QSAR for the Prediction of the Basicity of Nitrogen Heterocycles

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The electronic structure of a molecule is responsible for all the oberserved physico-chemical properties; this implies the existence of relations between different properties of the same molecule. An investigation of the role of certain calculated quantities of the electronic structure in nitrogen heterocycles is the aim of this paper.

Nitrogen heterocycles with a lone pair of electrons show a bunch of similar properties where this lone pair electrons are responsible for. Therefore 55 heterocyclic compounds were selected that belong to the compound classes of substituted **pyridines**, **pyrazoles** and **imidazoles**. These compound set was carefully divided into a training (37) and test set (18), and different descriptors of the electronic states were calculated by using the semi-empirical SCF-MO software MSINDO [1]. We have investigated the electronic structure of similar compounds of that family to predict some properties:

- proton affinity (gas phase)
- pK_B (condensed phase)
- complexation with Zn-cation

We thereby expect a relationship between the proton affinity, the pK_b-value and the strength of metal complexation.

In multi-linear regression analysis the following descriptors were identified and marked as important:

- Q_N – the total charge of the nitrogen atom (hardness)
- E_{LLP} – the energy of 'localized lone pair' (softness by Klopman [2])
- My – the dipole moment of that molecule

Using this set of descriptors a model was built and validated that predicts the experimental data for proton affinity with an R^2 of 0.93 and a Q^2 of 0.91.

[1] K. Bredow, G. Geudtner, K. Jug, J. Comput. Chem., **2001**, 22, 861-887
[2] G. Klopman, J. Amer. Chem. Soc., **1968**, 90, 223-234