On the Aggregation State and QSPR Models. The Solubility of Herbicides as a Case Study

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The goal of this article is to stress the importance of considering the phase in QSPR studies. It is found that the phase plays a fundamental role in the QSPR models from both a statistical and a physical point of view. From a statistical point of view, it is observed that the predictive performance drops drastically when the QSPR model, obtained for a given phase, is used to predict the solubility of the same set of compounds but in another phase. From a physical point of view, when the compounds in the training set are in different phases, the physical interpretation of the descriptors involved in the model is obscured because the descriptors which appear in the correlation equation are a sort of average encoding the different physical mechanisms underlying the property. It is shown that the use of compounds in the same phase, instead, allows a more transparent physical interpretation of the descriptors involved in the model and, at the same time, improves the statistics of the models.

INTRODUCTION

Quantitative structure−property relationships (QSPR) studies are unquestionably of great importance in modern chemistry and biochemistry.[1,2] The underlying assumption in a QSPR study is that the structural formula of an organic compound, in principle, contains coded within it all the information that predetermines the chemical, biological, and physical properties of that compound. If we could elucidate in detail how these properties are determined by structure, we could predict such properties simply from a knowledge of the molecular structure. Thus, the goal of a QSPR study is to find a mathematical relationship between the property and one or more descriptive parameters, known as descriptors, related to the structure of the molecule. These descriptors are numerical representations of structural features of molecules that attempt to encode important information that causes structurally different compounds to have different physical property values. Even though the descriptors used to build a QSPR model can be empirical, it is generally more useful to use descriptors derived mathematically from the 3D molecular structure, since this allows any relationship so derived to be extended to the prediction of the property of new compounds. The main types of molecular descriptors used in QSPR studies are classified as constitutional, topological, electrostatic, geometrical, and quantum-chemical descriptors.

So far QSPR models have been developed to predict almost all the imaginable physical properties,[3,4] namely, boiling point, critical temperature, vapor pressure, density, refractive index, melting point, solubility, partition coefficients, etc. To obtain generality, the models have been developed using a huge number of compounds in the training set, with a large structural diversity and different aggregation states. Generally, the goodness of the models are discussed in terms of the statistical performance, and some interpretation about the descriptors involved in the correlation is intended. However, this generality is obtained at the expense of the physical interpretation of the phenomenon. Thus, the QSPR models are generally used as a black box, figures enter and a figure comes out.

As it was mentioned above, descriptors encode information of structural features of molecules that cause structurally different compounds to have different physical property values. Therefore, those molecular characteristics, encoded by the descriptors, should play a role in the physical phenomenon underlying the property which it is intended to predict. However, when the training set used to develop the model include compounds in different states, the physical interpretation of the phenomenon is obscured and in rigor that interpretation has no validity since the physical mechanisms which determine the value of any physical property depend strongly on the aggregation state.

In literature it is possible to find quite a large number of articles on QSPR models for the same number of physical properties. In many of them no care about the different states of the compounds has been taken into account; however, some physical interpretation about the descriptors involved in the correlation is suggested. Thus, in a QSPR study on vapor pressure[5] of organic compounds, the differences between vapor pressure of solids and liquids are not considered. The most important descriptor involved in the correlation is interpreted in terms of cavity-formation effects in the bulk liquid media, interpretation that evidently cannot be applied to solids.

QSPR models for aqueous solubility[5,6] have the same drawback, i.e., include solids, liquids, and gases in the training set. The descriptors present in the correlation equations are justified mainly in cavity-size effects. Doubtless these effects are involved in the solubility phenomenon, nevertheless they are not the only ones; for instance, there

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Table 1. Best Four Descriptors Correlation Model of ln(S) for the Solid Phase

descriptor	coefficient	t-test
intercept	$4.05 \times 10^2 \pm 7.18 \times 10^1$	5.64
Kier shape index (order 3)	-1.02 ± 0.12	-8.82
LUMO+1 energy	1.19 ± 0.28	4.27
max. valency of a C atom	$-1.00 \times 10^2 \pm 18.01$	-5.55
no. of occupied electronic levels/ no. of atoms	-5.57 ± 1.13	-4.93

Table 2. Correlation Matrix of the Best Four Descriptors for the Solid Phase[a]

	A	B	C	D
A	1.000			
B	0.111	1.000		
C	0.480	-0.199	1.000	
D	-0.445	-0.689	-0335	1.000

[a] A − Kier shape index (order 3). B − LUMO+1 energy. C − max valency of a C atom. D − no. of occupied electronic levels/no. of atoms.

is no descriptor that accounts for the loss of lattice energy of solids. The mechanisms of solubility of solids, liquids, and gases are different, and therefore the descriptors involved in a QSPR model should account for these differences.

In this article we stress the importance of considering the phase if we want to go a step ahead in the physical interpretation of the QSPR models. In addition, we show how the predictive performance, of a model obtained for an specific phase, drops drastically when it is used to predict the same property for the same set of compounds but in another phase. We consider the aqueous solubility of herbicides as a case study.

THERMODYNAMICS

From a qualitative point of view, solubility can be viewed as the maximum concentration that an aqueous solution will tolerate just before the onset of phase separation. From a thermodynamic point of view, solubility is the concentration of solute A required to reach the following equilibrium

$$A(p) \leftrightarrow A(aq)$$

where p refers to a specific phase of the solute, namely, solid, liquid, or gas state. The condition of thermodynamic equilibrium, at T and P constant, requires that $\Delta G = 0$ implying that $\Delta G^\circ = -RT\ln[A]_{aq}$, where $[A]_{aq}$ is the solubility of the compound.

The mechanism required to reach this equilibrium depends on the state of the solute. For instance, in the solubility of a solid it is necessary, first, to overcome the forces responsible for the existence of the molecular solid as it (electrostatic and dispersion forces),[7] and then the insertion of the solute molecule in the solvent bulk, solvation process. This process is governed by solute−solvent interactions, namely, electrostatic, cavitation-dispersion, and hydrogen bonding. Evidently, in the case of the solubility of gases the scheme is reduced only to the solvation process.

It is clear from the above considerations that the descriptors present in any QSPR model should account for the physical processes behind the property which it is intended to be predicted. Consequently they should be dependent on the phase of the solute.

Table 3. Calculated and Experimental ln(S) for the Solid Phase

compound	CAS number	calc	exp	diff
alachlor	15972-60-8	-0.29	-0.12	-0.17
barban	101-27-9	-4.11	-3.15	-0.96
benefin	1861-40-1	-5.47	-5.81	0.34
butachlor	23184-66-9	-1.59	-2.6	1.01
butylate	2008-41-5	-1.50	-1.7	0.20
chlorbromuron	13360-45-7	-1.25	-1.77	0.52
chlortoluron	15545-48-9	-0.31	-1.11	0.80
diallate	2303-16-4	-2.09	-1.69	-0.40
dichlorophen	97-23-4	-1.59	-2.2	0.61
diphenamid	957-51-7	0.30	0.08	0.22
diuron	330-54-1	-0.84	-1.76	0.92
EPTC	759-94-4	-0.03	0.67	-0.70
fenuron	101-42-8	1.69	3.14	-1.45
fluometuron	2164-17	-1.63	-0.95	-0.68
fluorodifen	15457-05-3	-4.73	-5.1	0.37
fluridone	59756-60-4	-2.68	-3.32	0.64
isoproturon	34123-59-6	-0.04	-1.32	1.28
linuron	330-55-2	-1.17	-1.2	0.03
metobromuron	3060-89-7	0.05	0.24	-0.19
metolachlor	51218-45-2	-0.55	0.59	-1.14
metuxuron	19937-59-8	0.42	1.09	-0.67
molinate	2212-67-1	1.49	1.64	-0.15
monolinuron	1746-81-2	0.31	1.23	-0.92
monuron	150-68-5	0.82	0.01	0.81
neburon	555-37-3	-2.61	-4.07	1.46
oryzalin	19044-88-3	-4.27	-4.98	0.71
pebulate	1114-71-2	-1.04	-0.79	-0.25
propachlor	1918-16-7	1.03	1.04	-0.01
propanil	709-98-8	-1.00	-0.09	-0.91
propyzamide	23950-58-5	-3.15	-2.83	-0.32
thiobencarb	28249-77-6	-2.39	-2.6	0.21
triallate	2303-17-5	-3.22	-4.34	1.12
vernolate	1929-77-7	-0.87	-0.81	-0.06
chlorpropham	101-21-3	-1.31	-0.87	-0.44
dinoseb	88-85-7	-2.62	-1.57	-1.05
fluchloralin	33245-39-5	-6.23	-5.87	-0.36
amitrole	61-82-5	8.74	8.11	0.63
atrazine	1912-24-9	-0.37	-1.97	1.60
bromacil	314-40-9	0.60	1.14	-0.54
cyanazine	21725-46-2	-1.29	-0.34	-0.95
dichlobenil	1194-65-6	-1.89	-2.25	0.36
ioxynil	1689-83-4	-2.78	-2.00	-0.78
prometon	1610-18-0	-0.14	1.20	-1.34
propham	122-42-9	0.15	0.33	-0.18
terbacil	5902-51-2	1.97	1.19	0.78

CHEMICAL DATA

The data set of the aqueous solubility (S) at 25 °C was taken from the data reported by McKay.[8] The set contains the values of aqueous solubility of 45 herbicides, at their solid and liquid states. Since all the compounds are solid at 25 °C, the solubility reported for the liquid state corresponded to the supercooled liquid concentration. The data cover a ln(S) range from about −5 to 11 ln units.

COMPUTATIONAL METHODS

The QSPR models were developed using the Microsoft Windows version of the Codessa program.[9] This program performs the calculation of molecular descriptors and searches for the best multiple linear relationships between calculated descriptors and experimental property data.

Prior to the descriptor calculation and fitting of these descriptors to the experimental data, modeling was performed in order to set the chemicals in their lowest energy 3D conformations. To do this, initial three-dimensional geometries of the chemical structures were generated using the Hyperchem 7.0 molecular modeling package.[10] These 3D
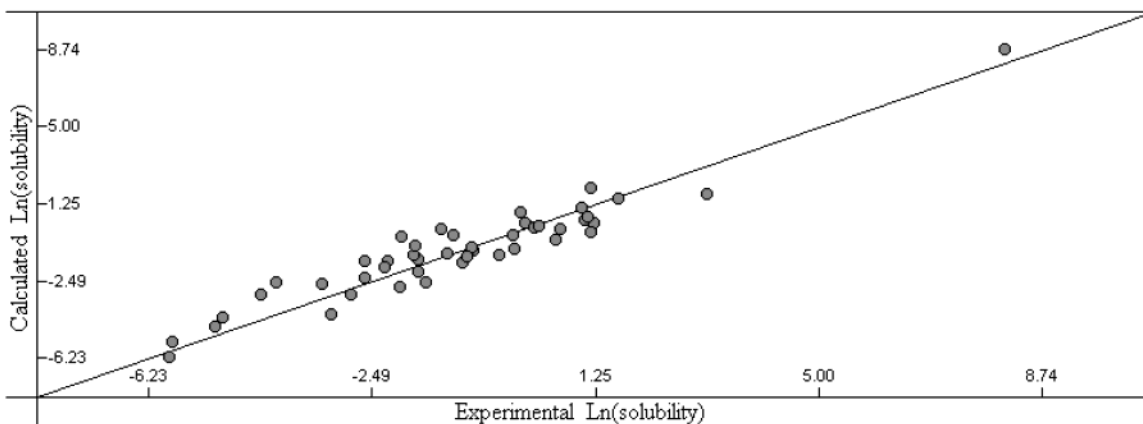
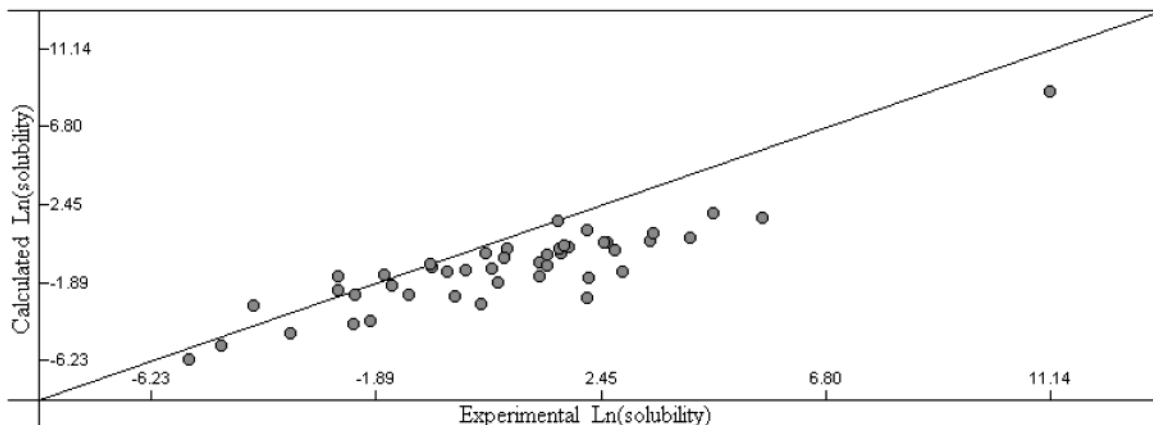**Figure 1.** Scatter plot of the calculated vs experimental ln(*S*) for the solid phase.

Figure 2. Scatter plot of the calculated vs experimental ln(*S*) for the liquid phase. Predicted values obtained from the QSPR model for the solid phase.

structures were refined later using Ampac 5.0, a semiempirical molecular modeling program,[11] using AM1 Hamiltonian. The Ampac output files containing the refined geometries and electron wave functions of individual compounds, along with the experimental solubilities, were loaded into the Codessa program to calculate the molecular descriptors and fitting of these descriptors to the experimental data.

RESULTS AND DISCUSSION

In this study, 598 molecular descriptors (including constitutional, geometric, topologic, electrostatic, and quantum chemical) were calculated for all 45 compounds. The number of descriptors to be used in the search for the optimal correlations was reduced by eliminating highly correlated descriptors, descriptors which are not defined for all compounds, and descriptors that individually correlate poorly with the solubility. With those remaining, the best correlations were identified by using the best multilinear regression option implemented in Codessa.

QSPR MODEL FOR THE SOLID PHASE

The best correlation equation for the solubility of the solid phase is

$$\ln(S) = 4.05 \times 10^2 - 1.02\,X_1 + 1.19\,X_2 - 1.00 \times 10^2\,X_3 - 5.57\,X_4$$

where X_1 is the Kier shape index (order 3), X_2 is the LUMO+1 energy, X_3 is the maximum free valency of a C atom, and X_4 is the number of occupied electronic levels/ number of atoms. Summary statistics for the correlation of experimental vs calculated ln(*S*) for the 45 compounds are $R^2 = 0.90$, $s^2 = 0.67$, and $F = 92.39$ where *R* is the correlation coefficient, *s* is the standard deviation of the fit, and *F* is the value of the Fisher test. Table 1 summarizes the results of the best four parameter QSPR model derived for ln(*S*). The first column contains the descriptors involved in the correlation; the second column contains the respective values of the regression coefficients along with their mean square errors; and finally the third column contains the t-student values for the correlation coefficients; these values reflect the significance of each parameter within the model.

In Table 2, the correlation matrix of the descriptors involved in the best multilinear regression equation is shown.

The most important descriptor involved in the regression equation is the Kier shape index (order 3). This descriptor encodes the shape of the molecule which depends on the number of skeletal atoms and the molecular branching. Therefore this descriptor is involved in the so-called cavitation contribution to the free energy of solvation, i.e., the cavity that must be formed in the solvent to receive the solute molecule. The negative value of its regression coefficient indicates the solubility decreases as the value of this descriptor increases, as expected.

Table 4. Best Four Descriptors Correlation Model of ln(S) for the Liquid Phase

descriptor	coefficient	t-test
intercept	6.36 ± 0.58	10.91
Kier shape index (order 3)	-1.29 ± 0.11	-11.92
LUMO+1 energy	1.45 ± 0.19	7.46
HACA-2	$6.95 \times 10^{-1} \pm 1.24 \times 10^{-1}$	5.58
Kier&Hall index (order 3)	-1.01 ± 0.18	-5.55

Table 5. Correlation Matrix of the Best Four Descriptors for the Liquid Phase[a]

	A	B	C	D
A	1.000			
B	0.394	1.000		
C	0.111	-0.331	1.000	
D	-0.218	-0.214	0.499	1.000

[a] A − Kier shape index (order 3). B − Kier&Hall index (order 3). C − LUMO+1 energy. D − HACA-2 (quantum-chemical PC).

The remaining three descriptors have nearly the same significance in the correlation equation, and their physical interpretation is as follows. The LUMO+1 energy is related to the second electronic affinity of the molecule. Presumably this descriptor is involved in the formation of charge-transfer complexes between solute and solvent. The presence in the correlation of the LUMO+1 instead of the LUMO energy is surprising. However, the occupation of a higher energy orbital might lower the electron−electron repulsion and result in a lower overall molecular energy. The picture, in terms of molecular orbital (MO), of this interaction is nearly as follows:[12] the delocalization of the lone pair of electrons lying on a no-bonding MO of the donor atom, in this case the oxygen of water, into a vacant antibonding MO of an acceptor molecule. This electronic delocalization creates a bond polarity and an electrostatic attraction which favors the solubility. Therefore, the larger the extent of this interaction the higher the solubility, as it is corroborated in the model because of the positive value of the correlation coefficient.

The above two descriptors account for the solute−solvent interactions; therefore, we expect they would be also present in any QSPR model for the solubility regardless of the phase.

The maximum free valency of the ith atom is defined as

$$V_i = V_{max} - \sum_{j \neq i} P_{ij}$$

where V_{max} is the maximum valency of the atom i and P_{ij} is the bond order. Thus, the free valency is a measure of the surplus valence available on the atom; therefore, it should enhance the polarizability of the molecule and consequently favor dispersion forces in the solid, i.e., the intermolecular bonding interactions in the crystal lattice.

The number of occupied electronic levels/number of atoms descriptor is also related to the polarizability of the molecule, namely, the higher the number of electrons, the more polarizable the molecule.

These two descriptors are roughly related to binding dispersion forces in the solid state, so these descriptors account for the loss of lattice energy of solids and hence their negative correlation coefficients in the model. In light of the above physical explanation we expect they should not be present in the QSPR model for the solubility in the liquid phase.

Table 6. Calculated and Experimental ln(S) for the Liquid Phase

compound	CAS number	calc	exp	diff
alachlor	15972-60-8	0.25	0.25	0.00
barban	101-27-9	-2.14	-1.99	-0.15
benefin	1861-40-1	-5.09	-4.87	-0.22
butachlor	23184-66-9	-2.48	-2.6	0.12
butylate	2008-41-5	-1.66	-1.7	0.04
chlorbromuron	13360-45-7	0.55	-0.15	0.70
chlortoluron	15545-48-9	2.68	1.69	0.99
diallate	2303-16-4	-2.24	-1.58	-0.66
dichlorophen	97-23-4	1.13	1.29	-0.16
diphenamid	957-51-7	1.66	2.6	-0.94
diuron	330-54-1	1.61	1.29	0.32
EPTC	759-94-4	0.75	0.67	0.08
fenuron	101-42-8	4.25	5.58	-1.33
fluometuron	2164-17	1.91	2.23	-0.32
fluorodifen	15457-05-3	-3.52	-3.53	0.01
fluridone	59756-60-4	-0.91	-0.35	-0.56
isoproturon	34123-59-6	2.19	1.66	0.53
linuron	330-55-2	0.92	0.37	0.55
metobromuron	3060-89-7	1.76	1.86	-0.10
metolachlor	51218-45-2	-0.39	0.59	-0.98
metuxuron	19937-59-8	2.05	3.41	-1.36
molinate	2212-67-1	2.60	1.64	0.96
monolinuron	1746-81-2	2.39	2.53	-0.14
monuron	150-68-5	3.03	3.47	-0.44
neburon	555-37-3	-1.35	-2.27	0.92
oryzalin	19044-88-3	-3.52	-2.31	-1.21
pebulate	1114-71-2	-0.97	-0.79	-0.18
propachlor	1918-16-7	2.05	2.2	-0.15
propanil	709-98-8	1.78	1.44	0.34
propyzamide	23950-58-5	-0.02	0.15	-0.17
thiobencarb	28249-77-6	-1.08	-2.6	1.52
triallate	2303-17-5	-3.53	-4.24	0.71
vernolate	1929-77-7	-0.94	-0.81	-0.13
chlorpropham	101-21-3	-0.29	-0.51	0.22
dinoseb	88-85-7	-0.58	-1.23	0.65
fluchloralin	33245-39-5	-5.37	-5.47	0.10
amitrole	61-82-5	10.91	11.14	-0.23
atrazine	1912-24-9	3.33	1.42	1.91
bromacil	314-40-9	3.87	4.19	-0.32
cyanazine	21725-46-2	2.49	2.89	-0.40
dichlobenil	1194-65-6	2.05	0.48	1.57
ioxynil	1689-83-4	1.23	2.19	-0.96
prometon	1610-18-0	2.07	2.73	-0.66
propham	122-42-9	0.99	1.76	-0.77
terbacil	5902-51-2	4.94	4.63	0.31

The calculated and experimental values of the ln(S) are compared in Table 3, and the scatter plot is shown in Figure 1.

The performance of the model drops drastically when one tries to predict the solubility for the same set of chemicals in the liquid phase, Figure 2. Summary statistics for the correlation of experimental vs calculated ln(S) for the 45 compounds are in this case $R^2 = 0.80$ and standard error of estimate $= 1.072$ in contrast to the values obtained for the solid phase.

QSPR MODEL FOR THE LIQUID PHASE

The best correlation equation for the solubility of the liquid phase is

$$\ln(S) = 6.36 - 1.29\,Y_1 + 1.45\,Y_2 - 0.69\,Y_3 - 1.01\,Y_4$$

where Y_1 is the Kier shape index (order 3), Y_2 is the LUMO+1 energy, Y_3 is the HACA-2 descriptor, and Y_4 is the Kier&Hall index (order 3). Summary statistics for the correlation of experimental vs calculated ln(S) for the 45 compounds are $R^2 = 0.94$, $s^2 = 0.60$, and $F = 151.30$. Table
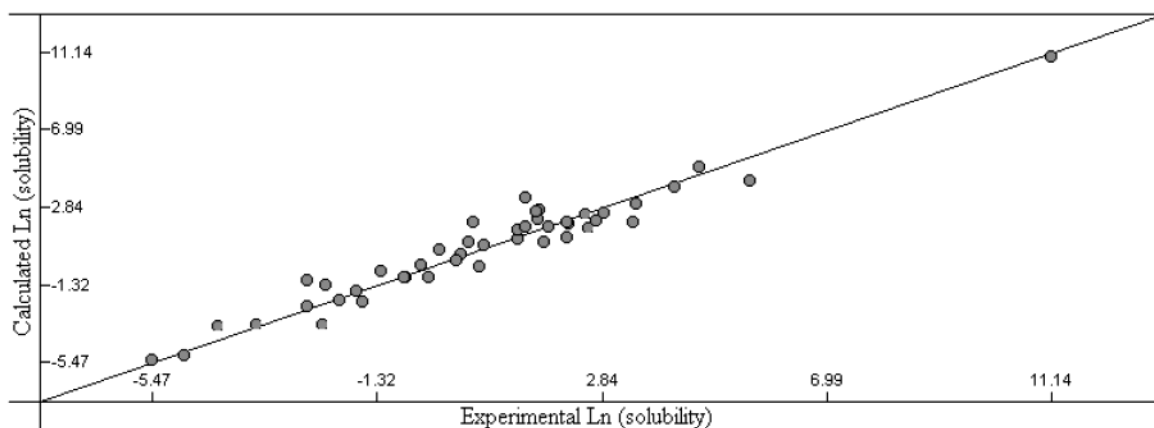
Figure 3. Scatter plot of the calculated vs experimental ln(*S*) for the liquid phase.
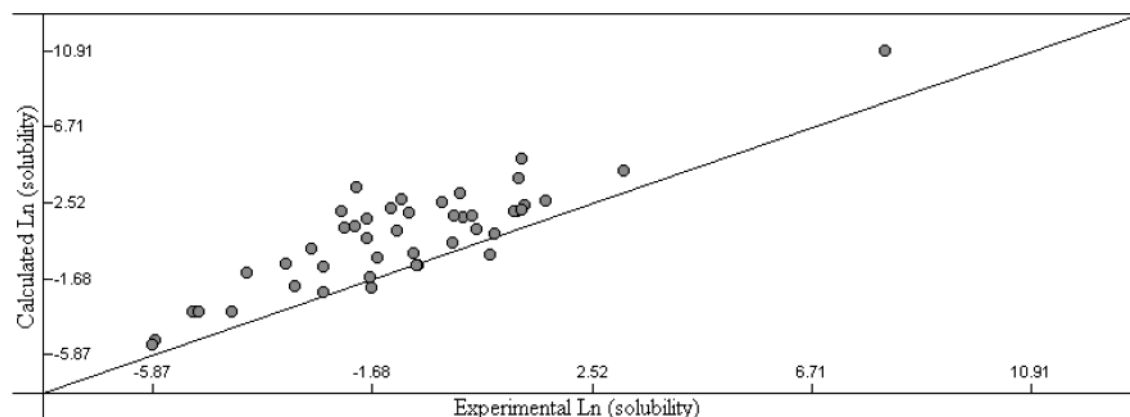

Figure 4. Scatter plot of the calculated vs experimental ln(*S*) for the solid phase. Predicted values obtained from the QSPR model for the liquid phase.

4 summarizes the results of the best four parameter QSPR model derived for ln(*S*). In Table 5, the correlation matrix of the descriptors involved in the best multilinear regression equation is shown.

The two more important descriptors in the model are the Kier shape index (order 3) and the LUMO+1 energy, respectively. The remaining two descriptors are the HACA-2 and Kier&Hall index (order 3) descriptors, both with the same significance in the model. The topological descriptors, the Kier shape, and Kier&Hall indices encode geometrical features of the molecules, namely, the shape and the molecular van der Waals volume; consequently these descriptors are involved in the cavitation contribution of the free energy of solvation. The two quantum chemical descriptors, the LUMO+1 energy and the HACA-2 descriptor, are involved in the so-called specific solvation component of the free energy of solvation, namely, formation of charge-transfer complexes and hydrogen bonding, respectively. As expected, descriptors related to binding dispersion forces in the solid state are not present in the correlation equation.

The calculated and experimental values of the ln(*S*) are compared in Table 6, and the scatter plot is shown in Figure 3.

The prediction of the solubility of solids using the QSPR model obtained for liquids leads to a lower predictive performance, Figure 4. Summary statistics for the correlation of experimental vs calculated ln(*S*) for the 45 compounds are $R^2 = 0.76$ and standard error of estimate $= 1.43$ in contrast to the values obtained for the liquid phase.

CONCLUSIONS

In this article we have shown that the aggregation states play a fundamental role in QSPR models from both a statistical and a physical point of view. From a statistical point of view, it is observed that the predictive performance drops drastically when the QSPR model, obtained for a property in a given phase, is used to predict such a property for the same set of compounds but in another phase. Thus, for instance, the prediction of the solubility of liquids, using the model obtained for the solid phase, underestimates the solubility values. Conversely, the prediction of the solubility of solids, using the model for the liquid phase, overestimates the respective values. This is due to the descriptors involved in the correlation equations are accounting for the differences existing in the mechanisms of solubility having solids and liquids and hence the observed differences in its values. Therefore, the combination of compounds in different phases in the training set probably may be responsible for the outliers observed in some QSPR studies.

From a physical point of view, when the compounds in the training set are in different phases, the physical interpretation of the descriptors involved in the model is obscured because the descriptors which appear in the correlation equation are a sort of average encoding the different physical mechanisms underlying the property. In many cases, descriptors which may be important to interpret some specific mechanism may be masked for others in the statistical procedure of obtaining the correlation equation. The use of compounds in the same aggregation state, instead, allows a

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more transparent physical interpretation of the descriptors involved in the model and, at the same time, improves the statistics of the models.

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