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Using conceptual density functional theory to rationalize regioselectivity: A case study on the nucleophilic ring-opening of activated aziridines

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ABSTRACT

Density functional theory calculations have been performed to rationalize the regiochemistry of the nucleophilic ring opening of activated aziridines. Atomic charges, lowest unoccupied molecular orbitals, Fukui functions and Fukui indices were calculated at the B3LYP/6-311G++(2d,2p) level of theory. Frontier molecular orbital theory, as well as the Fukui function were able to explain the experimentally observed ratios of opening products and a surprising change in regioselectivity upon nitrobenzenesulfonyl activation on the nitrogen. In addition, robustness of atomic charges and Fukui indices to the basis set quality was assessed.

1. Introduction

Nitrogen activated aziridines are versatile synthetic intermediates easily produced from β-amino-alcohols [1]. Stereo and regio-controlled nucleophilic opening of aziridines leads to highly valuable, 1,2-bifunctionalized chiral compounds and among them vicinal diamines are readily obtained [2]. Beside its interest in medicine and pharmacy, the 1,2-diamine moiety has taken a large place as chiral ligands in transition-metal catalyzed asymmetric synthesis [3].

During the last decades, density functional theory (DFT) has undergone fast development, especially in the field of organic chemistry, as the number of accurate exchange–correlation functionals increased. Indeed, the apparition of gradient corrected and hybrid functionals in the late 1980s greatly improved the chemical accuracy of the Hohenberg–Kohn theorem [4] based methods. The Kohn–Sham formalism [5] and its density-derived orbitals paved the way to computational methods. In parallel, a new field of application of DFT developed, the so-called conceptual DFT [6]. Parr and Yang followed the idea that well-known chemical properties as electronegativity, chemical potentials and affinities could be sharply described and calculated manipulating the electronic density as the fundamental quantity [7,8]. Moreover, starting from the work of Fukui and its frontier molecular orbitals (FMOs) theory [9], the same authors further generalized the concept and proposed the Fukui function $f(\vec{r})$ as a tool for describing the local reactivity in molecules [10,11].

The present study makes the use of DFT-derived reactivity descriptors to rationalize the regioselective ring opening of three types of activated aziridines and makes a comprehensive assessment of the electronic effects arising upon the different methods of activation. As aziridines consist in a three-membered ring with two electrophilic positions, the relative reactivity of these two electrophilic carbon atoms seems a perfect test for FMO theory and the Fukui function.

2. Theoretical background

Chemical DFT started to develop in the late 1970s with the identification of the chemical potential (μ) as the first derivative of the Kohn–Sham energy (E), with respect to the number of electrons (N) at constant external potential due to the nuclei ($v(\vec{r})$) [12]:

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(\vec{r})} = -\chi \tag{1}$$

The chemical potential (μ) is in fact the Lagrange multiplier from the normalization constraint of the DFT variational principle [13]. It should be noticed that the chemical potential is the negative of a well-known empiric chemical quantity, the electronegativity (χ). As a consequence of Eq. (1), electrons will have the tendency to flow from high μ zones to low μ zones until chemical potentials are equalized, μ being a global reactivity index of the

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molecule. Taking the derivative of μ with respect to the potential and applying the Maxwell relation, one can define the Fukui function [10,14]:

$$f(\vec{r}) \equiv \left(\frac{\partial \rho_{(\vec{r})}}{\partial N}\right)_{v(\vec{r})} = \left(\frac{\delta \mu}{\delta v(\vec{r})}\right)_N \tag{2}$$

However, owing to the discontinuity of N, at least two types of Fukui functions should be defined, one being the right-hand side and the other the left-hand side derivative at a given number of electrons ($N = N_0$):

$$f^+(\vec{r}) = \left(\frac{\partial \rho_{(\vec{r})}}{\partial N}\right)^+_{v(\vec{r})} \tag{3}$$

$$f^-(\vec{r}) = \left(\frac{\partial \rho_{(\vec{r})}}{\partial N}\right)^-_{v(\vec{r})} \tag{4}$$

A third type of Fukui function describing radical reactions can be used, as a mean of the two others:

$$f^0(\vec{r}) = \frac{1}{2}(f^+(\vec{r}) + f^-(\vec{r})) \tag{5}$$

Exploring the chemical significance of these functions, it can be seen that a site where the nucleophilic Fukui function $f^+(\vec{r})$ has a large value is a site capable of accepting electronic density and that a large value of $f^-(\vec{r})$ indicates an electron donating site. In other words, one measures the site reactivity towards nucleophilic attack while the other measures the site reactivity towards electrophilic attack. It should be emphasized that in the frozen core orbital approximation where orbital relaxation is neglected, these functions can be reduced to the squares of the lowest unoccupied and highest occupied molecular orbitals (respectively, the LUMO and the HOMO). Indeed, expressing the electronic density in terms of the Kohn–Sham spin–orbitals (Eq. (6)) and taking the derivative with respect to N, gives a mathematical expression of the Fukui functions as the frontier molecular orbitals plus a correct term that includes the orbital relaxation effects as seen in Eq. (7) and (8) [15]:

$$\rho(\vec{r}) = \sum_{i=1}^{N} |\phi^{(i)}_{(\vec{r})}|^2 \tag{6}$$

$$f^+(\vec{r}) = |\phi^{N+1}_{(\vec{r})}|^2 + \sum_{i=1}^{N}\left(\frac{\partial |\phi^{(i)}_{(\vec{r})}|^2}{\partial N}\right)_{v(\vec{r})} \approx |\phi^{\mathrm{LUMO}}_{(\vec{r})}|^2 = \rho^{\mathrm{LUMO}}_{(\vec{r})} \tag{7}$$

$$f^-(\vec{r}) = |\phi^{N}_{(\vec{r})}|^2 + \sum_{i=1}^{N}\left(\frac{\partial |\phi^{(i)}_{(\vec{r})}|^2}{\partial N}\right)_{v(\vec{r})} \approx |\phi^{\mathrm{HOMO}}_{(\vec{r})}|^2 = \rho^{\mathrm{HOMO}}_{(\vec{r})} \tag{8}$$

Practically, computing Fukui functions is not obvious and a solution is to take the finite difference approximation between the $N = N_0$ and $N = (N_0 \pm 1)$ electronic total densities, as expressed in the following equations:

$$f^+(\vec{r}) \approx \rho_{N+1} - \rho_N \tag{9}$$

$$f^-(\vec{r}) \approx \rho_N - \rho_{N-1} \tag{10}$$

Nevertheless, other schemes can be used to compute reactivity indices avoiding this rough estimation of derivatives due to the use of an integer change on N. These methods introduce fractional occupation numbers from Janak‘s theorem [16] to produce infinitesimal changes on the number of electrons [17–20]. The first method using the finite difference approximation has been employed in the present study.

A three dimensional representation of the functions is then obtained but a chemist's dream would be to assign indices to atoms, rather than dealing with spatially dependent functions. It therefore needs the integration of the Fukui function along the portion of space that could be attributed to a certain atom belonging to a molecule, leading to condensed to atoms Fukui functions (i.e. Fukui indices) [21]. This procedure is analogous to the condensation of the electronic density to atoms, leading to the assignment of atomic charges through population analysis or density partitioning [22]. We can thus describe, for the atom site k, Fukui indices (F^+ and F^-) in terms of atomic populations (p):

$$F_k^+ = \int \left(\frac{\partial \rho^k_{(\vec{r})}}{\partial N}\right)^+_{v(\vec{r})} d\vec{r} = \left(\frac{\partial p^k}{\partial N}\right)^+_{v(\vec{r})} = p^k_{N+1} - p^k_N = q^k_N - q^k_{N+1} \tag{11}$$

$$F_k^- = \int \left(\frac{\partial \rho^k_{(\vec{r})}}{\partial N}\right)^-_{v(\vec{r})} d\vec{r} = \left(\frac{\partial p^k}{\partial N}\right)^-_{v(\vec{r})} = p^k_N - p^k_{N-1} = q^k_{N-1} - q^k_N \tag{12}$$

Electrophilicity indices have recently been reviewed by Chattaraj et al. [23]. Reactivity indices were comprehensively discussed by Chermette [24].

Carving the molecular electronic density into its atomic constituents is far from trivial [25]. Different methods can be employed, often leading to significantly different results and misleading chemical interpretations. Moreover, it is not easy to choose the most appropriate method based on theoretical arguments. Three different charges schemes were used in the present study to compute atoms-in-molecules (AIMs) properties: Mulliken population analysis (MPA) [26] and natural population analysis (NPA) [27] as density matrix based methods and Hirshfeld partitioning (HP) [28–30] as a density method. Electrostatic potential fitted charges were not used as they are known to often produce unphysical results, despite the good reproduction of the multipolar environment of the molecule [31].

3. Computational details

All quantum mechanical calculations have been achieved using the Gaussian09 software package [32]. Geometries of all the investigated systems were optimized at the density functional theory level using the B3LYP functional (combination of exchange from Becke's three parameter hybrid exchange functional (B3) with the dynamical correlation functional of Lee, Yang and Parr (LYP)) [33,34]. The triple-zeta quality basis set with polarization and diffuse functions denoted 6-311G++(2p,2d) has been used. The bulk solvent effects (acetonitrile, toluene and N,N-dimethylformamide as in the experiments) have been included through the Integral Equation Formalism version of the Polarizable Continuum Model (IEF-PCM) [35]. All potential energy surface (PES) minima found upon optimization were confirmed by frequency calculation. Molecular orbitals and Fukui functions were rendered under GaussView; cube densities were generated and manipulated using the Cubegen and Cubman utilities from the Gaussian09 package. Conformational search was achieved at the molecular mechanics (MM) level of theory using the MM+ force field under Hyperchem 8.0 software, within a random generation scheme. Dihedral energy plots were generated with the same program at the Parameterized Model 3 (PM3) semi-empirical level of theory.

4. Investigated reactions

The herein studied reactions involve the nucleophilic ring opening of three activated aziridines, one neutral and two cationic species. Obviously, these reactions can occur on two positions (the carbons C_2 and C_3, see Scheme 1) affording distinct regioisomers with an inverse stereochemistry.