CORRELATION OF pK_a VALUES FOR SERIES OF BENZOIC ACIDS WITH THE THEORETICALLY CALCULATED ATOMIC CHARGES

Ž. J. Vitnik,[1] V. D. Vitnik,[2] S. V. Pokorni[1], I. O. Juranić[2]

[1] *Faculty of Chemistry, University of Belgrade, Belgrade, Serbia*
[2] *Department of Chemistry, IChTM, University of Belgrade, Belgrade, Serbia*

Abstract
The four-parameter linear-regression involving partial atomic charges was defined of all atoms of carboxylic group, as the quantum-chemical descriptor for predicting physico-chemical properties (pK_a). Based on these four-parameter equations, the new QSPR equations for prediction of pK_a values of series of benzoic acids have been derived.

Introduction
The acid dissociation constant, K_a, which describes the extent to which the compound dissociates in the gas phase or in the solution, is a fundamental property of many chemical compounds. It is a key feature which governs the chemical reactivity of the substances in any solvent, and the interaction with the solvent itself. In aqueous solution, the pK_a is responsible for several pharmacokinetic properties. Jointly with integrity, lipophilicity, solubility, and permeability, pK_a has been considered as one of the five key physico-chemical profiling screens to predict the key properties that affect ADME(T) characteristics [1].

Computational details
Two semiempirical models MNDO-AM1 and MNDO-PM3 from MOPAC program package version 7.01 have been used in this work, and the solvent has been simulated by COSMO model implemented in it. Program Gaussian 03 has been used for *ab initio* calculations at the HF/6-311++G** and B3LYP/6-311++G** levels, in vacuum and with the simulation of solvent (water) by CPCM model.

The geometries of all conformers are fully optimized; energies of conformers were calculated, as well as the atomic partial charges on all atoms of COOH group. The Boltzmann analysis was used for calculation of statistical contribution of conformers in equilibrium, N_i. By summing contribution of conformers N_i and charges for an atom $q_{i,A}$ by equation:

$$Q_A = \sum_i N_i \, q_{i,A}$$

we defined a new, so-called, 'equilibrium' charge Q_A [2].

Results and Discussions

The partial atomic charges of all atoms for carboxylic group, are exploited as quantum-chemical descriptors for estimating physico-chemical properties [3,4], such as pK_a, through a four-parameter linear regression equation, defined as:

$$pK_a = Aq(H) + Bq(\text{-O-}) + Cq(=O) + Dq(C) + E$$

where q(H), q(-O-), q(=O), q(C) are the partial atomic charge on hydrogen atom, hydroxylic oxygen, carbonyl oxygen, and carbon atom of the carboxylic group, A, B, C and D are parameters for corresponding descriptors, and E is interception on the y-axis.

In order to determine the applicability of the equation, as well as to find the most useful types of partial atomic charges (Coulson, Mulliken, NBO, ...), and the best calculation method for estimation of partial charge descriptors (AM1, AM1-COSMO, PM3, PM3-COSMO, HF/6-311++G**, HF/6-311++G**/CPCM, B3LYP/6-311++G**, B3LYP/6-311++G**/CPCM) for predicting pK_a values, the correlations have been made with series of benzoic acids that can exist in solution in different conformations and in differently charged states (cationic, anionic and zwitter-ion).

Correlation results of the four-parameter equation have been compared with the results acquired by other equations.

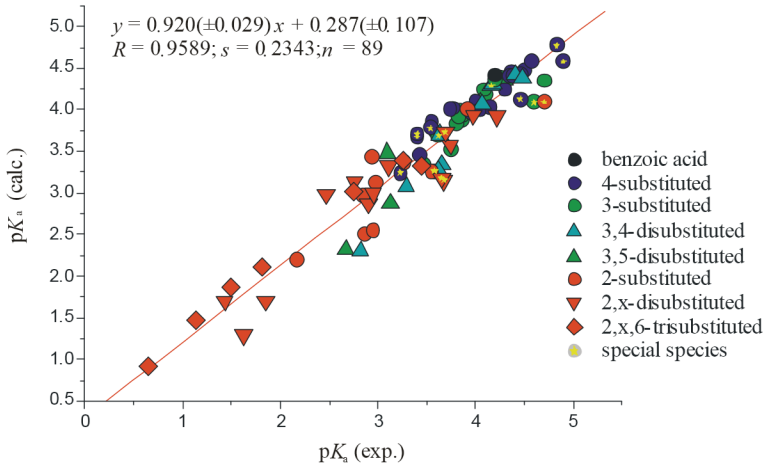

Figure 1. Relation between experimentaly determined and calculated pK_a values for series of 89 substituted benzoic acids.

For a series of 89 benzoic acids the best result was obtained from correlation of 'equilibrium' Mulliken charges obtained with semiempirical PM3 model with the simulation of solvent (water) by COSMO model. New QSPR equations for prediction of pK_a values for benzoic acids have been suggested based on this four-parameter equation:

$$pK_a(\text{calc.}) = -100.43Q_M(\text{H}) - 39.70Q_M(\text{-O-}) - 54.77Q_M(\text{=O}) - 68.81Q_M(\text{C}) + 29.02$$

and result of correlation is shown on Fig. 1.

Conclusion

This four-parameter equation has produced better correlation results in almost all series of benzoic acids we have examined, thus proving that partial charges of all atoms of carboxylic group must be used to obtain good QSPR equations for prediction of pK_a values. Unlike LFER equations, it can be successfully used to predict pK_a values of compounds with *orto*-substituents and/or other substituents that have no evaluated substituent constants.

It has been established that Coulson, Mulliken, and "natural" partial atomic charges obtained through semiempirical and *ab initio* calculations combined with our four-parameter equation produce good QSPR descriptors for prediction of pK_a values of benzoic acids. Analysis of the correlation results obtained, has shown that in order to provide good correlations, use of solvatation models (COSMO and CPCM) is mandatory in geometry optimization and calculation of atomic charges, as well as use of statistically averaged charges, calculated by Boltzmann analysis, in case when molecules can exist in multiple conformations or in states of different charge (cations, anions and zwitter-ions).

Comparing correlation results obtained by semiempirical models and those from *ab initio* models, it can be concluded that semiempirical models produce correlations that - in most situations - have similar or even higher quality than those acquired from *ab initio* models. It can be inferred that use of sophisticated, and computationally demanding methods, is not obligatory for producing good correlations. A good correlation result, as well as good predictivity of equations thus obtained, can be achieved through use of semiempirical methods.

Acknowledgments

This work has been financially supported by Ministry of Education and Science, Republic of Serbia, under Grant No. 172035 and by EU FP7 project HP-SEE, http://www.hp-see.eu/, contract number 261499.

References

[1] H. Wang, J. Ulander, Expert Opin. Drug Metab. Toxicol. 2006, 2, 139-155.
[2] Ž. Vitnik, Correlations between physical and chemical properties of carboxylic acids with a calculated atomic charges, PhD thesis, Belgrade, 2011.
[3] B. Jovanović, I. Juranić, M. Mišić-Vuković, D. Brkić, Ž. Vitnik, J. Chem. Research (S), 2000, 506-507; J. Chem. Research (M), 2000, 1257-1264.
[4] L. Pfendt, B. Dražić, G. Popović, B. Drakulić, Ž. Vitnik, I. Juranić, J. Chem. Research (S), 2003, 247-248; J. Chem. Research (M), 2003, 501-514.