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CHIH-DFT determination of the reactivity sites of the antiparasitic drug megazol

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Abstract

By using the CHIH-DFT (Density Functional Theory for Heterocyclic Systems) model chemistry, we have calculated some properties related to the reactive behavior, such as the electronegativity, E_{HOMO}, E_{LUMO}, gap energy, hardness, electron affinity and ionization potential, as well as the chemically active sites indicated by Fukui functions of the megazol molecule, an antiparasitic drug particularly effective against trypanosomes.

Keywords: Chagas disease; Sleeping sickness; Electronegativity; Hardness; Fukui functions; Chemical reactivity

1. Introduction

There are two diseases that affect millions of people in the world, the American trypanosomiasis or Chagas disease in America and the African trypanosomiasis or sleeping sickness in Africa [1]. Both are caused by a protozoa of the mathisgosphore class, the *Trypanosoma cruzi* and the *Trypanosoma brucei*, respectively [2].

Several compounds have been studied against these illnesses, but none of them are able to stop the disease in the chronic stages [3].

Megazol, a drug synthesized in 1968 and subsequently discarded because of its mutagenicity risk, is a nitroheterocyclic compound with antiparasitic activity particularly against trypanosomes [4]. Until now the mode of action of this drug is not known, but there is evidence that the key in the reaction mechanism is the reduction of megazol to its nitro radical anion [5].

The aim of this work is to determine the active sites of the megazol molecule by using the Fukui functions [6], as well as other properties derived from Conceptual Density Functional Theory that indicate the reactive behavior, such as the electronegativity, E_{HOMO}, E_{LUMO}, gap energy, hardness, electron affinity and ionization potential.

All this pretends to be an answer to the urgent need of new drugs against the protozoan parasites, and considering that as it takes a long time before a drug can be applied in humans, the governments and educational institutions have to give priority to the research and development of new ways to control these two sicknesses that affect the poorest people in the world.

2. Theory and computational details

By considering a model-chemistry specially designed to study heterocyclic compounds called CHIH-DFT (Density Functional Theory for Heterocyclic Systems), the megazol molecule has been characterized using the GAUSSIAN 03W program [7]. The PBE*g* functional was considered, which is analog to the PBE0 functional [8]. The difference resides in the *G* factor which is a measure of the amount of Hartree–Fock exchange incorporated in the hybrid functional, and whose value is dependent on the structure of the heterocycle being studied. For the megazol molecule it is equal to 0.205. The CBSB4 basis set was used and all this together is called CHIH(medium) theory. Look at the original papers for a complete description of the method [9–11].

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For the determination of the active sites of the megazol molecule, we have calculated the Fukui functions [6]. The Fukui function is a local property given by [12]

$$f(\vec{r}) = \left(\frac{\partial \rho(\vec{r})}{\partial N}\right)_{v(\vec{r})} = \left(\frac{\partial \mu}{\partial v(\vec{r})}\right)_N \quad (1)$$

where ρ is the electronic density of the system under consideration.

The condensed Fukui functions [6] are found by taking the finite difference approximations from Mulliken population analysis of atoms in molecules, depending on the direction of the electron transfer:

$$f_k^+ = q_k(N+1) - q_k(N) \quad \text{(for nucleophilic attack)} \quad (2)$$

$$f_k^- = q_k(N) - q_k(N-1) \quad \text{(for electrophilic attack)} \quad (3)$$

$$f_k^0 = \frac{q_k(N+1) - q_k(N-1)}{2} \quad \text{(for radical attack)} \quad (4)$$

where q_k is the gross charge of atom k in the molecule.

The energies of the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) were obtained applying the Koopmans theorem [13]. The frontier orbital energies are given by:

$$-E_{\text{HOMO}} = I \quad (5)$$

$$-E_{\text{LUMO}} = A \quad (6)$$

where I is the ionization potential and A is the electron affinity.

The value for the solvation energy was obtained through the calculation of the energy of megazol in the presence of water, by resorting to a modification of the Polarized Continuum Model (C-PCM) [14].

3. Results and discussion

Considering that any chemical system (atom, molecule, ion, radical) is characterized by its electronic chemical potential, μ, and by its absolute hardness, η [13], we have calculated these parameters for the megazol molecule.

In this work we have used the operational approximate definitions [13]:

$$-\mu = \frac{I+A}{2} = \chi \quad (7)$$

and

$$\eta = \frac{I-A}{2} \quad (8)$$

The electronegativity shows the way in which the electrons will flow (from lower electronegativity to higher electronegativity) and hardness is one of the useful concepts which enable chemists to understand reactivities [15]. This concept will be useful in the attempts to determine the interaction mechanism with a possible bioreceptor for the molecule of megazol.

Table 1
Chemical parameters indicative of the reactive behavior of the megazol molecule calculated with the CHIH(medium) model

Parameter	Calculated result
E_{HOMO} (eV)	−6.67854
E_{LUMO} (eV)	−2.88606
Energy gap $=\Delta E_{\text{LUMO}-\text{HOMO}}$ (eV)	3.79248
$I=-E_{\text{HOMO}}$ (eV)	6.67854
$A=-E_{\text{LUMO}}$ (eV)	2.88606
$\chi=(I+A)/2$ (eV)	4.78230
$\eta=(I-A)/2$ (eV)	1.89624

The total energy of the molecule obtained from an energy calculation with the CHIH-DFT model is −30161.01556 eV. The energy gap or $\Delta E = E_{\text{LUMO}} - E_{\text{HOMO}}$ is 3.79248 eV, which means a good stability of the chemical system.

In Table 1 we present the calculated parameters obtained by means of the application of CHIH (medium) theory for the molecule of megazol as: E_{HOMO}, E_{LUMO}, gap energy, electronegativity, hardness, electron affinity and ionization potential.

The reactivity was analyzed through Fukui indices, since they indicate the reactive regions as well as the nucleophilic and electrophilic behavior in the molecule [16]. This kind of analysis was performed for each one of the atoms that conform the molecule of megazol.

In Table 2 we display the values of the electronic charge over each atom calculated through the Mulliken Population

Table 2
Atomic charges on the megazol molecule obtained by using Mulliken Population Analysis (MPA), Natural Population Analysis (NPA) and Electrostatic Potential Fitted Charges (ESP) methods

Atom	MPA	NPA	EPS
C1	0.026047	0.18687	−0.05407
S2	0.541813	0.43460	−0.08104
C3	−0.251025	−0.02115	0.06631
C4	−0.445835	0.17476	0.59929
N5	−0.147224	−0.25153	−0.02890
N6	−0.003507	−0.32686	−0.49097
N7	0.062670	−0.34306	−0.09338
C8	−0.064950	0.32511	0.37483
H9	0.261233	0.44696	0.33892
N10	−0.205124	−0.85998	−0.73049
H11	0.242574	0.44087	0.34903
N12	−0.021911	−0.45814	−0.45019
C13	0.089520	−0.03577	0.06867
C14	−0.255082	−0.52837	0.01784
H15	0.162658	0.27216	0.08191
H16	0.181036	0.28882	−0.05605
H17	0.162807	0.27236	0.11069
H18	0.154612	0.27519	0.13748
O19	0.168846	−0.37489	−0.45303
N20	−0.755627	0.48082	0.74248
O21	0.096466	−0.39877	−0.44932