

## Prediction of Henry's Law Constants of Triazine Derived Herbicides from Quantum Chemical Continuum Solvation Models

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The Henry's law constants ( $H$ ) for triazine derived herbicides are calculated using quantum chemical solvation models, SM2, SM3, PCM-DFT, and CPCM-DFT, and their performances are discussed. The results show considerable differences in performance among the different levels of theory. The values of  $H$  calculated by the semiempirical methods agree much better with the experimental values than those obtained at the DFT level. The differences are discussed in terms of the different contributions, electrostatic and non-electrostatic, to Gibbs free energy of solvation. In addition, the Henry's law constants of some triazine derived herbicides whose values have not been reported earlier are predicted as well.

### INTRODUCTION

In the Food and Agricultural Organization of the United Nations Meeting on agricultural plagues, held in November 1996, it was stressed the necessity to increase the productivity per cultivation area. This demand is peremptory since, on one hand, the available surface is limited, even worse it has diminished due to the degradation of the soil; and on the other hand, it is necessary to supply the food demand of a steadily increasing population.

To supply this demand of the current world population, about six thousand million, it is required to produce more and more. To do this is necessary to use massively agrochemicals, known generically as pesticides (insecticides, herbicides, fungicides, acaricides, nematocides). The use of these chemicals has allowed for significant reduction of the agricultural plagues and consequently increased the productivity. However, the massive use of these agrochemicals has an environmental cost (due to their toxicity, their persistence, or their tendency to bioaccumulate) which is necessary to evaluate in order to conciliate productivity and environment protection.

Among the pesticides, the herbicides deserve special attention since, due to the resistance developed by weeds, new products are being steadily introduced to market. The importance of being able to predict the distribution of these chemicals in the environmental compartments is consequently of great importance in order to understand where they tend to accumulate, and how they migrate in, and between, the various media of air, water, soils, and sediments which compromise our biosphere.

Henry's law constant,  $H$ , determines how a chemical substance will partition between air and a given solvent. From an environmental point of view,  $H$  is a key parameter used to model the diffusive exchange of chemicals between aqueous phases and the atmosphere. Accurate knowledge of Henry's law constant is essential to predict the environmental behavior, transport, and fate of many types of pollutants.

Unfortunately, the lack of accurate  $H$  measurements is a major limitation in predicting the environmental distribution and transport of pollutants. The difficulty to obtain accurate experimental values arise from the limitations of analytical techniques to measure the solute concentration in both phases in equilibrium. In general, for reasons of cost, time, safety, and availability of techniques to measure  $H$  it is useful to be able to predict it. Therefore, the calculation of free energy of solvation is important for the design of novel pesticides since properties can be thus predicted prior to synthesis. Design of novel compounds may in this way be guided by the results of calculations.

There exist several approaches to compute free energy of solvation, e.g., quantum mechanical continuum methods,<sup>1</sup> methods relying on a discrete molecular description of the whole solution,<sup>2</sup> and methods based on computer simulations of liquids.<sup>3,4</sup>

In a previous article<sup>5</sup> we showed that the semiempirical quantum chemical continuum solvation models are a good alternative approach to estimate  $H$ . In that study, the Henry's law constants for all 12 chlorinated benzene congeners are reported. The values of  $H$  calculated by this approach are within the 95% confidence limit of error of the experimental mean.

In this article, we predict Henry's law constant for triazine derived herbicides using quantum chemical continuum solvation models (SM2, SM3, PCM-DFT, CPCM-DFT), and their performances are discussed. In addition, Henry's law constants for some herbicides whose values have not been previously reported in the literature are predicted.

### QUANTUM CHEMICAL CONTINUUM SOLVATION MODELS

The standard-state free energy of solvation  $\Delta G_s^\circ$  is a fundamental quantity characterizing the interaction of a solute molecule with a given solvent. In addition to its fundamental interest,  $\Delta G_s^\circ$  may be combined with other thermodynamic data to predict a variety of equilibrium constants, the most

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**Table 1.** Calculated and Literature Values of Henry's Law Constants

compound	$H$ (Pa m <sup>3</sup> /mol)					
	literature values		SM2	SM3	PCM	CPCM
	RIVM <sup>11</sup>	PHYSPROP <sup>10</sup>				
Thiotriazines						
ametryn		$2.43 \times 10^{-4}$	$1.12 \times 10^{-8}$	$9.24 \times 10^{-8}$	$1.80 \times 10^{-2}$	$1.37 \times 10^{-2}$
desmetryn	$2 \times 10^{-8}$		$7.24 \times 10^{-10}$	$2.54 \times 10^{-8}$	$9.16 \times 10^{-3}$	$6.53 \times 10^{-3}$
prometryn	$3.4 \times 10^{-7}$	$1.32 \times 10^{-3}$	$1.98 \times 10^{-7}$	$7.38 \times 10^{-7}$	0.194	0.115
terbutryn	$8.6 \times 10^{-7}$	$1.15 \times 10^{-3}$	$1.98 \times 10^{-7}$	$7.06 \times 10^{-7}$	0.139	$6.49 \times 10^{-2}$
Chlorotriazines						
atrazine	$1.2 \times 10^{-7}$	$2.30 \times 10^{-4}$	$3.63 \times 10^{-5}$	$2.51 \times 10^{-6}$	$3.16 \times 10^{-3}$	$1.91 \times 10^{-3}$
cyanazine	$1.2 \times 10^{-10}$	$2.57 \times 10^{-7}$	$2.24 \times 10^{-7}$	$9.67 \times 10^{-10}$	$2.54 \times 10^{-3}$	$1.31 \times 10^{-3}$
simazine	$1.6 \times 10^{-8}$	$9.42 \times 10^{-5}$	$1.83 \times 10^{-6}$	$2.50 \times 10^{-7}$	$6.36 \times 10^{-4}$	$5.11 \times 10^{-4}$
Other Triazines						
metamitron	$4.6 \times 10^{-7}$		$3.56 \times 10^{-8}$	$6.24 \times 10^{-8}$	$5.14 \times 10^{-5}$	$3.00 \times 10^{-5}$

important of which are solubility and the partitioning of a solute between immiscible phases.

In quantum chemical continuum solvation models<sup>1</sup> the Gibbs free energy of solvation is calculated as

$$\Delta G_S^\circ = \Delta G_{elec} + \Delta G_{nonelec}$$

where  $\Delta G_{elec}$  is the electrostatic contribution to  $G_S^\circ$ , and  $\Delta G_{nonelec}$  is the nonelectrostatic component. The standard state for both phases, gas and solution, is 1 mol L<sup>-1</sup>, and the temperature is taken as 298 K.

#### STANDARD GIBBS FREE ENERGY OF SOLVATION AND HENRY'S LAW CONSTANT

The Henry's law constant may be calculated from the Gibbs free energy of solvation considering a simple four stage thermodynamic cycle:<sup>5</sup> going from A(gas,  $P_A$ ) to A(gas,  $C = 1$  M) to A(ideal solution,  $C = 1$  M) to A(solution,  $a_A = \gamma_A C_A$ ), in equilibrium with the gas at pressure  $P_A$ . The expression obtained reads

$$\ln H = \ln RT + \frac{\Delta G_S^\circ}{RT}$$

where  $H$  is the Henry's law constant.

#### COMPUTATIONAL METHODS

Initial three-dimensional geometries of the chemical structures were generated using the Hyperchem 7.0 molecular modeling package.<sup>6</sup> Subsequent quantum chemical calculations in the gas phase and in solution were performed using AMPAC 5.0 package<sup>7</sup> (AM1, PM3, SM2, SM3) for the semiempirical calculations and GAUSSIAN 98<sup>8</sup> (B3LYP/6-31G(d), PCM-B3LYP/6-31G(d), CPCM-B3LYP/6-31G(d)) for the DFT calculations. The molecular geometries were optimized at the respective levels of theory.

#### CLASSICAL PHYSICAL ORGANIC CHEMISTRY PICTURE

The introduction of substituents into organic compounds often leads to charge shifts and significant dipole moments. This may have important consequences for structure, energy, reactivity, and solubility. The effect of substituents results from a combination of factors.<sup>9</sup> One of these, known as resonance effect, acts along the  $\pi$  electron system, involving multiple bonds, unshared electrons, and unfilled outer

electronic shells. Substituents whose resonance interactions with attached unsaturated systems result in electron withdrawal are said to have ( $-R$ ) effects, while resonance-electron donors have ( $+R$ ) effects.

There is also an effect that originates with the bond dipoles between groups of differing electronegativity. The resulting dipoles will influence the energy associated with development of charge elsewhere in the molecule. This is the result of through-space electrostatic interaction and is called a field effect. Another possible means of interaction of a substituent is called the inductive effect. This is transmission of bond dipoles through the intervening bonds by successive polarization of each bond. Groups withdrawing electrons inductively are said to have ( $-I$ ) effects, while those that donate electrons have ( $+I$ ) effects.

These effects, resonance and inductive, are important to have in mind when one analyzes and discusses the performance of the quantum-chemical methods to describe the electronic structure of the molecules and wants to validate the figures obtained from these calculations on physical ground.

#### RESULTS AND DISCUSSION

In Table 1, the values of Henry's law constants calculated by SM2, SM3, PCM-DFT, and CPCM-DFT methods, along with some values reported in the literature,<sup>10,11</sup> are shown. From this table it is possible to observe two facts that it is necessary to stress: on one hand, the great dispersion in the values reported. These differences are due to the method to measure or to estimate  $H$ . The values reported in the Physprop database, estimated by the direct ratio of vapor pressure and aqueous solubility, are lower than those reported in RIVM by about a magnitude order of 3 or 4.

On the other hand, the values of  $H$  obtained at DFT level are much lower than those calculated at the semiempirical level and the respective experimental reported values. The differences go from 2 to 6 orders of magnitude corresponding to differences of about 4 and 7 (kcal/mol) in the free energy of solvation, respectively, Table 2. Thus, PCM and CPCM methods show underestimation of the energy of stabilization through aqueous solvation compared to the semiempirical approach.

To get a better insight into possible causes for the observed deviations between theory and experiment we have decomposed the free energy of solvation into their electrostatic and

**Table 2.** Free Energy of Solvation  $\Delta G_s^\circ$  (kcal/mol)

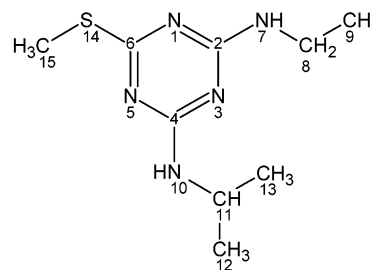
no.	compound	SM2	SM3	PCM	CPCM
Thiotriazines					
1	ametryn	-15.47	-14.22	-7.01	-7.17
2	desmetryn	-17.08	-14.98	-7.41	-7.61
3	prometryn	-13.77	-12.99	-5.60	-5.91
4	terbutryn	-13.77	-13.01	-5.80	-6.25
Chlorotriazines					
5	atrazine	-10.68	-12.26	-8.04	-8.34
6	cyanazine	-13.69	-16.92	-8.17	-8.58
7	simazine	-12.45	-13.63	-8.99	-9.12
Other Triazines					
8	metamitron	-14.78	-14.45	-10.48	-10.80

nonelectrostatic contributions, Table 3. Inspection of this table shows that the electrostatic contributions yield stabilizing energy contributions for all compounds, regardless of the level of theory. However, PCM and CPCM yield more negative values than those obtained at semiempirical level. The values obtained from these two methods show high squared correlation coefficients ( $r^2 = 0.99$ ) between them, which contrast to the poor correlation between the values obtained at semiempirical level ( $r^2 = 0.009$ ), being SM2 values, in general, smaller than the ones from SM3. Table 3 shows further that, for all compounds, both PCM and CPCM methods give the same destabilizing contribution to the solvation free energy of the nonelectrostatic components, while with the semiempirical methods negative values are achieved. From this table, it is possible to observe that SM2 and SM3 values of  $\Delta G_{nonelec}$  show a relatively high squared correlation coefficient ( $r^2 = 0.90$ ), being that the SM2 values are slightly smaller, in absolute magnitude, than the respective SM3 values.

Due to the bad performance of DFT based methods to calculate free energy of solvation compared to semiempirical methods we are going to focus the discussion on the last ones a little more thoroughly.

In general, there is not a significant difference in the values of  $H$  calculated by the SM2 and SM3 methods, as a consequence of the similarity in the values of Gibbs free energy of solvation calculated by both methods. However, there are differences in the electrostatic component ( $\Delta G_{elec}$ ) of the free energy of solvation which deserve some discussion.

To more transparently discuss the effect of substituents we have separated the chemicals in the following three groups: thiotriazines, chlorotriazines, and other triazines.

**Figure 1.** Ametryn.

**(i) Thiotriazines.** The electrostatic component ( $\Delta G_{elec}$ ) calculated by SM3 is always more positive when it is compared to the respective SM2 values. This is due to the fact that the SM2 method gives a greater polarization of the molecule because of a deficient description of the electronic structure. To isolate from the solvation effects and more transparently analyze the performance of AM1 and PM3 methods, the partial atomic charges in the gas phase were calculated for ametryn, Figure 1 and Table 4. The electronic picture for the other thiotriazines follows the same trend.

The AM1 method gives a charge separation of 0.6 units for the C–S bond of the methyl mercaptan group, Table 4. This behavior is in opposition to what one could expect from the negligible difference of electronegativities between C and S, about 0.03 units in the Pauling scale,<sup>12</sup> and it is corroborated by the charge distribution obtained using electrostatic potential-derived charges according to the Merz–Kollman–Singh scheme (MK), as implemented in Gaussian 98, which predicts a charge separation of just 0.14 units.

On the other hand, AM1 and MK methods assign a large negative charge on the nitrogen atoms of the alkyl amino substituents. This description seems to be inadequate, since the resonance effect is required to explain the fact that the alkyl amino substituent acts as an electron donor although nitrogen is more electronegative than carbon, and that the amino group is found to have (–I) effect when attached to saturated carbon.<sup>9</sup>

The PM3 method instead assigns a slight positive charge on the nitrogen atom of the alkyl-amino groups, Table 4, as it would be expected from (+R) resonance considerations. However, the absolute values of atomic charges obtained from the PM3 calculations must be taken with caution since it is well known that PM3 tends to predict nitrogen atoms to be much too electropositive.<sup>13</sup> In addition, PM3 gives a better

**Table 3.** Electrostatic and Nonelectrostatic Contributions to the Free Energy of Solvation (kcal/mol)

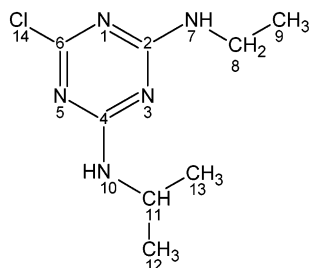
		electrostatic contribution				nonelectrostatic contribution			
no.	compound	SM2	SM3	PCM	CPCM	SM2	SM3	PCM	CPCM
Thiotriazines									
1	ametryn	−10.53	−7.70	−11.43	−11.59	−4.94	−6.52	4.41	4.41
2	desmetryn	−11.47	−7.58	−11.22	−11.43	−5.61	−7.40	3.82	3.82
3	prometryn	−9.48	−7.33	−10.50	−10.80	−4.29	−5.66	4.90	4.90
4	terbutryn	−9.54	−7.26	−9.82	−10.28	−4.23	−5.75	4.03	4.03
Chlorotriazines									
5	atrazine	−7.20	−7.12	−12.04	−12.34	−3.48	−5.15	4.00	4.00
6	cyanazine	−8.35	−9.07	−14.38	−14.79	−5.34	−7.84	6.21	6.21
7	simazine	−8.30	−7.61	−12.31	−12.44	−4.15	−6.01	3.32	3.32
Other Triazines									
8	metamitron	−9.65	−7.29	−12.94	−13.27	−5.13	−7.16	2.47	2.47

**Table 4.** Atomic Charges for Ametryn

atom	AM1	PM3	MK
1	-0.2870	-0.2364	-0.7460
2	0.2087	0.0590	0.9629
3	-0.3196	-0.2831	-0.7293
4	0.2075	0.0724	0.7154
5	-0.3098	-0.2825	-0.4428
6	-0.0560	0.0020	0.4954
7	-0.2899	0.1023	-0.7693
8	-0.0227	-0.0871	0.3616
9	-0.2305	-0.1212	-0.3064
10	-0.2694	0.0968	-0.6725
11	-0.0149	-0.0698	0.4914
12	-0.2428	-0.1401	-0.5264
13	-0.2214	-0.1204	-0.5121
14	0.3145	0.1392	-0.1589
15	-0.3676	-0.1888	-0.2976

**Table 5.** Atomic Charges for Atrazine

atom	AM1	PM3	MK
1	-0.2826	-0.2612	-0.7302
2	0.2162	0.0638	1.0511
3	-0.3179	-0.2852	-0.9663
4	0.2110	0.0688	1.1352
5	-0.2784	-0.2559	-0.8290
6	0.1123	0.0236	0.6532
7	-0.2939	0.1042	-0.6113
8	-0.0185	-0.0870	0.3228
9	-0.2317	-0.1215	-0.3294
10	-0.2713	0.1052	-0.8268
11	0.0171	-0.0718	0.5733
12	-0.2415	-0.1391	-0.4967
13	-0.2229	-0.1207	-0.5176
14	0.0487	0.1395	-0.1316

**Figure 2.** Atrazine.

description, compared to AM1, of the carbon–sulfur bond, decreasing the polarization of the bond.

**(ii) Chlorotriazines.** For this group, Gibbs free energy of solvation calculated by the SM3 method are always lower than those calculated by SM2, by about 1–2 kcal/mol. The nonelectrostatic component ( $\Delta G_{\text{nonelec}}$ ) of the Gibbs free energy of solvation is responsible for this difference, as it may be concluded from Table 3.

The electrostatic components  $\Delta G_{\text{elec}}$ , calculated by both methods, are comparable, and, therefore, this component does not account for the differences observed in  $\Delta G_{\text{S}}^{\circ}$ . Although the numerical values are comparable, there exist significant differences regarding the description of electron density given by these two methods. For the same reasons given for the case of thiotriazines, in this group we have calculated the partial atomic charges in the gas phase for a test molecule, atrazine, Figure 2 and Table 5. The electronic picture for the other chlorotriazines follows the same trend.

Semiempirical calculations assign a positive charge on the chlorine atom; this result could be explained assuming a

**Table 6.** Predicted Values of Henry's Law Constants for Herbicides Not Reported Previously

compound	$H$ (Pa m <sup>3</sup> /mol)	
	SM2	SM3
sebumeton	$1.13 \times 10^{-5}$	$8.42 \times 10^{-6}$
methoprotrotryne	$7.68 \times 10^{-10}$	$5.93 \times 10^{-9}$
terbumeton	$3.81 \times 10^{-5}$	$1.76 \times 10^{-5}$
terbuthylazine	$2.43 \times 10^{-4}$	$1.27 \times 10^{-5}$

donate electron character for the chlorine atom, i.e., an inductive effect (+I). This assumption is in opposition to what one could expect from the well-known chemistry of chlorine, while the MK method assigns a negative charge on this atom as expected from electronegativity considerations, Table 5. As well, like in the case of thiotriazines, this method yields an increase of the electron density on nitrogen atoms of the alkyl-amino groups indicating that the inductive effect (–I) of nitrogen is dominant over the resonance effect. However, as it was mentioned above, this description does not agree with the chemical evidence of alkyl-amino groups attached to aromatic rings. The PM3 method instead gives an electronic picture which is in better agreement with resonance considerations.

In conclusion, the electronic structures of chlorotriazines obtained by both methods AM1 and PM3 have deficiencies related to the description of electron density on chlorine atom and the nitrogen atom of the alkyl-amino groups; therefore, it is not possible to assess a better description of one over the other. This bad performance is enhanced in solution.

**(iii) Other Triazines.** In this group we have included a triazine which does not contain neither chlorine nor sulfur in its structure. For this triazine the values of Gibbs free energy of solvation calculated by the SM2 and SM3 are remarkably comparable. The differences between the calculated values are not greater than 0.3 kcal/mol. Again, it is possible to observe differences between the values of  $\Delta G_{\text{elec}}$  and  $\Delta G_{\text{nonelec}}$  calculated by the two methods; however, these differences cancel each other to give finally very similar values of free energy of solvation, like the case of thiotriazines. The Henry's law constants calculated from these values of  $\Delta G_{\text{S}}^{\circ}$  agree well with the experimental data reported in the literature, Table 1.

In addition, we have predicted the Henry's law constants for other four triazine derived herbicides whose values of  $H$  have not been reported yet, Table 6. The values of  $H$  obtained from the two methods are in agreement. The same considerations concerning the different components of Gibbs free energy of solvation given above are valid for these four cases.

## CONCLUSIONS

Quantitative structure–property relationship (QSPR)<sup>14,15</sup> models, based on the reliability of the experimental data to build the regression equations, seems not to be a good choice to predict Henry's law constants due to the great dispersion existing in the reported values. Moreover, the nature of the relationship between  $H$  and the molecular structure is difficult to interpret due to the number of parameters involved in the correlation.

Quantum chemical continuum solvation models<sup>1</sup> instead allow the prediction of molecular properties from first principles, and, therefore, they are not required to know the property experimental value in advance, and moreover their



results have a more transparent physical meaning allowing a clear interpretation of the phenomena.

In light of the results of the present article, we can say that the SM2 and SM3 models appear to be a better alternative than PCM and CPCM methods for the prediction of Henry's law constants of triazine derived herbicides. In addition, semiempirical calculations require much less CPU time than the DFT computations. Moreover, we want to stress the good agreement between the values of H reported by RIVM<sup>11</sup> with our results, in contrast to the values reported in the PHYSPROP<sup>10</sup> database. These great differences, 2 to 4 orders of magnitude, observed with respect to PHYSPROP values is attributed to the fact that these values are mainly obtained from the direct ratio of vapor pressure to solubility, a method which usually leads to significantly reduced accuracy like in the case of the present article.

Currently, quantum chemical continuous solvation models are being tested with other herbicides, and the results will be reported in future publications.

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