E_{an} & C_{an} & E_{bn} & C_{bn} \end{pmatrix} \times \begin{pmatrix} \partial_{di} \\ \partial_{pi} \\ E_{bi} \\ C_{bi} \\ E_{ai} \\ C_{ai} \end{pmatrix} \quad (14)$$

To simplify the presentation, we write the following form:

$$\begin{pmatrix} Y_{i1} \\ Y_{i2} \\ Y_{i3} \\ . \\ . \\ Y_{in} \end{pmatrix} = \begin{pmatrix} X_{11} & X_{12} & X_{13} & X_{14} & X_{15} & X_{16} \\ X_{21} & X_{22} & X_{23} & X_{24} & X_{25} & X_{26} \\ X_{31} & X_{32} & X_{33} & X_{34} & X_{35} & X_{36} \\ \dots & \dots & \dots & \dots & \dots & \dots \\ \dots & \dots & \dots & \dots & \dots & \dots \\ X_{n1} & X_{n2} & X_{n3} & X_{n4} & X_{n5} & X_{n6} \end{pmatrix} \times \begin{pmatrix} b_1 \\ b_2 \\ b_3 \\ b_4 \\ b_5 \\ b_6 \end{pmatrix}$$

$$(\ Y\ ) = (\ X\ ) \times (\ B\ )$$

X is an experiments matrix. Its orthogonality guarantees the exactness of the coefficients. The greater is the number of experiments, i.e., the number of lines; the better is the precision of the parameters: b_1, b_2, b_3, b_4, b_5, b_6.

However, it can be used if the inflation factors, F (b_i) [7-8], of each coefficient is between 1 and 10. Otherwise, the coefficients, b_i, are not independent of each other and are biased. In this case, the obtained values could not reflect reality.

$$F(\ b_i\ ) = C_{ii} \sum (\ x_{ji} - x_i)^2\ i=1,\ 6,\ j=1,n \quad (15)$$

$$1 \leq F(\ b_i\ ) \leq 10$$

$$C_{ii} = \text{diagonal terms of the matrix}\ (\ X^t\ X)^{-1} \quad (16)$$

7. USING INTERACTION SETTINGS

It is possible, through their interaction parameters, to classify [9] by calculation of the interaction energy concerning a substance taken for reference (enzyme or other) in ascending order, the activity of this family and to choose the most active.

The activity of any active ingredient molecule having a molecular structure with functional groups changes when one or more of these groups is modified without reaching its specificity. As a result, a family of this active ingredient is created following the mentioned changes and it is possible to choose the most active based on the interaction parameters.

In peptide studies, researchers measure the activity of a family of peptides after modifying substituent groups [10] in their structure. However, the use of interaction parameters to quantify their activity is more accurate.

For profit reasons, manufacturers have put on the market different drugs with the same specificity. But they do not have the same activity. So we can quantify their activity and compare them to know which of the families is the most active through interaction parameters.

The pharmaceutical industry, in the manufacture of drugs or in the form of micro-encapsulations, are concerned about the choice of solvent for the best performance. In particular, in the case of microencapsulation, there are always two successive reactions and for each reaction, there is a balance of the interaction energy, $\Delta E_{int,j}$ where j is the reaction number. In the case of microencapsulation j = 1,2.

Therefore, either by calorimetry or by calculation, we have to find the two values: $\Delta E_{int,1}$ and $\Delta E_{int,2}$ and establish the sum:

$$\Delta E_{int,1} + \Delta E_{int,2}$$

Since this sum comes from the interaction energy, it must be negative. The rule: The more the sum is negative, the more the return is bad. That is, the best solvent must give the greatest value. In absolute value it must be the smallest [11] for the best solvent:

$$\left| \Delta E_{int,1} + \Delta E_{int,2} \right| = \text{Minimum}$$

Any solid [12-16] or solid mixture, j, can be quantified by 6 interaction parameters or adsorption energy of gas i. We will choose the solid or solid mixture that gives the highest adsorption energy, $\Delta E_{ads(i,j)}$. The latter is related to the interaction capacity of the solid vis-à-vis the gas, so with 6 interaction parameters of the solid or the solid mixture.

The interactions, and therefore the interaction parameters, are the starting point for solving the problems of compatibility [17-18], adhesion, choice of surfactants, binders and lubricants.

In the field of biology, the choice of organic solvents for different biological systems is based on the affinity [19] of each concerning the others. But affinity is nothing more than the expression of the molecular interactions between the partners of a system. For this reason, we can always quantify them with the interaction parameters.

In biochemistry, the molecular interactions between DNA and enzymes [20-21] constitute a field of research in which researchers attempt to establish correlations between structure and thermodynamic properties. In the case of proteins, their associations and folded structure depends on intra- and intermolecular interactions. In particular, the thermodynamic studies of the interactions taking place in the systems: protein-inhibitor, protein-antibody, protein-enzyme, provide valuable information on the nature of the binding sites.

As for the antigen-antibody systems, the interaction studies allow having a look at the reaction mechanism.

All this work has the effect of highlighting the importance of molecular interactions whose interaction parameters are useful and practical tools.

8. CONCLUSION

This study aimed to provide a box of work tools related to the field of molecular interactions. Our objective was to propose a pathway using the parameters that characterize the interaction capacity of the substances to be studied.

This box has the following work tools:

8.1. To express the energy of the hydrogen bonding, Hansen uses, in the context of chemical cohesion, the only cohesive parameter $\boldsymbol{\partial_h}$.

To describe the interaction capacity of an acid or of a base, Drago attributes, as part of the quantitative **ECW model**, a pair of interaction parameters (E_a C_a) for acid and a pair (E_b, C_b) for a base. It should be noted that the pair (E, C)

Table 5: Magnetic or London interaction energy, $2V\partial_{d1}\partial_{dj}$ (kcal/ mol). Polar or Keesom interaction energy, $2V\partial_p\partial_p$ (kcal/ mol). V($cm^3\ mol^{-1}$). ∂_d, ∂_p , ∂_h ($cal^{1/2}cm^{-3/2}$)

Substance	V	∂_d	∂_p	$2V\partial_{d1}\partial_{dj}$	$2V\partial_{p1}\partial_{pj}$
t-butanol :=1	94.8	7.43	2.49	j= 2, 10	J =2.10
Diethyl ether :=2	104.89	7.03	1.41	10.95	0.74
i-Propyl ether :=3	142.2	6.69	1.02	14.13	0.72
n-Butyl ether : = 4	170.36	7.13	2.10	18..04	1.78
Triethylalamine :=5	140.00	7.13	1.80	14.83	1.25
Diethylamine : = 6	102.90	6.55	3.42	10.01	1.75
Pyridine = :7	80.87	9.28	4.30	11.15	1.73
Dimethylformamide :=8	77.40	8.50	6.69	9.77	2.57
Dimethylacetamide :=9	93.04	8.21	5.62	11.35	2.60
Acetonitril :=10	52.86	7.47	8.79	5.86	2.31

refers, respectively, to the electrostatic, the charge transfer and the orbital overlap, i.e., covalent contributions to the strength of the chemical bonds that the acid and base will form.

In the context of chemical bonds, of which the hydrogen bonding is one, this manuscript assigns to each of the two partners entering into reaction, and without exception, four interaction parameters: (E_a, C_a, E_b, C_b) as the pure covalent contribution. That's what **Pearson's HSAB theory**, **Hansen's cohesive parameter ∂_h, Drago's ECW** model doesn't know

8.2. A descriptive model of the ΔE_{inter}, of which the variables are interaction parameters of interacting partners.

8.3. A proposal to choose the molecule probes that are amphoteric and how to resolve the problem of Drago's four parameters.

8.4. A quality check of the experiment matrix before beginning the experiment.

8.5. A method to extract the six interaction parameters through multi-linear regression, after obtaining an experiment matrix of quality.

Determining the interaction parameters of the molecule probes is the most difficult step. These great efforts will be largely rewarded after by the very important information on the substances to be studied:

a. The energy of interaction between the probes and the substances to be studied.

b. The released parameters of the substances to be studied give information on the nature of ΔE_{inter}: magnetic, electrical, and chemical bond between substances 2 and 1.

According to Hansen's and Drago's School of Thought

$$\Delta E_{inter}:\ \underset{\substack{\Uparrow\\ \text{London}}}{\overset{\substack{\text{Dispersive}\\ \Downarrow}}{V_2\,\partial_{d1}\partial_{d2}}} + \underset{\substack{\Uparrow\\ \text{Keesom}}}{\overset{\substack{\text{Polar}\\ \Downarrow}}{V_2\,\partial_{p1}\partial_{p2}}} + \underset{\substack{\Uparrow\\ \text{Debye?}}}{\overset{\substack{\text{Chemical bonding}\\ \Downarrow}}{(E_{a1}E_{b2}+C_{a1}C_{b2}+E_{b1}E_{a2}+C_{b1}C_{a2})}} \quad (17)$$

According to the Van de Waals's School of Thought

According to our interaction model and Table VIII, the magnetic interaction energy (London energy) is overwhelming compared to the polar interaction energy (Keesom energy). This is very interesting information.

c. By combining the different parameters of two substances, it is possible to know the extent of their interaction.

d. For drug studies, initially, the solvent probes are used to release the interaction through the interaction parameters of the drugs. Following which the six interaction parameters of these drugs will be used to probe the interaction capacity of the sites to be studied.

e. There are other interesting applications of the proposed interaction model and the probes for which the interaction parameters are known.

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