Theoretical Study of Alkaline Acetylation of p-Methylaniline

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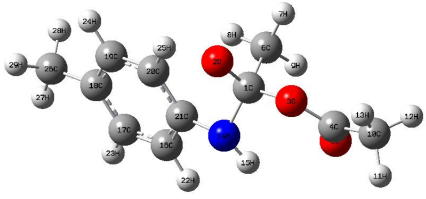
The acetylation of amines is one of the most frequently used transformations in organic synthesis as it provides an efficient and inexpensive means for protecting amino groups in a multistep synthetic process and the amide bond is found to be present in a large number of pharmacologically active molecules.

Acetylation of amine is a nucleophilic substitution reaction. This reaction is carried out with acetic anhydride in the presence of amine bases such as tertiary amine and pyridine. The nitrogen from the amine produces the nucleophilic attack on the carbonyl carbon of the anhydride to obtain tetrahedral intermediate, decisive step of the reaction rate. Subsequent loss of a proton will yield the amide and acetic acid as products.

Computational investigation[1] and an experimental work[2], agreed that this reaction takes place with the formation of a tetrahedral intermediate.

A theoretical study of alkaline acetylation of p-methylaniline from the analysis of intermediate of the reaction was carried out. Geometries of all species involved in the acetylation were made and identified. All of the geometry optimizations were performed by the method at the Density Functional Theory (DFT) with B3LYP level of theory and was adopted the 6-31G* basis set. Energies of all reagents and products and the energy of activation for the reaction were calculated using the MP2- 2nd order Mo/ller–Plesset method. Following the same procedure it was identified the geometric parameters and energy of intermediate.

The Figure show the optimized structure of the intermediate and the Table lists the geometric parameters, lengths and binding angles values, obtained. The calculations show 12.80 kcal/mol of activation energy.



Lengths	(Å)	Angles	(º)
r (C_1-O_2)	1.41	θ (C_1-O_3-C_4)	121.65
r (C_1-O_3)	1.46	θ (C_1-N-C_{21})	103.54
r (C_1-C_6)	1.54	θ (C_6-C_1-N)	116.78
r (C_1-N)	1.49	θ (N-C_1-O_2)	112.95
r (H_{15}-N)	1.00	θ (O_3-C_1-C_6)	110.49

1. X. Tong, Z. Ren, X. Qü, Q. Yang, W. Zhang, *Res.Chem Intermediat*. **2012**, 38, 1961-1968.
2. V. K. Yadav, K. G. Babu, M. Mittal, *Tetrahedron Lett*. **2001**, 57, 7047-7051.