Tautomerizmu pasižyminčių junginių rūgštingumo konstantų modeliavimas tankio funkcionalo teorijos metodais

DFT predictions of acidity constants for compounds exhibiting tautomerism

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Consideration of tautomeric species in the field of computer-aided drug design represents significant challenges. Different tautomers of the same molecule typically exhibit different properties such as hydrophobicity or acidity constant, pK_a, and they might even adopt considerably different spatial arrangements. For these reasons the pharmacological activity of the different tautomeric forms can also be rather different. For example, proteins are known to often preferentially bind the tautomer which has lower abundance in aqueous solution. Because the tautomerization rates are typically high, measured properties like pK_a are averages over all tautomers, unless experiments have been specifically designed to detect only one of the tautomers. Because microscopic pK_a values for specific tautomers are rearly known, it is thus difficult to train the so-called empirical QSPR or QSAR approaches in order for these methods to predict tautomeric pK_a values with acceptable accuracy.

Problems met herein can be in principle lifted by using electronic structure calculations of molecular thermochemical properties. These calculations can be combined with different thermodynamic cycle based schemes to provide the acidity or tautomeric equilibrium constants, pK_a and pK_T, respectively. The accuracy of these approaches depends on the reliability of the electronic structure method and solvation model, as well as on the nature of the thermodynamic cycle. While satisfactory agreement of predicted and experimental acidity constants has been documented, generally valid conclusions have not yet been reached, and theoretical predictions of the pK_a values for (drug-like) molecular compounds is thus still an active research area.

We have recently demonstrated that computational schemes based on density functional theory (DFT) methods, on the so-called SMD solvation model and on the so-called proton exchange thermodynamic cycle provide accurate predictions of acidity constants for the family of primary benzenesulfonamides [1]. In present work, we aim to test similar computational strategies in the predictions of acidity and tautomeric equilibrium constants for the 2-, 3- and 4-phenacylpyridines, see Fig. 1. The underlying pK_a and pK_T constants for different tautomeric forms of these molecules have been reported [2]. Our approach involves the use of two different DFT functionals as well as a couple of one-electron basis sets of different quality. We have also considered the composite CBS-QB3 approach for extremely accurate predictions of gas-phase thermochemical properties. We have relied on the SMD solvation model. We have considered both the direct and the proton exchange thermodynamic cycles for the calculation of acidity constants.

We were able to demonstrate that computed acidity constants for 5 different tautomeric forms of each molecule in neutral and cationic states are typically overestimated as compared to experimental data when direct thermodynamic cycle is employed. The errors are smaller when larger Dunning type cc-pVTZ basis set is used as compared to the Pople style 6-31G* double-zeta basis, yet most importantly these errors are found to systematically follow a rather linear trend. The use of proton exchange thermodynamic cycle has lead to improved pK_a values in some cases, yet achievable errors were found to be difficult to control as different reference compounds had to be used for different tautomeric forms.

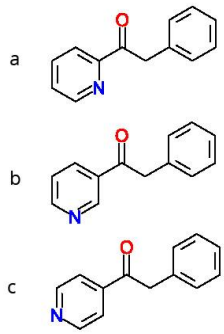

Figure 1. Molecular structure of 2-, 3- and 4-phenacylpyridine, a, b and c, respectively.

Keywords: acidity constant, density functional theory, thermodynamic cycle.

Acknowledgment
Computations were performed on resources at the High Performance Computing Center „HPC Sauletekis“ of Vilnius University. A.C. acknowledges support from Lithuanian Ministry of Education and Science.

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