Theoretical study on 5-nitrofuryl thiosemicarbazone radicals electronic properties

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Abstract

Theoretical studies of molecular conformations and electronic properties calculations of eight 5-nitrofuryl thiosemicarbazone free radicals, by means of ab initio (R/UHF), and DFT (R/UB3LYP) methods are presented and discussed in comparison with ESR and electrochemical experimental data. DFT calculated hyperfine coupling constants were used for the simulation of experimental spectra. We observed the molecules adopt mainly two conformations, both showing a pattern of spin density delocalization unusual for free radicals formed from aromatic nitrocompounds. Energy potential surfaces scaning through a determined dihedral angle were drawn to evaluate whether these conformations could coexist in equilibrium. Fukui and molecular orbital analysis were compared with ESR data as reactivity local indexes.

Keywords: Nitrofurane; Electronic properties; Fukui

1. Introduction

5-Nitrofuranes have found popular use in the treatment of parasitic infections because of their antiprotozoal–antibacterial activity [1]. In Latin America parasitic diseases represent a major health problem. In particular Chagas' disease (American Trypanosomiasis), caused by the protozoan parasite *Trypanosoma cruzi*, affects approximately 20 million people from Southern California to Argentina and Chile [2–3].

The current chemotherapy against this parasite is still inadequate due to its undesired side effects [4]. Previous investigations suggest that the mode of action of several drugs against *T. cruzi* involves the generation of radical species through a reductive pathway, which can cause cellular damage directly by reacting with various biological macromolecules, or indirectly by generation of the highly reactive oxygen species like the hydroxyl radical, which is generated via iron mediated Haber–Weiss and Fenton reactions [5,6]. Other modes of action could involve the interaction of the drugs with certain proteins acting as cysteine-protease inhibitors [7] or trypanothione reductase inhibitors [8,9].

For these reasons it is important to study the different conformations that potential antiparasitic drugs can adopt, and to determine how these conformations and their ability to generate free radical species are related, in order to get an idea on which conformations could promise higher biological activities.

Studies of nitrofuran families have been performed where the structural differences caused the variation of some electronic properties like the reduction potential or the hyperfine coupling constants [10]. On the other hand we have previously reported electrochemical and ESR studies on antiprotozoal 5-nitrofurfural and 5-nitrothiophene-2-carboxaldehyde derivatives. These have been shown to generate nitro anion radicals, which were characterized using ESR spectroscopy [11]. These techniques are now widely accepted and well developed as powerful tools in the identification of paramagnetic intermediates and other reaction products [12,13]. Likewise density functional methods are known as capable of providing reasonable predictions for ESR properties, the best results being obtained with the hybrid method B3LYP [14].

A theoretical study of molecular conformations of eight 5-nitrofuryl thiosemicarbazones, by means of a DFT (B3LYP) method is presented and discussed in comparison with ESR data (Fig. 1). A study of this kind was presented elsewhere [15]

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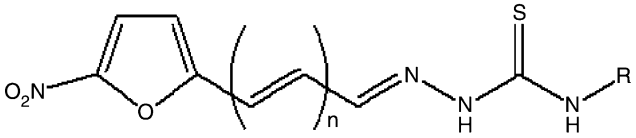


	n	R
NS1:	0	Ethyl
NS2:	1	Ethyl
NS3:	0	Phenyl
NS4:	1	Phenyl
NS5:	0	Methyl
NS6:	1	Methyl
NS7:	0	H
NS8:	1	H

Fig. 1. 5-Nitrofuryl thiosemicarbazones.

with semiempirical geometry optimizations. In order to maintain a consistency in the calculations, as hyperfine coupling constants were calculated using B3LYP, the same study is presented here with optimizations at a B3LYP/6-31G* level.

The objective of the present work is to study theoretically the electronic properties of a family of 5-nitrofuryl thiosemicarbazone radicals at a B3LYP level. The resulting data is compared with experimental electrochemical and ESR data presented by Rigol et al. (2005).

2. Theory, models and methods

Considering the importance of the evaluation of the ability of these drugs to accept electrons, we also explored a possible relationship between the electron affinity (EA) and the electrophilicity index, and the reduction potential obtained experimentally as the cathodic peak potential (E_{cp}). This latest (ω) is an important reactivity descriptor that measures the energy stabilization upon electronic saturation of the system when electrons flow from the surroundings with a higher chemical potential than that of the system [16]. The EA and the electrophilicity index were calculated using the equation given by Koopman's theorem [17]

$$\omega = \frac{\mu^2}{2\eta} = \frac{(\mathrm{IP}+\mathrm{EA})^2}{4(\mathrm{IP}-\mathrm{EA})} \cong \frac{(-\varepsilon_{\mathrm{HOMO}}-\varepsilon_{\mathrm{LUMO}})^2}{4(-\varepsilon_{\mathrm{HOMO}}+\varepsilon_{\mathrm{LUMO}})}$$

where μ and η are the chemical potential and hardness, respectively, IP and AE are the ionization potential and the electron affinity of a molecular system, and $\varepsilon_{\mathrm{HOMO}}$ and $\varepsilon_{\mathrm{LUMO}}$ are the energies of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), respectively. From Koopmans theorem, the electron affinity (EA) and the ionization potential (IP) are related to HOMO and LUMO energies acording to $\mathrm{IP} = -\varepsilon_{\mathrm{HOMO}}$ and $\mathrm{EA} = -\varepsilon_{\mathrm{LUMO}}$.

These theoretical electronic properties (EA and ω) are both interpreted in this study as global indexes of the ability to generate radical anion species, and correlated with the experimental reduction potentials presented previously [15].

Condensed Fukui nucleophilic attack functions were calculated to determine the local reactivity of the molecule when it encounters an electron. The Fukui functions were defined by Parr and Yang according to Eqs. (1) and (2) [18,19]

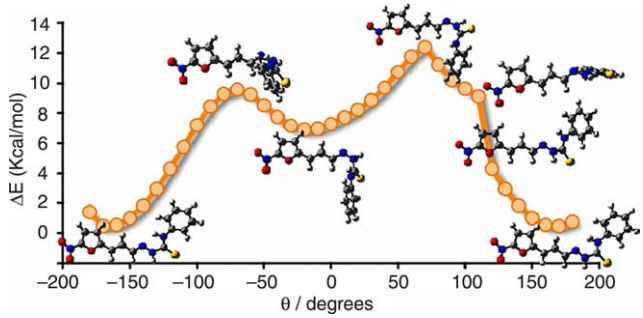


Fig. 2. Energy surface of compound NS4.

$$f^{-}(r) = \rho_N(r) - \rho_{N-1}(r) \quad (1)$$

$$f^{+}(r) = \rho_{N+1}(r) - \rho_N(r) \quad (2)$$

where ρ is the electronic density. Condensing under Yang and Mortier atoms in molecules resolution (AIM) we obtain (3) and (4) [20]

$$f_k^{-} = q_{\mathrm{k}}^{N-1} - q_{\mathrm{k}}^{N} \quad (3)$$

for the electrophilic attack, and

$$f_k^{+} = q_{\mathrm{k}}^{N} - q_{\mathrm{k}}^{N+1} \quad (4)$$

for the nucleophilic attack, where q_k is the Mulliken atomic charge over the atom k.

The density functional theory implemented in the GAUSSIAN 98 [21] computational package was used to optimize the geometry of the eight nitrofuryl derivatives. All the optimizations have been performed using Becke's three parameter exact exchange functional (B3) [22] combined with gradient corrected correlation functional of Lee-Yang-Parr (LYP) [23] of DFT method (U)B3LYP/6-31G* and calculations of electronic properties at (U)B3LYP/6-31G* and HF/3-21G [24,25] levels. HF/3-21G was used when B3LYP/6-31G* displayed negative LUMO energies. Otherwise a consistency in the methodology was maintained using B3LYP/6-31G* in all calculations. The calculation of hyperfine coupling constants and Mulliken atomic charges were performed in the same DFT method as the geometry optimizations in order to maintain a consistency in the results.

These results were compared with lumo orbital analysis and ESR coupling constants as local reactivity descriptors.

Table 1
Correlations between the electronic affinity (as the difference of energies and as the $-\varepsilon_{\mathrm{LUMO}}$) and the electrophilicity (ω) versus the experimental reduction potentials (E_{cp})

Compound	E_{pc} (V)	$E_{NE}-E_{RA}$ (eV)	$-\varepsilon_{\mathrm{LUMO}}$ (eV)	ω (eV)
NS1	−0.79	1.69	−0.09	1.01
NS2	−0.79	1.54	−0.53	0.85
NS3	−0.78	1.74	−0.31	0.94
NS4	−0.77	1.85	−0.15	1.00
NS5	−0.79	1.60	−0.17	1.01
NS6	−0.79	1.42	−0.62	0.83
NS7	−0.84	1.31	−0.73	0.84
NS8	−0.84	1.58	−0.73	0.28

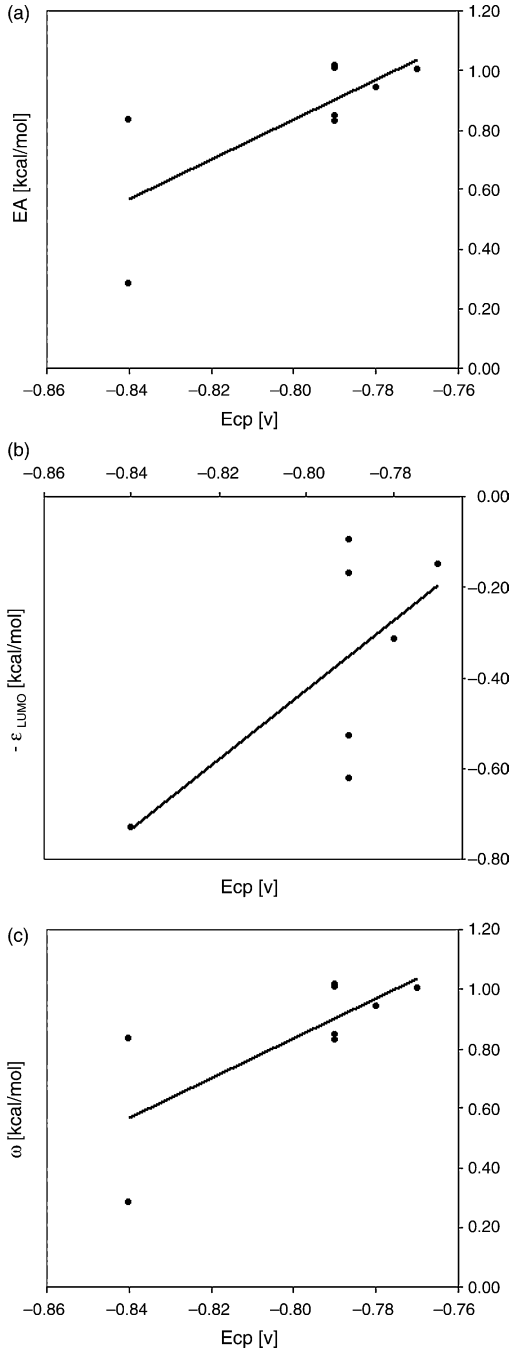


Fig. 3. Plots of the correlations between the electronic affinity (as the difference of energies and as the $-\varepsilon_{LUMO}$) and the electrophilicity (ω) versus the experimental reduction potentials (E_{cp}).

3. Results and discussion

Two different conformations where obtained from the DFT geometry optimizations in the nitrofuryl family whether the molecules have got a short ($n=0$) or a long ($n=1$) side chain according to the similarities between the theoretical ESR spectra obtained from the DFT hyperfine coupling constants and the experimental spectra. The $n=0$ molecules adopt a folded conformation stabilised by the presence of a hydrogen

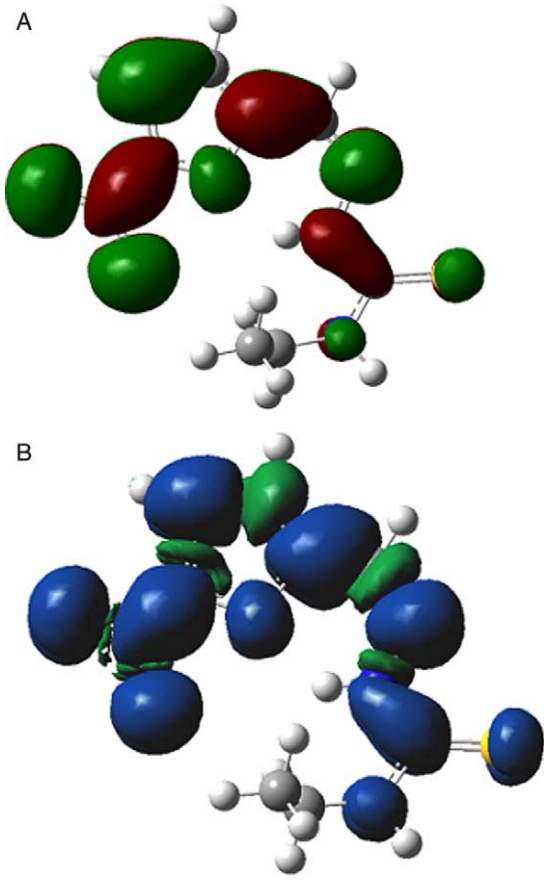


Fig. 4. LUMO orbital (A) and spin density (B) surfaces on compound NS1.

bond, while the $n=1$ molecules expand their side chain searching for a stabilisation through planarity.

In order to find out whether these two conformations coexisted in equilibrium we performed an energy scan along a dihedral angle in the molecule. The dihedral angle (NNCN)

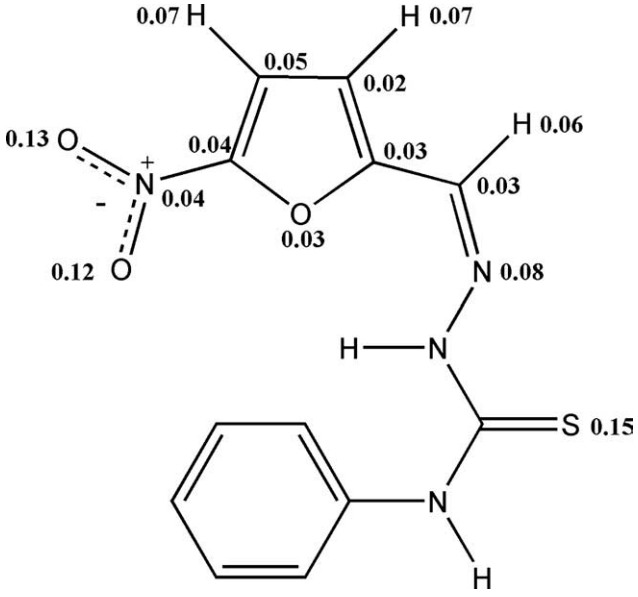
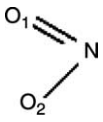
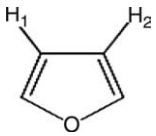


Fig. 5. Nucleophilic Fukui functions of the most reactive atoms on compound NS3.

Table 2
f_k^+ Values of most relevant nuclei of eight 5-nitrofuryl thiosemicarbazone derivatives

										
		n	R	O1	O2	N	S	H1	H2	H
f_k^+	NS1	0	Et	0.13	0.14	0.08	0.14	0.07	0.07	0.06
	NS2	1	Et	0.11	0.10	0.06	0.11	0.06	0.06	0.05
	NS3	0	Ph	0.13	0.12	0.08	0.15	0.07	0.07	0.06
	NS4	1	Ph	0.10	0.10	0.06	0.15	0.05	0.05	0.05
	NS5	0	Met	0.13	0.14	0.08	0.14	0.07	0.07	0.06
	NS6	1	Met	0.10	0.10	0.05	0.10	0.05	0.02	0.07
	NS7	0	H	0.12	0.13	0.07	0.13	0.07	0.07	0.07
	NS8	1	H	0.11	0.10	0.06	0.12	0.06	0.06	0.06

was chosen for its possibility of changing the conformation of the molecules from folded to extended (Fig. 2). We found in that for these two conformations to coexist, they must overpass an energy barrier of 10 kcal/mol approximately, which corresponds to the breakage of the hydrogen bond.

These results showed none significant differences with the semiempirical optimizations presented by Rigol et al. [15]. It is needless to say that the optimizations were extremely more demanding regarding computational characteristics and time when performed at DFT level, providing not much more accurate results, as mentioned.

However, regarding the rationalization of the electrochemical experimental data, semiempirical optimizations delivered poor correlations with theoretical data (correlation coefficients (r) between 0.30 and 0.40).

The same study was repeated using the DFT optimized geometries. Table 1 shows the experimental cathodic reduction potential, the Electron Affinity (EA), the negative of the LUMO energy, and the electrophilicity index (ω) of the eight nitrofuryl derivatives studied.

Fig. 3 shows the correlations between the Electronic Affinity (as the difference of energies and as the $-\varepsilon_{LUMO}$) and the electrophilicity (ω) versus the experimental reduction potentials (E_{cp}) which resulted 0.67, 0.76 y de 0.73, respectively. We observe an improvement in these results compared to those obtained semiempirically (0.39, 0.36 y 0.40, respectively, data not shown).

Fig. 4 shows how the LUMO orbital and the spin density are distributed along molecule NS1 ($n=0$, R = ethyl). We observe a good agreement between both surfaces finding a localization of the radical spin density in the nuclei where the lowest energy orbital is spread, i.e. the nitro group, the furanic protons and the semicarbazonic nitrogen atom. The condensed Fukui functions calculated from the Mulliken charges were compared with the spin density localization in order to determine the reactive zones of the molecules. As shown in Fig. 5 the reactivity is displayed as the nucleophilic Fukui function f_k^+, being the oxygen atoms of the nitro moiety, the sulfur and one of the semicarbazonic nitrogen atoms the most reactive centers when facing the attack of an electron. These values agree with surface shown in Fig. 4, which shows a localization of the spin density in those same regions. As we see in Table 2, electrophilic Fukui functions in the most relevant nuclei, i.e. those with better reactivity, show a dependence with the length of the molecule's side chain ($n=0$, 1). As we know this is strictly related to the two different conformations, folded and extended, these compounds can adopt. Folded conformations increase the local reactivity (when comes to accepting an electron) of the nitro group, as well as extended conformations favor the electrophilic local reactivity of the semicarbazone nitrogen atom (N–N). The substituent moieties are not relevant regarding local reactivities. We must keep in mind that the Fukui functions were calculated from the closed shell structures, this means f_k^+ represents the system's ability to accept an electron, or better said, it shows where it's staying once accepted. With these results we can say the Fukui function worked as a very good projector of electron localisation. This also agreed with the experimental ESR data of these molecules [15]. From these results we can state that the methodology chosen for this sort of calculations displays accurate and consistent results.

4. Conclusions

The two conformations analysed are able to coexist in equilibrium, once a barrier corresponding to a hydrogen bond is passed. On the other hand, this theoretical study, in which the geometry optimizations and the determinations of the electronic properties were performed using DFT based calculation methodologies, showed a good agreement between experimental and theoretical properties. The good correlation between theoretical electronic properties and experimental reduction potentials showed, in addition to the theoretical–experimental agreement, that the studied reductions, those of the nitro moiety, are probably purely electrochemical type reactions, with no chemical reactions involved.

Acknowledgements

This research was supported by FONDECYT 1030949 grant, CONICYT AT-4040020 grant, U. de Chile DID graduate grant PG-65.

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