

Theoretical Calculation of pKa Values of Amidines in Aqueous Solution Using an Implicity Solvation Model

Authors: Bruna L. Marcial^{1,2}, Elfi Kraka²

Address: ¹Núcleo de Química, Instituto Federal Goiano, Campus Morrinhos, Morrinhos, GO 75650-000, Brazil ²Computational and Theoretical Chemistry Group (CATCO), Department of Chemistry, Southern Methodist University, Dallas, Texas 75275-0314, USA.

Abstract: Amidines are special nitrogen analogues of the carboxylic acid, containing two N of different functionality. One is formally single bonded like-amino nitrogen (N^1) and the other is a formally double-bonded imino nitrogen (N^2) , where protonation occurs first. The pKa's of amidines vary from neutral to slightly acidic (pKa ranges from 4.4 to 14) depending on their substitution pattern. Amidines are present in numerous bio-related compounds and can be found important medicinal and biochemical agents [1]. Since there are no theoretical studies on the reliability of computational methods in the prediction of the pKa's of amidines. A benchmark of different computational methods against experimentally determined pKa values available in the literature is necessary to validate a reliable protocol, which could be used to make accurate predictions for complex systems containing an amidine group.

The pKa is one of the most important properties of drug compounds, since it is directly connected to their chemical and biological activity. 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. In this work, we have calculated the pKa values of a set of 16 amidines. From these set, 12 amidines had their values compared against experimental values, and the other 4 were possible candidates to be tested as enedyines warhead for the development of a new pH sensitive cancer drug [2]. Calculations in aqueous medium were carried out with the density-based solvation model (SMD)[3] and three hybrid exchange-correlation functionals (B3LYP, M06-2X and MN15) with two basis sets (6-31+G(d,p)) and 6-311++G(d,p)). The effect of including explicit water molecules on the calculated pKa's was assessed by having up to one water molecule at the protonated site.

The inclusion of one explicit water forming a hydrogen bonding with the imino N was found to reduce the error by about 1 pKa unit, whereas the addition of another water molecule did not improve the pka values. Among the DFTs tested B3LYP is the least reliable with errors larger than 2 pKa units. The most reliable method is M06-2X combined with 6-31+G(d,p) basis set and one explicit water (mean unsigned error MUE = 0.57 ± 0.82). However, MN15 with 6-311++G(d,p) basis set and one explicit water performed similarly well (MUE = 0.85 ± 0.86) as illustrated in Figure 1. On the basis of the molecules studied here, MN15/6-311++G(d,p) and M06-2x/6-31+G(d,p) with one



explicit water can be used to calculate pKa's directly without the need for statistical adjust or thermodynamic cycles.



/v~-m-Bromophenyi,/v~,/v~-dimethyilormamidines

Figure 1. Linear correlation of experimental pKa's [1] and values calculated by using new DFT functional MN15 with SMD solvation model and the arrangement of one explicit water in the protonated site.

Key-words: Amidine. Acid dissociation. Polarization solvation model.

Support: This work has been supported by NSF-CHE 1464906, SMU, IFGoiano

References:

- Saul Patai, Z. R., Ed. Amidines and Imidates; John Wiley & Sons, Ltd., 1991; Vol. 2; pp 1–918.
- [2] Kraka, E.; Cremer, D. Mol. Sci. 2014, 4, 285–324.
- [3] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G., J. Phys. Chem. B 2009, 113, 6378–6396.