Comparison of Theory and Practice in the Framework for Quantifying Interaction Capacity through Six Interaction Parameters Using tert-Butanol as a Target Molecule

Nam Tran Ho* and Michel Buchmann

ABSTRACT: Molecular interactions are important for various areas of research. Interactions between a target molecule and probe molecules having their own interaction capacity can be quantified via six interaction parameters. The theoretical interaction energy can be calculated from the interaction parameters, while that of experimental is measured using a calorimeter. These two methods are proposed in this work to calculate them. The first is based on an equation linking Hansen’s and Drago’s parameters. The second method is based on an experimental matrix formed by the interaction energies of tert-butanol with the probe molecules characterized by their six interaction parameters. Finally, the quality of the experiment matrix is checked for the effectiveness of the six experimental interaction parameters of the target molecule, which is tert-butanol. Then, these experimental values are compared with theoretical values from interaction parameters.

INTRODUCTION

Studying molecular interactions, which are also called non-covalent or intermolecular interactions, is essential for understanding biological structures and processes. They are important in various fields such as drug design, material science, sensors, anotechnology, separation, and origins of life. Furthermore, complex solid and liquid molecules have their own interaction capacities, which can be quantified using a set of six molecular interaction parameters $\partial_d$, $\partial_p$, $E_a$, $E_b$, $C_a$, and $C_b$.

Here, $\partial_d$ and $\partial_p$ (MPa$^{-1/2}$) are Hansen’s magnetic and electrical parameters,15,16 and $E_a$, $E_b$, $C_a$, and $C_b$ (kcal$^{-1/2}$ mol$^{-1/2}$) are Drago’s interaction parameters17 concerning chemical bonds having charge transfer and orbital overlap as processes. This indicates that there are three types of interactions, each of which has a well-determined origin.

The most important result of molecular interactions is the interaction energy of the interacting molecules. The latter can be determined experimentally via the mixing energy or via theoretical calculations based on interaction parameters. To experimentally determine interaction energy, the use of probe molecules in addition to their six interaction parameters is required.

### RESULTS

The two main results are presented in Tables 1 and 2. The demonstration has been done to know that it is possible to calculate the interaction energies between molecules based on the knowledge of the interaction capacity defined by the six interaction parameters $\partial_d$, $\partial_p$, $E_a$, $E_b$, $C_a$, and $C_b$. The relative errors between the calculated and experimental values are low and acceptable.

| solvents          | $Y_{exp}$ | $Y_{cal}$ | relative error (%) |
|-------------------|-----------|-----------|--------------------|
| diethyl ether     | 14.20     | 13.67     | 3.73               |
| i-propylether     | 13.48     | 12.86     | 4.59               |
| n-butylether      | 14.93     | 14.27     | 4.42               |
| triethylalmine    | 16.40     | 14.88     | 9.26               |
| diethyl amine     | 16.2     | 14.93     | 8.29               |
| pyridine          | 19.58     | 18.81     | 3.93               |
| dimethylformamide | 19.77     | 19.18     | 2.98               |
| dimethylacetamide | 19.08     | 18.42     | 3.45               |
| acetonitrile      | 17.09     | 17.10     | −0.05              |

Received: December 21, 2019
Accepted: February 28, 2020
Published: March 11, 2020
Finally, the capacity of the interaction of the target molecule tert-butanol has been defined by the same six parameters. It is possible to explain the important deviation on \( E_a \) that can be seen on the second table.

**DISCUSSION**

The objective of this work was to demonstrate that it is possible to define the interaction capacity of molecules using the mixing model proposed recently \(^1 \) by determining a group of six interaction parameters and then calculating the interaction energy of the same molecule in different solvents using these parameters. To this end, tert-butanol mixed with nine different solvents was used in this study.

The prediction of the solubility in different solvents was not considered in this work. In such a case, it would have been necessary to use an appropriate model taking into account of the enthalpic and entropic parts of the dissolution process.\(^{25} \)

In this research paper, each molecule is characterized by its six interaction parameters and its molar volume. So from the point of view of the interaction, our paper works with a space of six dimensions and these six independent parameters (\( \partial_{\nu}, \partial_{\rho}, E_\nu, E_\rho, C_\nu, C_\rho \)) characterizing different types of interactions.

The reason for the six-dimensional space in this work is as follows. The energy of the cohesion or interaction, obviously, comes from three types of interactions: magnetic dipole–dipole (mobile charges), electric dipole–dipole (localized charges), and transfer processes of charges and orbital recovering.

For the hydrogen bonding interaction, it is necessary to mobilize the four parameters \( E_\nu, C_\nu, E_\rho \) and \( C_\rho \). In the case of a solute, moreover, our proposed model still requires the use of its molar volume \( V \) giving the notion of the molecular size.

For many authors having worked with the three Hansen’s parameters (\( \partial_{\nu}, \partial_{\rho}, \) and \( \partial_{d} \)), their space is a three-dimensional space. However, these three parameters are not homogenous because the parameter \( \partial_{d} \) is a function of four interaction components according to the equation

\[
\partial_{d} = (n(E_\nu E_\rho + C_\nu C_\rho)/V)^{1/2}
\]

Therefore, different combinations of these four parameters \( E_\nu, C_\nu, E_\rho \), and \( C_\rho \) having different values can give the same value of \( \partial_{d} \).

Consequently, the Hansen’s sphere is an apparent interaction sphere. Considering the hydrogen bonds, it is necessary to introduce several kinds of corrections, including thermodynamic corrections to get closer to reality.\(^{26} \)

It is impossible to build any thermodynamic descriptive model with these three Hansen parameters, including the volume of the molecules as in our model. One of the important goals of scientific research is to be able to predict phenomena; we can only predict something on the basis of a descriptive model.

Experience shows that the nature of the solvents plays an important role in chemical reactions. Between our method of quantification of interaction energy and the QSAR method,\(^{27} \) the common point lies in obtaining an experiment matrix in which the parameters characterizing the solvents can be figured explicitly.

The cited work\(^{27} \) used a \( 412 \times 76 \) experiment matrix, while our work used a \( 9 \times 6 \) experiment matrix. The difference between the two methods is in the choice of parameters for solvents. Our work uses six interaction parameters—two from Hansen’s type and four from the Drago type. All of which are extracted from the cohesion energy and the quality of the experiment matrix tested; in contrast, the work with the QSAR method used 24 parameters or descriptors for the solvents; these did not necessary arise from the energy of cohesion and there was no test conducted to ascertain the quality of the \( 412 \times 76 \) experiment matrix used. This is a significant difference from the point of view of rigor. Ref \( 14 \) has been cited in our paper for comparison purposes.

The introduction of six interaction parameters and the construction of the interaction model were done gradually, and the first applications are in the choice of solvents to have the best performance for microencapsulation. The following Refs\(^3 \) and \( 28 \) have been cited in our paper for comparison purposes.

Although the nine solvents are not amphoteric,\(^{24} \) it is an important condition for obtaining suitable values for \( V \partial_{\nu}/n = E_\nu E_\rho + C_\nu C_\rho \). They have been chosen because of their interaction parameters, which are partially published (Table 3). In addition, their experimental mixing energies with tert-butanol have also been published,\(^{18} \) and these are indispensable for the subsequent comparison of the theoretical and experimental interaction energies (Table 11).

As can be seen from Table 3, it is impossible to directly determine the values of the six interaction parameters for tert-butanol and the nine solvents. Therefore, a method has been

---

**Table 2. Estimated and Calculated Values of the Six Interaction Parameters \( \partial_{\nu}, \partial_{\rho}, (\text{cal}^{1/2} \text{cm}^{-3/2}) \), \( E_\nu, C_\nu, E_\rho \), and \( C_\rho \) (kcal\(^{1/2} \text{mol}^{-1/2}) \) of the Target Molecule tert-Butanol**

| Interaction parameters of tert-butanol | \( \partial_{\nu} \) | \( \partial_{\rho} \) | \( E_\nu \) | \( C_\nu \) | \( E_\rho \) | \( C_\rho \) |
|----------------------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| estimated value (Table 7)              | 7.43                | 2.49                | 1.25                | 0.46                | 1.80                | 0.57                |
| experimental value                     | 6.72                | 2.41                | 2.58                | 0.20                | 1.74                | 0.80                |

**Table 3. Published Values of Molar Volumes \( V \) (cm\(^3\)/mol) of Hansen’s Cohesive Parameters \( \partial_{\nu}, \partial_{\rho}, \) and \( \partial_{d} \) (cal\(^{1/2} \text{cm}^{-3/2}) \) and Drago’s Chemical Interaction Parameters \( E_\nu, C_\nu, E_\rho \), and \( C_\rho \) (kcal\(^{1/2} \text{mol}^{-1/2}) \)**

| Solvent        | \( V \) | \( \partial_{\nu} \) | \( \partial_{\rho} \) | \( \partial_{d} \) | \( E_\nu \) | \( C_\nu \) | \( E_\rho \) | \( C_\rho \) |
|----------------|--------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| tert-butanol   | 94.80  | 7.43                | 2.49                | 7.28                | 1.36\(^{21} \) | 0.51\(^{21} \) | 1.80                | 1.63                |
| diethyl ether  | 104.89 | 7.03                | 1.41                | 2.49                | 1.95                | 1.66                | 1.89                | 1.67                |
| t-propyl ether | 142.20 | 6.69                | 1.02                | 1.19                | 1.22                | 5.38                | 1.32                | 5.73                |
| n-butyl ether  | 170.36 | 7.13                | 2.10                | 2.20                | 1.78                | 3.54                | 1.22                | 4.54                |
| triethylamine  | 140.00 | 7.13                | 1.80                | 0.92                | 2.19                | 3.11                | 2.35                | 1.31                |
| diethylamine   | 102.90 | 6.55                | 3.42                | 3.08                | 1.26                | 4.54                | 1.64                | 0.71                |
| pyridine       | 80.87  | 9.28                | 4.30                | 2.88                | 2.19                | 1.31                | 2.35                | 1.31                |
| dimethylformamide | 77.40   | 8.50                | 6.69                | 5.52                | 1.78                | 3.54                | 1.22                | 4.54                |
| dimethylacetamide | 93.04   | 8.21                | 5.62                | 4.98                | 2.19                | 3.11                | 2.35                | 1.31                |
| acetonitrile   | 52.86  | 7.47                | 8.79                | 2.98                | 1.64                | 0.71                | 2.19                | 3.11                |
proposed herein for approaching them using the equation $V\tilde{d}_i/n = E_iE_b + C_iC_b$. This equation has an infinite number of solutions even in a very limited range. However, there is only one solution that corresponds to the actual case. Various solutions were tested via an iterative method. The solution $X_{a1} = 9/10X_{imax}$ was retained as it was the most optimal. The complete list of the six parameters estimated for the ten molecules as a result of using the optimal solution is presented in Table 7.

Furthermore, multilinear regression was applied to an experimental matrix; this allowed us to determine the values of the tert-butanol interaction parameters. Considering the part of the work as a control of the quality of the proposed interaction model, the chosen experimental matrix presented a result that is similar to the estimated values presented in Table 7.

However, $E_s = 2.58$ (kcal/mol) was significantly higher. Using this value, the expression $V\tilde{d}_i/n = E_iE_b + C_iC_b$ gives $(2.58 \times 1.74 + 0.20 \times 0.80) = 4.65$ (kcal mol$^{-1}$) compared to a Hansen’s value of 2.51 (kcal mol$^{-1}$). This difference is due to the fact that the nine solvents are not amphoteric.24 This means that their $V\tilde{d}_i/n$ value is close to zero, which must have had repercussions on the multilinear regression results.

Using them to calculate the interaction energies between tert-butanol and the nine solvents, results (Table 8) that match well with the experimentally determined energies (Table 10) were obtained with the mean relative error for the nine solvents being 4.51%.

Finally, by observing the different values of the interaction parameters presented in Table 13, we can determine whether the target molecules are basic or acidic. In the case of tert-butanol, the charge transfer ($E_a, E_b$) is substantially more important than the overlap orbital ($C_a, C_b$) process.

### CONCLUSIONS

The comparison of theoretically and experimentally determined values in the context of the interactions of tert-butanol with nine solvent molecules shows that the ability of a molecule to interact can be quantified using its six interaction parameters $\partial_{\alpha}, \partial_{\beta}, E_a, C_a, E_b, C_b$.

The bridging equation $V\tilde{d}_i/n = E_iE_b + C_iC_b$ is essential for elucidating the nature of $\partial_{\alpha}$.

The experimental energy of the interaction with different molecules can be determined using the expression

$$\Delta E_{\text{inter}(s)} = -\Delta E_{\text{mix}(i,j)} + \Delta E_{\text{vap}} + \Delta E_{\text{cav},i}$$

The components of the energy of the theoretical interaction can be calculated according to the following equation (Figure 1).

$$\Delta E_{\text{inter}} = 2V_j\partial_{\alpha}\partial_{\beta} + 2V_j\partial_{\alpha}\partial_{\beta} + (E_aE_b + C_aC_b) + (E_aE_b + C_aC_b)$$

\[\text{According to Hansen's and Drago's School of Thought}\]

- Dispersive
- Polar
- Chemical bonding

\[\text{According to Van der Waals' School of Thought}\]

- London
- Keesom
- Debye

Calculation program used: Python program.

### THEORETICAL SECTION AND CALCULATION

To achieve the objectives of this work, it is necessary to have an innovative mixing model; this has been developed

$$-\Delta E_{\text{mix}(i,j)} + \Delta E_{\text{vap}} + V(\partial_{\alpha}^2 + (\partial_{\beta}^2/2)) + n_i\partial_{\alpha}^2/n_j$$

where $i$ is the solute, $j$ is the solvent, $-\Delta E_{\text{mix}(i,j)} + \Delta E_{\text{vap}} + V(\partial_{\alpha}^2 + (\partial_{\beta}^2/2)) + n_i\partial_{\alpha}^2/n_j$ is the interaction energy, $\Delta E_{\text{interexp}}$, $\Delta E_{\text{mix(i,j)}}$ is the mixing energy of solute $i$ into solvent $j$, $\Delta E_{\text{vap}}(i)$ is the vaporization energy of solute $i$, $V(\partial_{\alpha}^2 + (\partial_{\beta}^2/2)) + n_i\partial_{\alpha}^2/n_j$ is the experimental interaction energy, $\Delta E_{\text{interexp}}$, $\Delta E_{\text{mix(i,j)}}$ is the mixing energy of solute $i$ into solvent $j$, $\Delta E_{\text{vap}}(i)$ is the vaporization energy of solute $i$, $V(\partial_{\alpha}^2 + (\partial_{\beta}^2/2)) + n_i\partial_{\alpha}^2/n_j$ is the theoretical interaction energy, $\Delta E_{\text{intertheo}}$ between solute $i$ and solvent $j$, computable using the six interaction parameters.

With these definitions being recalled, eq 1 becomes

$$\Delta E_{\text{interexp}} = -\Delta E_{\text{mix}(i,j)} + \Delta E_{\text{vap}} + \Delta E_{\text{cav}}$$

$$\Delta E_{\text{intertheo}} = 2V_i\partial_{\alpha}\partial_{\beta} + 2V_i\partial_{\alpha}\partial_{\beta} + (E_aE_b + C_aC_b) + (E_aE_b + C_aC_b)$$

\[\text{ tert-Butanol was used as a solute, and the following nine solvents were used: diethylether, i-propylether, n-butylether, triethylamine, diethyamine, pyridine, dimethylformamide, dimethylacetamide, and acetonitrile.}\]

The bridge equation linking the Hansen’s parameter $\partial_{\alpha}$ to Drago’s four parameters $E_a, E_b, C_a, C_b$ was used

$$V\tilde{d}_i/n = (E_aE_b + C_aC_b)$$

From ref 18, the nine mixing energies of tert-butanol $-\Delta E_{\text{mix(i,j)}}$ in the nine-selected solvents were obtained. Hansen’s calculated vaporization energy of tert-butanol ($\Delta E_{\text{vap}}$), Hansen’s cohesion parameters $\partial_{\alpha}, \partial_{\beta}$, and $\partial_{\alpha}$ (ref 19), and Drago’s chemical interaction parameters17 for the nine-selected solvents were used.

### ISSUE REGARDING DRAGO’S CHEMICAL INTERACTION PARAMETERS

For the ten substances used in this study, the values of Drago’s parameters, $E_a, C_a, E_b$, and $C_b$, are incomplete.17,20 A method for determining the missing values needs to be proposed.

### DETERMINATION OF THE MISSING VALUES OF DRAGO’S PARAMETERS

First, it needs to be highlighted that the experimental method proposed by Drago is not efficient enough to eliminate the polar contribution of the chemical interaction energy. According to Drago’s ECW model17

$$\Delta H = E_aE_b + C_aC_b$$

However, according to our model,14 $\Delta H$ in fact must be...
Table 4. Published Molar Volumes \( V \) (cm\(^3\)/mol), Hansen’s Cohesive Parameters \( \partial_h \) (cal\(^{1/2}\) cm\(^{-3/2}\)) and Drago’s Chemical Interaction Parameters \( E_a, C_a, E_b, C_b \) (kcal mol\(^{-1/2}\)) for Methanol and Ethanol

| solvent     | \( V \) | \( \partial_h \) | \( V\partial_h^2/2 \) (Hansen) | \( E_a \) | \( C_a \) | \( E_b \) | \( C_b \) | \( E_b + C_b \) (Drago) |
|-------------|--------|-----------------|-------------------------------|--------|--------|--------|--------|---------------------|
| methanol    | 40.7   | 10.93           | 2.43                          | 1.25   | 0.75   | 1.80   | 0.70   | 2.78                |
| ethanol     | 58.5   | 9.51            | 2.65                          | 1.34   | 0.69   | 1.85   | 1.10   | 3.24                |

Table 5. Molar Volumes \( V \) (cm\(^3\)/mol), Hansen’s Cohesive Parameters \( \partial_h, \partial_p, \) and Drago’s Corrected Chemical Interaction Parameters \( E_a, C_a, E_b, \) and \( C_b \) (kcal mol\(^{-1/2}\))

| solvent       | \( V \) | \( \partial_h \) | \( \partial_p \) | \( \partial_b \) | \( E_a \) | \( C_a \) | \( E_b \) | \( C_b \) |
|---------------|--------|-----------------|-----------------|-----------------|--------|--------|--------|--------|
| tert-butanol  | 94.80  | 7.43            | 2.49            | 7.28            | 1.25   | 0.46   |        |        |
| diethyl ether | 104.89 | 7.03            | 1.41            | 2.49            |        |        | 1.66   | 1.50   |
| i-propyl ether| 142.20 | 6.69            | 1.02            | 1.19            |        |        | 1.80   | 1.53   |
| n-butyl ether | 170.36 | 7.13            | 2.10            | 2.20            |        |        | 1.74   | 1.54   |
| triethylamine | 140.00 | 7.13            | 1.80            | 0.92            |        |        | 1.21   | 1.27   |
| diethylamine  | 102.90 | 6.55            | 3.42            | 3.08            |        |        | 1.12   | 4.18   |
| pyridine      | 80.87  | 9.28            | 4.30            | 2.88            |        |        | 1.64   | 3.26   |
| dimethylformamide | 77.40 | 8.50            | 6.69            | 5.52            |        |        | 2.01   | 1.21   |
| dimethylecetamide | 93.04 | 8.21            | 5.62            | 4.98            |        |        | 2.16   | 1.21   |
| acetonitrile  | 52.86  | 7.47            | 8.79            | 2.98            |        |        | 1.51   | 0.65   |

Table 6. Molar Volumes \( V \) (cm\(^3\)/mol), Hansen’s Cohesive Parameters \( \partial_h \) (cal\(^{1/2}\) cm\(^{-3/2}\)), \( V\partial_h^2/n \) (kcal mol\(^{-1}\)), and the Ten Equations of the Formed \( V\partial_h^2/n = E_aE_b + C_aC_b \) (kcal mol\(^{-1}\)) Corresponding to the Solute tert-Butanol and the Nine Solvents

| solvent       | \( V \) | \( \partial_h \) | \( n \) | \( V\partial_h^2/n \) | \( V\partial_h^2/n = E_aE_b + C_aC_b \) |
|---------------|--------|-----------------|------|----------------------|----------------------------------------|
| tert-butanol  | 94.80  | 7.28            | 2    | 2.51                 | 2.51 = 1.25E_b + 0.46C_b                |
| diethyl ether | 104.89 | 2.49            | 2    | 0.33                 | 0.33 = 1.66E_b + 1.50C_b               |
| i-propyl ether| 142.20 | 1.19            | 2    | 0.10                 | 0.10 = 1.80E_b + 1.53C_b              |
| n-butyl ether | 170.36 | 2.20            | 2    | 0.41                 | 0.41 = 1.74E_b + 1.54C_b              |
| triethylamine | 140.00 | 0.92            | 2    | 0.05                 | 0.05 = 1.21E_b + 5.27C_b              |
| diethylamine  | 102.90 | 3.08            | 2    | 0.50                 | 0.50 = 1.12E_b + 4.18C_b              |
| pyridine      | 80.87  | 2.88            | 2    | 0.21                 | 0.21 = 1.64E_b + 3.26C_b              |
| dimethylformamide | 77.40 | 5.52            | 2    | 1.18                 | 1.18 = 2.01E_b + 1.21C_b               |
| dimethylecetamide | 93.04 | 4.98            | 2    | 1.15                 | 1.15 = 2.16E_b + 1.21C_b               |
| acetonitrile  | 52.86  | 2.98            | 2    | 0.23                 | 0.23 = 1.51E_b + 0.65C_b              |

\[ \Delta H = 2V\partial_p\partial_b + (E_aE_b + C_aC_b) + (E_aE_b + C_aC_b) \]

This is because the apolar solvent used in the mixing process cannot eliminate the polar contribution \( 2V\partial_p\partial_b \) from \( \Delta H \).

However, Drago gave the following expression for \( \Delta H \)

\[ \Delta H = E_bC_b \]

\[ = 2V\partial_p\partial_b + (E_aE_b + C_aC_b) + (E_aE_b + C_aC_b) \]

Then,

\[ \Delta H = E_bC_b \]

where \( W \) must be\n
\[ W = 2V\partial_p\partial_b + (E_aE_b + C_aC_b) \]

In this study, the following equation will be considered

\[ E_bC_b = E_aE_b + C_aC_b \]

Therefore, the values of Drago’s parameters \( E_a, E_b, C_a, \) and \( C_b \) are over-estimated, and they need to be corrected so that they can be reverted to the Hansen’s scale.

The proposed correction method is the following. From the Drago-Wayland parameters, methanol and ethanol were chosen because the values of their four parameters are exceptionally published (Table 4).

\[ V\partial_h^2/n = E_bC_b \] (kcal mol\(^{-1}\))

For methanol, \( (Hansen)/(Drago) = 2.43/2.78 = 0.87 \), the over estimation is approximately 14%. For ethanol, \( (Hansen)/(Drago) = 2.65/3.24 = 0.82 \), the over estimation is approximately 22%.

Given that the errors for methanol and ethanol are 0.87 and 0.82, respectively, the value of the correction factor will be the mean value, 0.85.

Finally, we obtained

\[ V\partial_h^2/2 = 0.85(E_bC_b) \]

\[ = (0.92E_b, 0.92C_b, 0.92C_b) \]

Thus, using 0.92 as a correction factor, it is possible to obtain the values of Drago’s parameters adapted to the Hansen’s scale (Table 5).

Now, the equation \( V\partial_h^2/n = (E_bC_b) \) (kcal mol\(^{-1}\)), with the values given in Table 5, is used to construct ten equations, which are presented in Table 6.

Each of these equations has two unknowns, and they are \( E_b \) and \( C_b \) for tert-butanol and \( E_a \) and \( C_a \) for the nine solvents.

Substitute \( X_{1s} = E_a \) for each of the nine chosen solvents and \( X_{1i} = E_b \) for tert-butanol. In addition, substitute \( X_{2s} = C_a \) for each of the nine chosen solvents and \( X_{2i} = C_b \) for tert-butanol in the ten equations.
Then, all of the ten equations shown in Table 6 having the two unknowns $X_i$ and $X_{j2}$ can be represented in the following form:

\[ Y_i = aX_i + bX_{j2} \]

with $i = 1.9$ (4)

\[ X_{i2} = -(b/a)X_i + Y_i/a \] (5)

A graph of $X_{i2}$ as a function of $X_{i1}$ is given in Figure 2.

Figure 2. Graph of $X_{i2}$ as a function of $X_{i1}$.

Any point on the straight line plotted in the above figure is a solution of the equation

\[ X_{i1} = -(b/a)X_{i2} + Y_i/a \]

$X_{i1} = X_{i1\text{max}}$ when $X_{i2} = 0$, and $X_{i2} = X_{i2\text{max}}$ when $X_{i1} = 0$.

For tert-butanol, which is our target molecule, the values of $E_b$ and $C_b$ must be in the following limits according to the equation 2.51 = 1.25$E_b$ + 0.45$C_b$

\[ 0 < E_b < 2.00 \]

\[ 0 < C_b < 5.58 \] (6)

The most optimal case $X_{i1} = (9/10)X_{i1\text{max}}$ has been chosen after having tested many options to obtain solutions that respect these limits. Using $X_{i1} = (9/10)X_{i1\text{max}}$, it is possible to calculate all values of the variable $X_{i2}$ (Table 7).

The expression of the theoretical interaction energy between tert-butanol and the nine solvents has the following form:

\[ \Delta E_{\text{intertheo}} = 2V_d d_1 d_2 + 2V_d p_1 p_2 + (E_{1a} E_{2b} + C_{1a} C_{2b}) \]

\[ + (E_{1a} E_{2b} + C_{1a} C_{2b}) \text{ solute} = 2, \text{ solvent} = 1. \] (7)

The chemical bonding interaction has two parts:

\[ \Delta E_{\text{chem}} = (E_{1a} E_{2b} + C_{1a} C_{2b}) + (E_{1a} E_{2b} + C_{1a} C_{2b}) \]

chemical bond 1 \[ = (E_{1a} E_{2b} + C_{1a} C_{2b}) \]

chemical bond 2 \[ = (E_{1a} E_{2b} + C_{1a} C_{2b}) \] (9)

\[ \Delta E_{\text{inter}} = -\Delta E_{\text{max}} + \Delta E_{\text{vap}} + V(\frac{\partial^2 p_j}{\partial T^2}) + n_j \frac{\partial^2 V}{\partial p_j^2} - n_j \Delta V(\frac{\partial^2 V}{\partial T^2} + 3/2RT/Y) \] (11)

in a simpler form:

\[ \Delta E_{\text{inter}} = -\Delta E_{\text{max}} + \Delta E_{\text{vap}} + \Delta E_{\text{capit}} \] (12)

Table 9 gives an overview of different contributions to cavity formation energy.

The addition of the published mixing energies and the vaporization energy of the solute with the cavity formation energies allows us to obtain the nine experimental energies of interaction between tert-butanol and the solvents (Table 10).

### DETERMINATION OF THE EXPERIMENTAL INTERACTION ENERGY

The expression for the experimental interaction energy is

\[ \Delta E_{\text{interexp}}(i) = -\Delta E_{\text{max}} + \Delta E_{\text{vap}} + \Delta E_{\text{capit}} \] (11)

in a simpler form:

\[ \Delta E_{\text{inter}} = -\Delta E_{\text{max}} + \Delta E_{\text{vap}} + \Delta E_{\text{capit}} \] (12)

Table 9 gives an overview of different contributions to cavity formation energy.

The addition of the published mixing energies and the vaporization energy of the solute with the cavity formation energies allows us to obtain the nine experimental energies of interaction between tert-butanol and the solvents (Table 10).

### OVERVIEW OF THE EXPERIMENT MATRIX TO BE USED FOR CALCULATING THE INTERACTION PARAMETERS OF TERT-BUTANOL

From Tables 7 and 10, the experiment matrix can be written as follows:

\[
\begin{array}{cccccccccccc}
14.20 & 1.33 & 0.26 & 0.18 & 0.02 & 1.66 & 1.50 & \times b_1 \\
13.48 & 1.26 & 0.19 & 0.05 & 0.007 & 1.80 & 1.53 & \times b_2 \\
14.93 & 1.35 & 0.39 & 0.21 & 0.03 & 1.74 & 1.54 & \times b_3 \\
16.40 & 1.35 & 0.34 & 0.04 & 0.0003 & 1.21 & 5.27 & \times b_4 \\
16.28 & 1.24 & 0.65 & 0.40 & 0.11 & 1.12 & 4.18 & \times b_5 \\
19.58 & 1.75 & 0.82 & 0.12 & 0.004 & 1.64 & 3.26 & \times b_6 \\
19.77 & 1.61 & 1.27 & 0.53 & 0.094 & 2.01 & 1.21 & \times b_7 \\
19.08 & 1.56 & 1.06 & 0.48 & 0.093 & 2.16 & 1.21 & \times b_8 \\
17.09 & 1.41 & 1.67 & 0.14 & 0.03 & 1.51 & 0.65 & \times b_9 \\
\end{array}
\]

\[ (Y_{\text{exp}}) = (2V_1 d_1/1000)(2V_1 d_1)/(1000) + E_{1a} E_{2b} C_{1a} C_{2b} \times (h_i) \]

### Table 7. Molar Volume $V$ (cm$^3$/mol) of Hansen’s Cohesive Parameters $d_1$, $d_2$, and $d_3$ (cal$^{1/2}$/cm$^{3/2}$), Drago’s Corrected Chemical Interaction Parameters $E_{1a}$, $C_{1a}$, $E_{2b}$, and $C_{2b}$ (kcal/mol$^{1/2}$), and $Vd_1 p_j$ (kcal/mol$^{1/2}$) for the Case Where $X_{i1} = 9/10X_{i1\text{max}}$

| solvent     | $V$   | $d_1$ | $d_2$ | $d_3$ | $Vd_1 p_j/2$ | $E_{1a}$ | $C_{1a}$ | $E_{2b}$ | $C_{2b}$ |
|-------------|-------|-------|-------|-------|-------------|---------|---------|---------|---------|
| tert-butanol| 94.80 | 7.43  | 2.49  | 7.28  | 2.51        | 1.25    | 0.46    | 1.80    | 0.57    |
| diethyl ether| 104.89 | 7.03  | 1.41  | 2.49  | 0.33        | 0.18    | 0.02    | 1.66    | 1.50    |
| i-propyl ether| 142.20 | 6.69  | 1.02  | 1.19  | 0.10        | 0.05    | 0.007   | 1.80    | 1.53    |
| n-butyl ether| 170.36 | 7.13  | 2.10  | 2.20  | 0.41        | 0.21    | 0.03    | 1.74    | 1.54    |
| triethylamine| 140.00 | 7.13  | 1.80  | 0.92  | 0.05        | 0.04    | 0.0003  | 1.21    | 5.27    |
| diethylamine| 102.90 | 6.55  | 3.42  | 3.08  | 0.50        | 0.40    | 0.11    | 1.12    | 4.18    |
| pyridine     | 80.87 | 9.28  | 4.30  | 2.28  | 0.21        | 0.12    | 0.004   | 1.64    | 3.26    |
| dimethylformamide| 77.40 | 8.50  | 6.69  | 5.52  | 1.18        | 0.53    | 0.094   | 2.01    | 1.21    |
| dimethyacetamide| 93.04 | 8.21  | 5.62  | 4.98  | 1.15        | 0.48    | 0.093   | 2.16    | 1.21    |
| acetonitrile | 52.86 | 7.47  | 8.79  | 2.98  | 0.23        | 0.14    | 0.03    | 1.51    | 0.65    |
Table 8. Various Contributions Made to the Theoretical Interaction Energy (kcal/mol) by tert-Butanol and the Nine-Selected Solvents

| solvent         | \(2V_d_\delta d_\delta\) dispersive interaction | \(2V_d_\delta d_\delta\) polar interaction | \(E_a_\delta E_b_\delta + C_{a_\delta} C_{b_\delta}\) chemical bond 1 | theoretical interaction energy |
|-----------------|-----------------------------------------------|---------------------------------------------|----------------------------------------------------------------|-------------------------------|
| diethyl ether   | 9.88                                         | 0.65                                        | 0.34                                                             | 13.67                         |
| i-proplylether  | 9.36                                         | 0.47                                        | 0.09                                                             | 12.86                         |
| n-butyl ether   | 10.03                                        | 0.96                                        | 0.40                                                             | 14.27                         |
| triethylalamine | 10.03                                        | 0.85                                        | 0.07                                                             | 14.88                         |
| diethyl amine   | 9.21                                         | 1.62                                        | 0.78                                                             | 14.93                         |
| pyridine        | 13.00                                        | 2.04                                        | 0.22                                                             | 18.81                         |
| dimethylformamide | 11.95                                       | 3.16                                        | 1.00                                                             | 19.18                         |
| dimethycetamide | 11.60                                        | 2.64                                        | 0.92                                                             | 18.42                         |
| acetonitrile    | 10.48                                        | 4.16                                        | 0.27                                                             | 17.10                         |

Table 9. Dispersive Contribution \(V_d^2 d_\delta\), Polar Contribution \(V_d^2 p_\delta/2\), Chemical Contribution \(V_d^2 b_\delta/2\), and Mechanical Contribution \(\Delta V_f(\partial^2 a_\delta + 3/2RT/V_f)\) (Ref 18) to the Cavity Formation Energy \(\Delta E_{cav(i,j)}\)

| solvent         | \(V_d^2 d_\delta\) (kcal/mol) | \(V_d^2 p_\delta/2\) (kcal/mol) | \(V_d^2 b_\delta/2\) (kcal/mol) | \(\Delta V_f(\partial^2 a_\delta + 3/2RT/V_f)\) | \(\Delta E_{cav(i,j)}\) (kcal/mol) |
|-----------------|-------------------------------|---------------------------------|-------------------------------|----------------------------------|----------------------------------|
| diethyl ether   | 4.69                          | 0.09                            | 0.33                          | 0.04                             | 5.15                             |
| i-proplylether  | 4.24                          | 0.09                            | 0.10                          | 0.02                             | 4.45                             |
| n-butyl ether   | 4.82                          | 0.20                            | 0.41                          | -0.03                            | 5.40                             |
| triethylalamine | 4.82                          | 0.15                            | 0.05                          | 0.24                             | 5.26                             |
| diethyl amine   | 4.07                          | 0.55                            | 0.50                          | 0.25                             | 5.37                             |
| pyridine        | 8.16                          | 0.87                            | 0.21                          | -0.03                            | 9.21                             |
| dimethylformamide | 6.84                        | 2.12                            | 1.18                          | -0.01                            | 10.13                            |
| dimethycetamide | 6.38                          | 1.50                            | 1.15                          | 0.06                             | 9.09                             |
| acetonitrile    | 5.29                          | 3.66                            | 0.23                          | -0.18                            | 9.00                             |

**Note:** \(V_f = 94.8 \text{ cm}^3 \text{ mol}^{-1}\).

Table 10. Mixing Contributions \(\Delta E_{mix}\) (kcal/mol) (Ref 18), Cavity Contributions \(\Delta E_{cavity(i,j)}\) (kcal/mol), and Vaporization Contributions \(\Delta E_{vap}\) (kcal/mol) of tert-Butanol to the Experimental Interaction Energy \(\Delta E_{interexp(i,j)}\) (kcal/mol) between tert-Butanol and the Nine Solvents Obtained from Colorimetric Measurements

| solvent         | \(\Delta E_{mix}\) | \(\Delta E_{cavity(i,j)}\) | \(\Delta E_{vap}\) | \(\Delta E_{interexp(i,j)}\) |
|-----------------|-------------------|-----------------------------|-------------------|-----------------------------|
| tert-butanol    |                   |                             |                   |                             |
| diethyl ether   | -1.67             | 5.15                        | 10.72             | 14.2                        |
| i-proplylether  | -1.69             | 4.45                        | 10.72             | 13.48                       |
| n-butyl ether   | -1.19             | 5.40                        | 10.72             | 14.93                       |
| triethylalamine | 0.42              | 5.26                        | 10.72             | 16.40                       |
| diethyl amine   | -0.35             | 9.21                        | 10.72             | 19.58                       |
| pyridine        | -1.08             | 10.13                       | 10.72             | 19.77                       |
| dimethylformamide | -0.73         | 9.09                        | 10.72             | 19.08                       |
| dimethycetamide | -2.63             | 9.00                        | 10.72             | 17.09                       |

(13)

where \((Y)\) represents the matrix column of experimental interaction energies, \((X)\) represents the experiment matrix, and \((b)\) is the column matrix of coefficients to be calculated.

Ideally, the experiment matrix \((X)\) must be orthogonal so that the coefficients \((b)\) are independent.

However, in the case where the inflation factor (Table 12), \(F(b_i)\), of each coefficient, \(b_i\) is in the range of \(1 \rightarrow 10\), \((X)\) can be used. Outside of this range, the coefficients \((b)\) are biased.22,23

The inflation factor, \(F(b_i)\), of each coefficient, \(b_i\) can be calculated according the following equations

\[ F(b_i) = a_\parallel \sum_{j=1}^{9} (X_{ji} - \bar{X}_i)^2 \]  

(14)

where

\[ \bar{X}_i = \sum_{j=1}^{9} (X_{ji})/9 \]  

(15)

and

\(a_\parallel = \) diagonal term of the matrix \((X^T X)^{-1}\)
0 < F(b_i) < 10

**CALCULATION OF THE SIX INTERACTION PARAMETERS OF THE TARGET TERT-BUTANOL**

The multilinear regression when applied to the proposed experiment matrix gives the estimated values for the six interaction parameters. We can now compare these experimental values (Table 13) with the estimated values presented in Table 7.

**Table 13. Estimated Values (from Table 7) and Calculated Values of the Six Interaction Parameters, \( \partial_d, \partial_b \) (cal \( \text{cm}^{-3/2} \)), \( E_b, E_a, E, \) and \( C_b \) (kcal \( \text{mol}^{-1/2} \)) of tert-Butanol for the Chosen Case where \( X_{11} = 9/10X_{\text{max}} \)**

| interaction parameters of tert-butanol | \( \partial_d \) | \( \partial_b \) | \( E_b \) | \( E_a \) | \( C_b \) |
|----------------------------------------|---------|---------|--------|--------|--------|
| estimated value (Table 7)             | 7.43    | 2.49    | 1.25   | 0.46   | 1.80   |
| experimental value                     | 6.72    | 2.45    | 2.58   | 0.20   | 1.74   | 0.80   |

**AUTHOR INFORMATION**

**Corresponding Author**
Nam Tran Ho — *Institute d’Analyse Pharmaceutique, Ancienne École de Pharmacie, Université de Lausanne, B.E.P., Lausanne CH-1015, Switzerland.* [orcid.org/0000-0002-3495-1272; Phone: 0041216918502; Email: honamtran55@gmail.com]

**Author**
Michel Buchmann — *Institute d’Analyse Pharmaceutique, Ancienne École de Pharmacie, Université de Lausanne, B.E.P., Lausanne CH-1015, Switzerland*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.9b04399

**Notes**
The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

N.B. This document is dedicated to the memory of our beloved and respected guy Professor Russel S. Drago. It is at the same time a “thank you” to the eminent scientist Charles M. Hansen, father’s cohesive or solubility parameters.

**REFERENCES**

(1) Afzelius, L.; Zamora, I.; Ridderström, M.; Andersson, T. B.; Karlén, Å.; et al. Competitive CYP2C9 Inhibitors: Enzyme Inhibition Studies, Protein Homology Modeling, and Three-Dimensional Quantitative Structure-Activity Relationship Analysis. *Mot. Pharmaco*. 2001, 59, 509–919.

(2) Powell, M. F.; Stewart, T.; Otvos, L.; Jr., Urge, L.; Gaeta, F. C. A.; et al. Peptide Stability in Drug Development II Effect of Single Amino Acid Substitution and Glycosylation on Peptide Reactivity in Human Serum. *Pharm. Res.* 1993, 10, 1269–1273.

(3) Gander, B.; Johansen, P.; Hō, N. T.; Merkle, H. Thermodynamic Approach to Protein Microencapsulation into Poly(D,L-Lactide) by Spray Drying. *Int. J. Pharmaceutics* 1996, 129, 51–61.

(4) Phuc, N. H.; Liu, R. P. T.; Munafo, A.; Ruelle, P.; Nam-tran, H.; et al. Determination of Partial Solubility Parameters of Lactose by Gas-Solid Chromatography. *J. Pharm. Sci. 1986*, 75, 68–72.

(5) Mitsuda, H.; Kawa, F.; Yamamoto, A.; Nakajima, K. Carbon dioxide-protein interaction in a gas-solid phase. *J. Nutr. Sci. Vitaminol. 1975*, 21, 151–162.

(6) Rowe, R. C. Interactions in the ternary powder system microcrystalline cellulose, magnesium stearate and colloidal. *Int. J. Pharm.* 1988, 45, 259–261.

(7) Rowe, R. C. Interactions in powders and granules—a reappraisal. *Int. J. Pharm.* 1992, 79, 257–261. Get rights and content

(8) Backensfeld, T.; Müller, B. W.; Kolter, K. Interaction of NSA with cycloexetrins and hydroxyspropyl cycloexetrin derivatives. *Int J Pharmaceutesics* 1991, 74, 85–93.

(9) Prasad, G. K.; Singh, B.; Vijayaraghavan, R. Respiratory Protection Against Chemical and Biological Warfare Agents. *Def. Sci. J.* 2008, 58, 686–697.

(10) Lemaire, V.; Tobin, F. L.; Greller, L. D.; Cho, C. R.; Suva, L. J. Modeling the interactions between osteoblast and osteoclast activities in bone remodeling. *J. Theor. Biol.* 2004, 229, 293–309.

(11) Hansen, C. M.; Anderssen, B. H. The affinities of organic solvents in biological systems. *Am. Ind. Hyg. Assoc. J.* 1988, 49, 301–308.

(12) Wung, J. C. Interaction between DNA and an Escherichia colioprotein. *J. Mol. Biol.* 1971, 55, 23–IN16.

(13) Chautard, E.; Thierry-Mieg, N.; Ricard-Blum, S. Interaction networks: From protein functions to drug discovery. A review Les réseaux d’interactions: de la fonction des protéines à la conception de médicaments. *Pathol. Biol.* 2009, 57, 324–333.

(14) Buchmann, M.; Ho, N.-T.; Lamartine, R.; Bonnamour, I. New General Models for Evaluating Interactions in Non-Regular Solutions and Adsorption Energies Based on Both Hansen’s and Drago’s Parameters. *J. Appl. Solution Chem. Model.* 2016, 5, 57–70.

(15) Hansen, C. M. Hansen Solubility parameters. *A user’s Handbook;* 2nd ed, CRC Press: Boca Ratun, 2013, https://www.crcpress.com/Hansen-Solubility-Parameters-A-Users-Handbook-Second-Edition/Hansen/p/book/9780849372483.

(16) Hansen, C. M. 50 Years with solubility parameters—past and future. *Prog. Org. Coat.* 2004, 51, 77–84.

(17) Drago, R. S. *Applications of Electrostatic-Covalent models in Chemistry; Surfside Scientific Publishers: Gainsville, 1994, DOI: 10.1021/j100071a029. http://r.takjoo.pr.ofcms.um.ac.ir/;* Surfside Scientific Publishers: Gainsville, 1994, http://www.worldcat.org/title/crc-handbook-of-solubility-parameters-and-other-cohesion-parameters/oclc/8553409/editions?referer=di&editionsView=true.

(18) Nam-Trân, H. A new Model for Evaluating Interaction in Liquids. *J. Phys. Chem.* 1994, 98, 5362–5367.

(19) Barton, A. F. *Handbook of Solubility Parameters and Other Cohesion Parameters;* Second Edition, CRC Press: Boca Ratun Ann Arbor Boston London, 1991. http://www.worldcat.org/title/crc-handbook-of-solubility-parameters-and-other-cohesion-parameters/oclc/8553409/editions?referer=di&editionsView=true.

(20) Drago, R. S.; Dadmun, A. P.; Vogel, G. C. Addition of New Donors to the E and C Model. *Inorg. Chem.* 1993, 32, 2473–2479.

(21) Drago, R. S.; Wayland, B. B. A Double-Scale Equation for Correlating Enthalpies of Lewis Acid-Base Interactions. *J. Am. Chem. Soc.* 1965, 87, 3571–3577.

(22) Marquardt, D. W. Generalized Inverses, Ridge Regression, Biased Linear Estimation, and Nonlinear Estimation. *Technometrics 1970*, 12, 591–612.

(23) Heskdalsen, A. PLS regression methods. *J. Chemom.* 1988, 2, 211–228.

(24) Tran, H. N.; Michel, B. How to Resolve the Problem of Drago’s Four Parameters in the Context of Molecular Interaction. *J. Appl. Solution Chem. Model.* 2019, 8, 7–15.

(25) Ruelle, P.; Rey-Mermet, C.; Buchmann, M.; Nam-Tran, H.; Kesselring, U. W.; Huykens, P. L. A NEW PREDICTIVE EQUATION FOR THE SOLUBILITY OF DRUGS BASED ON THE THERMODYNAMICS OF MOBILE DISORDER. *Pharm. Res.* 1991, 08, 840–850.

(26) Loubverse, M. J.; Maldonado, A.; Rousseau, S.; Moreau-Masselon, C.; Roux, B.; Rothenberg, G. Revisiting Hansen Solubility Parameters by Including Thermodynamics. *ChemPhysChem 2017*, 18, 2999–3006.

(27) Burello, E.; Furrusseng, D.; Rothenberg, G. Combintorial Explosion in Homogeneous Catalysis: Screening 60,000 Cross-Coupling Reactions. *Adv. Synth. Catal.* 2004, 346, 1841–1853.
(28) Gander, B.; Merkle, H. P.; Nguyen, V. P.; Hồ, N.-T. A New Thermodynamic Model To Predict Protein Encapsulation Efficiency in Poly(lactide) Microspheres. *J. Phys. Chem.* 1995, 99, 16144−16148.