

Theoretical calculation of partition coefficients of dimethoxypyrimidinylsalicylic acids

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Abstract Despite their importance as herbicides, dimethoxypyrimidinylsalicylic acids has been poorly characterized from a physical-chemical point of view. This lack of information has prevented the assessment of their impact in the environment once they are released. In this study, environmentally important properties (free energy of solvation, Henry's law constant, octanol/air, and octanol/water partition coefficients) of 39 dimethoxypyrimidinylsalicylic derived compounds are calculated by density functional theory (DFT) methods at B3LYP/6-31G(d,p) level of theory using the Poisson-Boltzmann solvation model. These properties have not been reported previously for this family of compounds, neither experimentally or theoretically.

Keywords DFT · Calculation · Environmental partitioning · Herbicides · Thermodynamics

Introduction

The use of herbicides has allowed for significant reduction of weeds and consequently increased 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 reach an equilibrium between produc-

tivity and environmental protection. Among pesticides, the herbicides deserve special attention since new products are being steadily introduced to market because the resistance developed by weeds. 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, soil, and sediments which comprise our biosphere [1].

Dimethoxypyrimidinylsalicylic acids (DMPS) show potent herbicidal activity as a consequence of the inhibition of the acetohydroxyacid synthase enzyme. Unfortunately, DMPS derived compounds have been poorly characterized from their physico-chemical point of view. This lack of information has prevented the assessment of their impact in the environment, for instance in which environmental compartment they will tend to accumulate once they are released. The difficulty to obtain accurate experimental values arise from the limitations of analytical techniques to measure the solute concentration in both phases in equilibrium. For this reason, along with motives of cost, time and safety; it is desirable to be able to predict them.

Free energy of solvation ΔG_S^0 , in addition to its fundamental interest, may combined with other thermodynamic data to predict a variety of equilibrium constants, being one of the most important the partitioning of a solute between two immiscible phases. Therefore, ΔG_S^0 is a key property to estimate the fate of a chemical once it is released in the environment. From an environmental point of view, three of the most important partition coefficients are the Henry's law constant (H), the octanol/air (K_{OA}), and the octanol/water (K_{OW}) partition coefficients which can be calculated straightforwardly from the free energies of

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solvation in water and octanol by means of the following equations [2–4]:

$$\ln H = \ln(RT) + \Delta G_s^0(\text{water})/RT \quad (1)$$

$$\log K_{OA} = -\Delta G_s^0(\text{oct})/2.303RT \quad (2)$$

$$\log K_{OW} = \{\Delta G_s^0(\text{water}) - \Delta G_s^0(\text{oct})\}/2.303RT. \quad (3)$$

In this article, continuing with the physicochemical characterization of this family of compounds, initiated in an earlier paper [5], we report environmentally important partition coefficients, Henry's law constant, octanol/air and octanol/water partition coefficients, for 39 DMPS based herbicides, Fig. 1. These coefficients are determined using the above equations and the free energies of solvation, obtained by density functional theory (DFT) calculations using the Poisson-Boltzmann Solvation model (PB). To our knowledge the partition coefficients for this important family of herbicides have not been reported earlier, neither theoretically or experimentally.

Computational methods

Initial three-dimensional geometries of the chemical structures were generated using Hyperchem 7.0 molecular modeling package [6]. These 3D structures were refined later using the Jaguar package [7] and its graphic interface Maestro [8]. Gas-phase molecular geometries and electronic energies were obtained by density functional theory (DFT) calculations at the same level of theory, basis set including polarization functions on all atoms in conjunction with the hybrid functional B3LYP, which uses a combination of the three-parameter Becke exchange functional along with the Lee-Yang-Parr nonlocal correla-

tion functionals: B3LYP/6-31G(d,p). To determine the lowest-energy conformation for each molecule, geometry optimizations were carried out allowing one or more torsional angles to vary systematically. Free energies of solvation in water and octanol were computed by single point calculations, including implicit solvation, on the gas-phase optimized geometry using the Poisson-Boltzmann solvation model (PB) [9].

The reliability of the values of the solvation free energy in water, calculated using this solvation model and the same methodology, was confirmed in a recent article [5] via the calculation of the acid-dissociation constant for this family of compounds. The calculated pK_a values were validated by two checking tests based on the Hammett equation.

Results

The calculated free energies of solvation in water and octanol, along with the respective values of the Henry's law constants, the octanol/air partition, and the octanol/water partition coefficients are shown in Table 1. From this table it is possible to observe that all these compounds have low values of gas/solvent partition coefficients, consequently they show low volatility and a clear preference for the condensed phases. The preferred condensed phase, either water or octanol, is determined by the value of K_{OW} . The calculated values of $\log K_{OW}$ range from -0.50 to about 3.0 , breaking down in the following way: two cases, compounds 35 and 39, with negative values; three cases, compounds 24, 26 and 38, with values greater than 2; and the remaining compounds having intermediate values between 0 and 2.

Those with negative values show preference for the aqueous phase. This behavior is explained, in the case of compound 35, by the high polar nature of the sulfonyl group which provides a highly hydrophilic character. Moreover, it is well known that sulfones are able to stabilize negative charges on neighbor atoms, such as those of the carboxylic group. On the other hand, in compound 39, the hydroxyl group in *meta* position with respect to the carboxylic group strengthens the acidity by inductive effect, favoring in consequence its water solubility.

The compounds with values of $\log K_{OW} > 2$ will have preference for the octanol phase. This behavior is explained in terms of the high hydrophobic character provided by the OC_6H_5 and NO_2 substituent groups present in compounds 24, 26, and 38. This finding is in agreement with the empirical evidence of the surprisingly low solubility in water of these compounds, therefore in the ambient they will be preferably found in the lipids of aquatic and animal biota and potentially they could scale in the food chain.

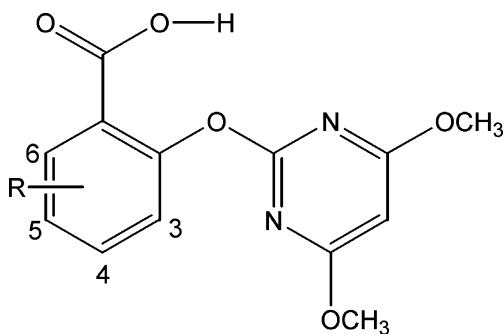


Fig. 1 Structure of R-substituted dimethoxyypyrimidinylsalicylic acids

Table 1 Calculated free energy of solvation in water and octanol, Henry's law constant, octanol-air partition coefficient and octanol-water partition coefficient for R-substituted O-pyrimidinylsalicylic acids

	R	$\Delta G_S^0(\text{water})$ (kJ mol ⁻¹)	$\Delta G_S^0(\text{octanol})$ (kJ mol ⁻¹)	H (Pa m ³ mol ⁻¹)	K _{OA}	Log K _{OW}
1	6-H	-44.22	-49.20	4.44E-05	4.17E+08	0.87
2	6-F	-42.80	-48.79	7.88E-05	3.53E+08	1.05
3	6-Cl	-43.39	-47.82	6.21E-05	2.39E+08	0.78
4	5-F	-42.47	-48.20	9.00E-05	2.78E+08	1.00
5	5-Cl	-40.46	-46.74	2.02E-04	1.54E+08	1.10
6	3-F	-43.89	-48.41	5.08E-05	3.03E+08	0.79
7	5,6-(Cl) ₂	-40.79	-46.11	1.77E-04	1.20E+08	0.93
8	6-C ₆ H ₅	-49.75	-55.10	4.77E-06	4.51E+09	0.94
9	6-CH ₃	-38.99	-45.69	3.66E-04	1.01E+08	1.17
10	6-C ₂ H ₅	-40.25	-45.77	2.20E-04	1.05E+08	0.97
11	6-C ₃ H ₇	-39.96	-45.35	2.48E-04	8.84E+07	0.94
12	6-CF ₃	-42.09	-47.99	1.05E-04	2.56E+08	1.03
13	5-CH ₃	-43.64	-48.33	5.61E-05	2.93E+08	0.82
14	5-C ₂ H ₅	-42.30	-47.78	9.64E-05	2.35E+08	0.96
15	5-CN	-52.93	-64.22	1.32E-06	1.79E+11	1.98
16	5-CCH	-44.35	-53.76	4.22E-05	2.63E+09	1.65
17	3-CH ₃	-44.89	-45.40	3.39E-05	8.99E+07	0.09
18	6-OCH ₃	-43.43	-52.43	6.11E-05	1.53E+09	1.58
18	6-OC ₂ H ₅	-42.89	-51.76	7.60E-05	1.17E+09	1.55
20	6-OC ₃ H ₇	-42.47	-51.55	9.00E-05	1.07E+09	1.59
21	6-OCH(CH ₃) ₂	-48.74	-54.77	7.17E-06	3.94E+09	1.06
22	6-OC ₄ H ₉	-41.63	-51.34	1.26E-04	9.87E+08	1.70
23	6-OCHF ₂	-45.06	-55.23	3.17E-05	4.74E+09	1.78
24	6-OC ₆ H ₅	-37.74	-54.35	6.07E-04	3.33E+09	2.91
25	5-OCH ₃	-45.98	-54.81	2.18E-05	4.01E+09	1.55
26	5-OC ₆ H ₅	-39.08	-56.74	3.53E-04	8.71E+09	3.09
27	6-SCH ₃	-45.06	-50.12	3.17E-05	6.05E+08	0.89
28	6-SC ₂ H ₅	-44.98	-50.58	3.27E-05	7.29E+08	0.98
29	6-SC ₃ H ₇	-44.77	-50.25	3.56E-05	6.37E+08	0.96
30	5-SCH ₃	-43.64	-48.33	5.61E-05	2.93E+08	0.82
31	6-CO ₂ CH ₃	-52.26	-59.41	1.73E-06	2.57E+10	1.25
32	6-COC ₆ H ₅	-55.31	-61.21	5.07E-07	5.30E+10	1.03
33	6-COCH ₃	-55.61	-59.12	4.49E-07	2.28E+10	0.61
34	6-NO ₂	-50.25	-61.42	3.90E-06	5.77E+10	1.96
35	6-CH ₃ SO ₂	-76.36	-74.64	1.04E-10	1.20E+13	-0.30
36	6-NH ₂	-53.76	-57.24	9.47E-07	1.07E+10	0.61
37	5-NH ₂	-65.73	-66.32	7.58E-09	4.16E+11	0.10
38	5-NO ₂	-48.41	-61.04	8.20E-06	4.96E+10	2.21
39	5-OH	-69.50	-66.40	1.66E-09	4.30E+11	-0.54

Discussion

The validation of the calculated figures unfortunately cannot be made in a direct way since for this family of compounds there is no experimental data available to check the calculated values. However, indirectly we can have an estimation of their reliability. For instance, in a recent paper Qiao *et al.* [10] reported the following model, based on the fragmental method, to predict the log K_{OW} of

halogenated benzoic acids in terms of certain group and factor values:

$$\log K_{OW}^{HBz} = \sum_{i=1}^{11} n_i g_i + \sum_{j=1}^2 l_j f_j + 1.117 \quad (4)$$

where n_i is the number of i -type groups, g_i is the value of the group i , l_j is the number of j -type factors, f_1 and f_2 denote the factors for *ortho* and *para* substituents,

respectively. The model reproduces the experimental data of $\log K_{OW}$ for halogenated benzoic acids with an average absolute error of 0.22 log units. Since, the DMPS-compounds of our study can be viewed as benzoic acids substituted in the *ortho* position with a *O*-dimethoxypyrimidinyl (ODMP) group, we hypothesize this model should be also valid to our compounds. If it is so, we could apply the model to determine the group value for the ODMP group using our calculated values of $\log K_{OW}$ and the group and factor values reported by Qiao for the analog *R*-substituted benzoic acids. The results of these calculations are shown in Table 2; the resulting mean is -0.768 . If this value for the ODMP group is correct, we should be able to reproduce the experimental values of $\log K_{OW}$ for *R*-substituted benzoic acids from the calculated $\log K_{OW}$ for the analog *R*-substituted DMPS acid, since structurally benzoic acids can be viewed as DMPS acids without the ODMP group; therefore the application of Eq. 4 leads to the following equation:

$$\log K_{OW}^{HBz} = \log K_{OW}^{DMPS} - g_{ODMP} - f_2 - \Delta g \quad (5)$$

where g_{ODMP} is the value for the ODMP group, f_2 is the factor value for *ortho* substituents, and Δg accounts for the difference in the group value of the benzene ring with two and three substituents. The results of these calculations are shown in Table 3. The average absolute error of $\log K_{OW}$ is 0.26, quite comparable with the reported error (0.22) for the original data set of halogenated benzoic acids. This result allows to confirm the quality of the values of K_{OW} calculated in this study, and also it validates the applicability of Eq. 4 for this family of compounds.

The value of the Henry's law constant is determined fundamentally by the free energy of solvation in water according to Eq. 1. The reliability of the methodology used in this article to calculate ΔG_S^0 in water was confirmed in an earlier article [5], and consequently the values of H derived from it.

Since the calculated values of K_{OW} and H are supported by the above checking procedures, then the calculated

Table 2 Group values for the *O*-dimethoxypyrimidinyl group (ODMP)

Substituent	ODMP group value
6-H	-0.679
6-F	-0.260
6-Cl	-1.039
5-F	-0.726
5-Cl	-1.135

Table 3 Experimental and calculated $\log K_{OW}$ for benzoic acids

Compound	Exp. $\log K_{OW}$ [9]	Calc. $\log K_{OW}$ (Eq.4)
Benzoic acid	1.87	2.06
<i>o</i> -chlorobenzoic acid	2.05	1.87
<i>m</i> -chlorobenzoic acid	2.68	2.19
<i>o</i> -fluorobenzoic acid	1.77	2.14
<i>m</i> -fluorobenzoic acid	2.15	2.09

values of K_{OA} should also be checked considering that these three coefficients are related by the well known equation [11]:

$$K_{OA} = RT \frac{K_{OW}}{H} \quad (6)$$

Thus, the plot of K_{OA} , calculated according to Eq. 2, vs. (K_{OW} / H) should give rise to a straight line whose slope equals to RT . The plot, shown in Fig. 2, confirm this fact and therefore supports the calculated values of K_{OA} . Moreover, the value of the slope corresponds to the value of RT at 298 K, within the error of the methodology.

Conclusions

Environmentally important properties, free energy of solvation in water and octanol, Henry's law constant, octanol/air, and octanol/water partition coefficients of 39 dimethoxypyrimidinylsalicylic derived compounds are reported for the first time. The reliability of the calculated

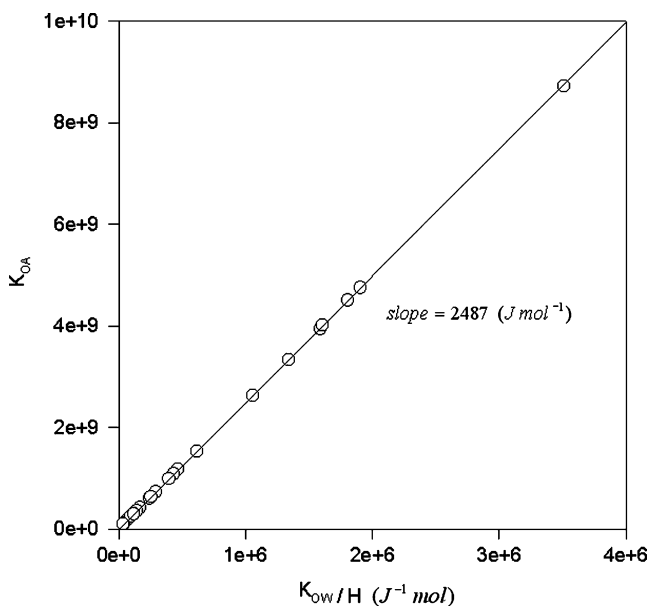


Fig. 2 Calculated K_{OA} (Eq. 2) vs. (K_{OW} / H)

values is confirmed by individual checking tests. The values of K_{OA} indicate that all these compounds show low volatility and therefore a clear preference for the condensed phases either water or octanol. The results also show that considering these compounds as neutral species, two of them, 35 and 39, have preference for the aqueous phase; whereas three compounds, 24, 26 and 38, have preference for the octanol phase; therefore in the ambient they will be found in the lipids of aquatic and animal biota. The remaining compounds have an intermediate behavior between these two limit trends.

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References

1. Stangroom SJ, Lester JN, Collins CD (2000) Abiotic behavior of organic micropollutants in soils and the aquatic environment. A review: I partitioning. *Environ Technol* 21:845–863
2. Delgado EJ, Alderete JB (2002) On the calculation of Henry's law constant of chlorinated benzenes in water from semiempirical quantum chemical methods. *J Chem Inf Comput Sci* 42:559–563
3. Delgado EJ, Alderete JB (2003) Prediction of Henry's law constants of triazine derived herbicides from quantum chemical continuum solvation models. *J Chem Inf Comput Sci* 43:1226–1230
4. Cramer CJ (2002) *Essentials of computational chemistry: theories and models*. Wiley, Chichester
5. Delgado EJ (2009) DFT calculation of pK_a 's for dimethoxypyrimidinylsalicylic based herbicides. *Chem Phys Lett* 471:133–135
6. Hyperchem 7.0 (2002) Hypercube Inc, Gainesville
7. Jaguar, Version 7.0 (2007) Schrodinger, New York
8. Maestro, Version 8.0 (2007) Schrodinger, New York
9. Marten B, Kin K, Cortis C, Friesner RA, Murphy RB, Ringnalda MN, Sitkoff D, Honig B (1996) New model for calculation of solvation free energies: correction of self-consistent reaction field continuum dielectric theory for short-range hydrogen-bonding effects. *J Phys Chem* 100:11775–11788
10. Qiao Y, Xia S, Ma P (2008) Octanol/water partition coefficient of substituted benzene derivatives containing halogens and carboxyls: Determination using the shake-flask method and estimation using the fragment method. *J Chem Eng Data* 53:280–282
11. Meylan WM, Howard PH (2005) Estimating octanol-air partition coefficients with octanol-water partition coefficients and Henry's law constants. *Chemosphere* 61:640–644