

## Chapter 30

# Probing the Reactive Center for Site Selective Protonation in a Molecule by the Local Density Functional Descriptors

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### ABSTRACT

*In this study, the authors have explored the efficacy of the local density functional descriptors like the Fukui functions ( $f$ ), the local softness ( $s$ ) and the local philicity as probe for the reactive centers and site selectivity of the chemico-physical process of protonation of some molecules having multiple site for protonation, viz  $\text{CH}_3\text{NCO}$  (Methyl isocyanate),  $\text{CH}_3\text{NCS}$  (methyl isothiocyanate),  $\text{NH}_2\text{OH}$  (hydroxyl amine),  $\text{NH}_2\text{OCH}_3$  (*o*-methylhydroxylamine),  $\text{CH}_3\text{NHOH}$  (*N*-methylhydroxylamine),  $\text{NH}_2\text{CH}_2\text{COOH}$  (glycine),  $\text{CH}_3\text{CH}(\text{NH}_2)\text{COOH}$  (alanine) and  $\text{OHCH}_2\text{CH}_2\text{NH}_2$  (ethanol amine). The authors have seen in terms of the numerical values of the local descriptors measures the reactivity (nucleophilicity) of a particular atomic site of a donor center towards a proton. In all cases, it can be said that the dynamic chemico-physical process of site selectivity can nicely be correlated in terms of the computed values of the local descriptors. Thus, it is found that the theoretical descriptors of the DFT can be efficiently exploited to study the mechanism of site selectivity in a chemical reaction.*

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## INTRODUCTION

The protonation reactions or the physico-chemical process of protonation are ubiquitous in almost all the areas of chemistry and biochemistry (Stewart, 1985; Carrol, 1998; Zhao & Zhang, 2004; Kennedy, Mayhew, Thomas & Watts, 2003; Bouchoux, 2007). The majority of chemical reactions occur in acid medium. The chemical process of protonation is fundamental of many chemical rearrangements, and enzymatic reactions (Kennedy, Mayhew, Thomas & Watts, 2003). The resulting protonated molecule is frequently a pivotal intermediate that guides the succeeding steps of the overall process. The knowledge of the intrinsic basicity and the site of protonation of a compound are central for the understanding of the mechanism of chemical reactions. The legend proton affinity is defined as the negative of the enthalpy change of a protonation reaction at the standard conditions. The gas-phase proton affinities are a quantitative measure of the intrinsic basicity of a molecule (Deakyne, 2003). The study of thermochemistry of the proton transfer reaction in the gas phase is well-known experiment of acid-base reaction (Lias et al., 1984). Dynamics of proton transfer is also important for ionization processes in mass spectroscopy (Hansel, Oberhofer, Lindinger, Zenevich & Billing, 1999).

## THE PHYSICO-CHEMICAL PROCESS OF PROTONATION

In the physico-chemical process of protonation, when a proton dynamically approaches towards a nucleophile from a long distance, it is attracted by the electron cloud of the molecule. Thus a proton acting as an electrophile starts soaking the electron density from the entire skeleton of the nucleophile (Ghosh, 1976) and as a result, the electron cloud of the nucleophile is redistributed and remains under the influence of nucleus of the electrophile.

Ultimately the proton fixes at a site of lone pair—the site of protonation, of the molecule. However, if there is no lone pair in the structure of the molecule, the proton remains weakly attached to the sphere of the charge cloud of the molecule. The polarizing power of the proton induces a physical process of structural and energetic changes in the molecule. This phenomenon is, in particular, at the origin of the site of protonation, has considerable effect on the strength and length of the bonds (Bouchoux, 2007). The structural and energetic changes induced by the polarizing power of the proton are expected to be at its maximum at the gas phase of the molecule. Thus, the gas-phase basicity is certainly the ideal revelator of the structural and energetic characteristics of the molecular protonation process.

## THE PREFERRED SITE OF PROTONATION

If a molecule has more than one donor sites i.e lone pairs and if a proton approaches such a molecule, the proton will not find all the donor sites to be attacked equally likely. The proton will select the most preferred site in the structure of the molecule. In the dynamic process of protonation reaction, the preferred site may be identified by the attaching proton in a kinetic and thermodynamic process. But the selection of preferred site will be decided by the thermodynamically controlled process. When the proton is fixed at the preferred site, the enthalpy change is more and when the proton fixes at non-preferred site liberation of energy is less. The procedure follows the hierarchical steps:

1. Calculate energy of the molecule first,
2. Then attach proton at different probable sites to generated protonated species one after another, and
3. Then compute the energy of the protonated species theoretically and/or experimentally.

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