Theoretical pKa prediction of halogenated compounds in aqueous solution using an implicit solvation model

Evellyn E. Soares¹, Vytor P. Oliveira² e Bruna L. Marcial¹.

bruna.marcial@ifgoiano.edu.br

¹Núcleo de Química, Instituto Federal Goiano, Campus Morrinhos, Morrinhos, GO 75650-000, Brasil

²Computational and Theoretical Chemistry Group (CATCO), Southern Methodist University, Dallas, Texas 75275-0314, USA.

Keywords: pKa prediction, SMD, halogens.

Introduction

The pKa is one of the most important properties of drug compounds, since it is directly connected to their chemical and biological activity¹. Although, the calculation of pKa has received considerable attention and many different approaches were developed, accurate prediction of the pKa (with 1 unit) is still a challenging task. The pKa of compounds can be modified by including halogens substituents (F, Cl, Br and I), which are capable of altering the electronic structure of the compounds and their respective reactivity^{1,2}. There is a large number of drugs available on the market that have some halogenated substituent in order to increase the potentiality of the drugs². The present study aims to explore theoretical methods of acidity prediction based on the pKa calculation of halogenated compounds with pharmaceutical.

Methodology

In this work, the pKa values of a set of 18 halogenated compounds in aqueous medium were carried out with the density-based solvation model (SMD)³ and the hybrid exchange-correlation functional M06-2X with the 6-31+G(d,p) basis sets. The effect of including explicit water molecules on the calculated pKa's was assessed by having one water molecules at the protonated site. The experimental data were compared with the results obtained, to verify the method accuracy.

Results and Discussion

The results obtained for the carboxylic acid derivatives with halogens substituents showed deviations of less than 1.7 pKa units, the errors for the phenol derivatives were much higher (around 3.0 pKa units) compare to the experimental values. The inclusion of one explicit water forming a hydrogen bonding with the O at the phenol protonated group was found to reduce the error by about 1 pKa unit. Based on these results, the next step will evaluate the inclusion of two and three explicit water molecules on the phenol protonated site to verify the effect in the theoretical prediction. Finally, the hydrogen bond effect at the pKa values can be analyze.

Conclusions

On the basis of the molecules studied here, M06-2X/6-31+G(d,p) is a good approach to predict pKa values for carboxylic derivatives. However, to obtain accurate pKa values without resulting to statistical adjustment or thermodynamic cycles, the addition of at least one explicit water on the protonated site is required.

Acknowledgments

PIBIC-IF Goiano SMU

References

- [1] Manallack, D. T. et al. Chem. Soc. Rev. Aug. 2013, v. 42, p. 485-497.
- [2] Ghalami-Chooabar, B et al. Inter J. Quant. Chem. 2012, v. 112, p. 2275-2280.
- [3] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G., J. Phys. Chem. B 2009, 113, 6378-6396.