XIX SBQT
Simpósio Brasileiro de Química Teórica 2017
12 a 17/Nov, 2017, Águas de Lindóia/SP, Brasil

Conformational Dependence of the Hydrophobicity of Fluorine-containing Agrochemicals

Authors: Daniela Rodrigues Silva, Matheus Puggina de Freitas, Joyce Karoline Daré

Universidade Federal de Lavras, Lavras-MG

Abstract:

Fluorine-containing compounds are an important subclass of bioactive organic molecules being present in around 20% [1] of current pharmaceuticals and 30% of agrochemical candidates [2]. For agrochemicals, hydrophobicity is a relevant parameter to be analyzed because some important environmental properties can be estimated from the octano/water partition coefficient (logP), such as soil sorption and bioconcentration. This primary measurement along with the pH-dependent distribution coefficient ($logD_{ph}$) have been exhaustively used to explore the structure-property relationships of bioactive molecules, which gives insights about their solubility and interaction with physiologically relevant macromolecules and environments [3].

The controversial influence of fluorine in logP has caught attention of many researchers in the last years, mainly, because flaws were found in the generalization that a change of a hydrogen with a fluorine substituent on a carbon atom always results in a lipophilicity increment [4]. Therefore, the present project aims to determine the conformational isomerism of some fluorine-containing agrochemicals (Pyroxsulam, Penoxsulam, Trifluralin, Ethalfluarin e Flumioxazin) and correlate their molecular dipole moment with the respective logP data, in order to show the subtle dependence of the hydrophobicity with the molecular conformation. Thus, compounds with and without rotamers originated from the rotation around the C-C(F) bonds will be taken into account. Those whose C-C(F) rotation yields different rotamers have dependence of the molecular dipole moment (and, therefore, of logP) with the rotation around this bond.

Therefore, to guarantee uniformity in the experimental measurements used, the logP values for the whole set of molecules were selected from a unique producer (Safety Data Sheet available in the website of **The Dow Chemical Company**). Next, the molecular dipole moment values for the agrochemical molecules were obtained from their optimization using the computational method ωB97X-D/6-31g(d,p) available in the *Gaussian 09* software. Finally, a correlation plot was built (dipole moment *vs.* logP) including each relevant conformation of Penoxsulam and a tendency line was added, according to Figure 1.

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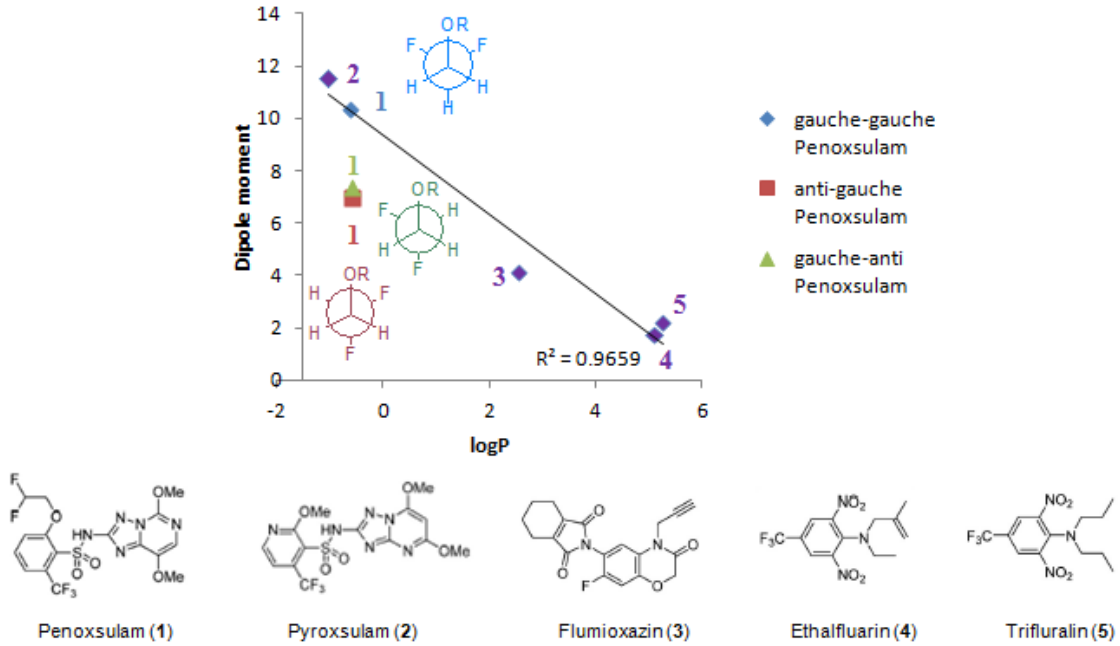

Figure 1. Plot of experimental logP *vs* calculated dipole moment (Db).

Based on the graph above, the *gauche-gauche* conformation of Penoxsulam is the only matching the linear correlation with the other compounds. This finding can be rationalized by the dominant conformation, which is stabilized by a double gauche effect owing to $\sigma_{CH} \rightarrow \sigma^*_{CF}$ and by $\sigma_{CH} \rightarrow \sigma^*_{CO}$ hyperconjugative interactions. Thus, subtle structural changes describe accurately the lipophilicity of fluorine-containing agrochemicals. Now, we aim to increase the number of fluorine-containing compounds in order to feed the model and make the correlation more reliable.

Key-words: Fluorine-containing agrochemicals, logP, molecular dipole moment.
Support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) e Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq)

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