

Basicity of substituted 5-amino-3-mercapto-1,2,4-triazole derivatives: Theoretical study

Maksym Fizer^{1*}, Mikhailo Slivka¹, Ruslan Mariychuk², Vjacheslav Baumer³ and Vasil Lendel¹

¹*Organic Chemistry Department, Chemical Faculty, Uzhhorod National University, 46 Pidhirna Str., Uzhhorod 88000, Ukraine*

²*Department of Ecology, Faculty of Humanity and Natural Sciences, University of Prešov in Prešov, 17th November 1, Prešov 08116, Slovak Republic*

³*State Scientific Institution "Institute for Single Crystals" NAS of Ukraine, 60 Nauky Ave., Kharkiv 61001, Ukraine*

DFT modeling was applied to study the protonation and tautomeric equilibrium in the raw of 5-R-amino-3-mercapto-4-phenyl-1,2,4-triazoles, where R can be electron-donating methyl group, "electron-inactive" hydrogen atom and electron-withdrawing phenyl ring. The calculations were carried out by considering the Gibbs free energy of protonation reaction in water solution. According to the literature data[1], the nitrogen in position one of the triazole cycle was chosen as the protonation site.

The pKa values of basic compounds can be conveniently presented as deprotonation of conjugated acid: $BH^+(\text{solvent}) = B(\text{solvent}) + H^+(\text{solvent})$. This equation was used to calculate the pKa of nine model triazoles. The change in reaction's free energy was computed as $\Delta G = G[B(\text{solvent})] + G[H^+(\text{solvent})] - G[BH^+(\text{solvent})]$. An acidity constant is related to change in the standard Gibbs free energy of the reaction as $pK_a = G/2.303RT$ (where T is 298.15 K in our study).

For validation and calibration of the obtained values/chosen method, we provided a small calibration set of compounds with well-known pKa values. In the calibration set we included 18 nitrogen-containing heterocyclic compounds. All thermochemical corrections and optimized structures were computed at PBE/6-311G(d,p) level. For optimized geometries, a single point energy calculation was performed at PBE0-D3/6-311++G(2d,2p) level of theory with SMD solvation model. Very good correlation ($R^2=0.9533$) was found between the theoretical and experimental data.

It is interesting to note that 5-amino-1,2,4-triazole-3-thiones in thiol form are medium strength organic bases and their pKa are in the range of 4.0-6.2 which is between the pKa value of 3-amino-1,2,4-triazole and lutidine. Also, all considered S-methyl derivatives are more basic than analogues structures with carboxymethyl group, which can be explained by the electron withdrawing effect. The influence of groups near exocyclic nitrogen are in an agreement with the known fact that electron donating group increase basicity and electron withdrawing groups have opposite effect. Basicity increases in a raw $Ph < H < Me$, which is similar for 4-R-1,2,4-triazole cycle and for simpler amines: aniline < ammonia < methylamine. Thiones are very weak bases, but their basicity increases upon substituent near exo-nitrogen in the same order.

[1] M. Fizer, M. Slivka, R. Mariychuk, V. Baumer, V. Lendel. 3-Methylthio-4-phenyl-5-phenylamino-1,2,4-triazole hexabromotellurate: X-ray and computational study. *Journal of Molecular Structure* 1161 (2018) 226-236.

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