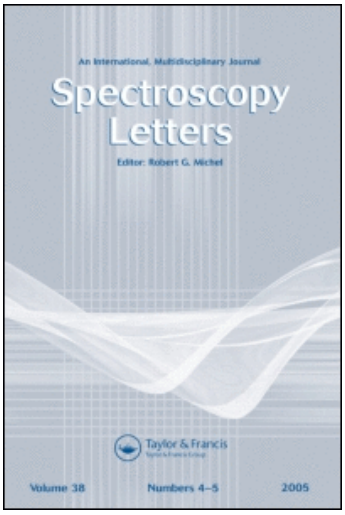

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ELECTRON SPIN RESONANCE AND CYCLIC VOLTAMMETRY STUDIES OF NITROFURANE AND NITROTHIOPHENE ANALOGUES OF NIFURTIMOX.

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ABSTRACT

The electron spin resonance (ESR) of radicals obtained by electrolytic reduction of 4-[2-(3,4-Dimethoxiphenyl)ethyl]-1-(5-nitrofurfurylidine)semicarbazide and 4-[2-(3,4-Dimethoxyphenyl)ethyl]-1-(5-nitrothienilydene)semicarbazide were measured in DMSO. The electrochemistry of these compounds was studied in DMSO, DMF and ACN using cyclic voltammetry.

INTRODUCTION

American tripanosomiasis is caused by several strains of *Trypanosoma Cruzi* (1). Nifurtimox and benznidazole are currently used to treat this disease. A characteristic ESR signal corresponding to the nitro anion radical ($R\text{-}NO_2^{\cdot}$) appears when nifurtimox is added to intact *T. cruzi* cells (2). This and other experiments (3-5) suggest that intracellular reduction of nifurtimox followed by redox cycling, yielding $O_2^{\cdot-}$ and H_2O_2, may be the major mode of action against *T. cruzi*. However, the use of nifurtimox has disadvantageous side

effects (6). Mester et al. (7) synthesized new nifurtimox analogues in which the tetrahydrothiazine moiety was replaced by unsaturated five- and six-membered nitrogen heterocycles. Most of the new compounds proved to be more effective than nifurtimox (8). Cerecetto et al. (9) correlated the electrochemical parameters of the nitro compound analogues of Nifurtimox with their biological activities in vivo for *T. Cruzi*. The results suggest that the nitrocompounds as well as Nifurtimox present the same electrochemical behavior involving the formation of a nitro-anion radical

In general, the biological effects of nitroheterocyclic compounds, especially *T. cruzi*, are believed to involve redox cycling of the compounds and oxygen radical production, two processes in which the nitroanion radicals play an essential role. (10).

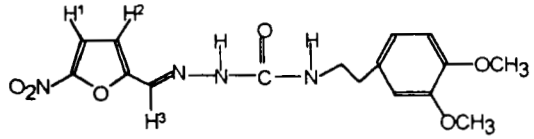
In the present work, we report electrochemical studies of 4-[2-(3,4-Dimethoxiphenyl)ethyl]-1-(5-nitrofurfurylidine)semicarbazide (MOLECULE 1) and 4-[2-(3,4-Dimethoxyphenyl)ethyl]-1-(5-nitrothienilydene)semicarbazide (MOLECULE 2) (Fig 1) in dimethylsulfoxide (DMSO), dimethylformamide (DMF) and acetonitrile (ACN). The formal one electron transfer potential for the new nitro-heterocyclic compounds were compared with that of Nifurtimox. The anion radicals produced in the electrochemical process were characterized by ESR.

EXPERIMENTAL SECTION

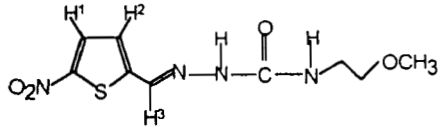
Reagents

The DMSO, DMF and ACN (spectroscopy grade) were obtained from Aldrich. The tetrabutylammonium perchlorate (TBAP) used as the supporting electrolyte was obtained from Fluka.

The new semicarbazone derivatives were prepared using a three step synthetic route from 5-nitro-2-furaldehyde and 5-nitrothiophene-2-carboxaldehyde.



MOLECULE 1



MOLECULE 2

FIGURE 1

Electrochemical and ESR Measurement

Cyclic voltammetry was carried out using a Weenking POS 88 instrument with a Kipp Zenen BD93 recorder, in DMSO, DMF or ACN (ca. $1.0x10^{-2}$ moles dm^{-3}), under a nitrogen atmosphere, with TBAP (ca. 0,1 moles dm^{-3}) using three-electrode cells. A mercury dropping electrode was used as the working electrode, a platinum wire as the auxiliary electrode and saturated calomel as the reference electrode.

The radicals were generated by eletrolyltic reduction *in situ* at room temperature. ESR spectra were recorder in X band (9.85 GHz) on a Bruker ECS 106 using a rectangular cavity with a 50 KHz field modulation. The hyperfine splitting constants were estimated to be accurate within 0.05 G.

RESULTS AND DISCUSSION

CYCLIC VOLTAMMETRY

Table 1 lists the values of the voltammetric peaks and the anodic and cathodic currents for two compounds and Nifurtimox. The new nitrocompounds display comparable voltammetric behavior, showing two well-defined reduction waves in DMSO, DMF and ACN

Table 1
Cyclic Voltammetric parameters vs saturated calomel electrode

Molecules	E_{pc1}/V	E_{pa1}/V	ΔE/V	ip_a/ip_c	E_{pc2}/V	E_{pa2}/V
1						
DMSO	-0.86	-0.79	0.07	1.05	-1.54	-
DMF	-0.84	-0.78	0.06	0.96	-1.50	-
ACN	-0.80	-0.73	0.07	0.98	-0.9	-0.80
2						
DMSO	-0.78	-0.72	0.06	1.05	-1.44	-
DMF	-0.80	-0.73	0.07	1.02	-1.35	-
ACN	-0.68	-0.60	0.08	1.05	-0.85	-0.78
Nifurtimox						
DMSO	-0.91	-0.85	0.06	1.01	-1.60	-
DMF	-0.89	-0.84	0.05	1.03	-1.30	-
ACN	-0.82	-0.76	0.06	0.98	-1.10	-

The first wave for the two nitrocompounds studied corresponds to a reversible one-electron transfer. The reverse scan showed the anodic counterpart of the reduction waves. The breadth of the cathodic wave at its half intensity has a relatively constant value of 60 mV. The intensity ratio ipa/ipc has a value close to one. According to the standard reversibility criteria this couple corresponds to a reversible diffusion-controlled one-electron transfer. It is attributable to the reduction of $R\text{-}NO_2$ to $RNO_2^{\cdot}$, a stable anion radical at room temperature. It can be seen that Nifurtimox has more negative potential reduction than the new compounds The second cathodic peak is irreversible in the whole range of sweep rates used (50-1000 mV/s). We can attribute this wave to the production of the hydroxylamine derivative.

ESR SPECTRA

The electrochemical reductions to the radical forms (*in situ*) in all solvents were carried out by applying the potential corresponding to the first wave for the nitroheterocyclic compounds, as obtained from the cyclic voltammetry experiments.

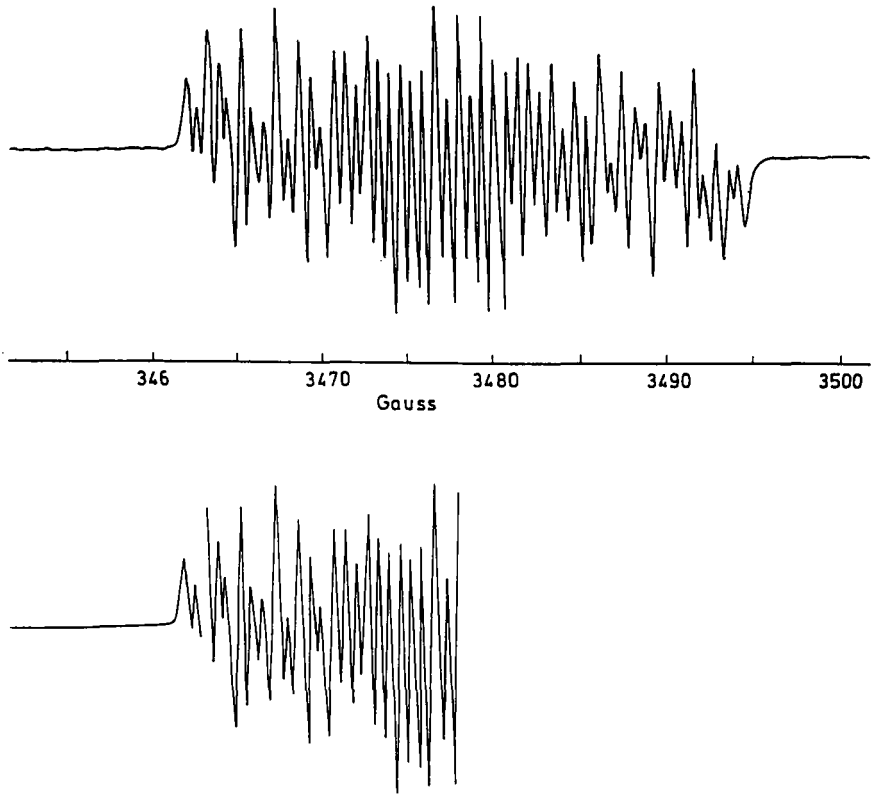


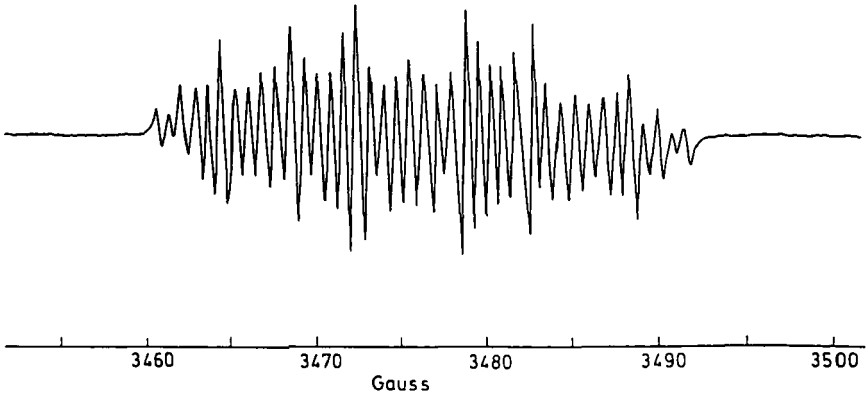
FIGURE 2

Top: ESR experimental Spectrum of the radical-anion of molecule 1 in ACN.

Bottom: Computer Simulation of the Same Spectrum.

The interpretation of the ESR spectra by means of a simulation process has led to the determination of the coupling constants for all magnetic nuclei.

Molecules **1** and **2** presented the a different hyperfine pattern, The ESR of molecule **1** was analyzed and simulated in terms of a triplet from the nitrogen nucleus of the nitro group, three doublets due to hydrogens 1, 2 and 3 , and a triplet due to the nitrogen of the azomethine bond (Fig 2).



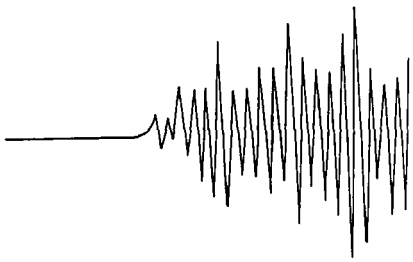


FIGURE 3

Top: ESR experimental Spectrum of the radical-anion of molecule 2 in ACN.

Bottom: Computer Simulation of the Same Spectrum.

The ESR spectra of molecule **2** was resolved into 36 lines. These spectra were simulated in terms of one triplet due to the nitrogen nucleus of the nitro group, two doublets due to hydrogens 1 and 2 which are not equivalent, and two triplets due to the nitrogens of the azomethine bond. A small hyperfine constant was attributed due hydrogen 3 (Fig. 3). The hyperfine constants are listed in Table 2.

Recently, we have reported and ESR studies of other nitrocompounds analogues of nifurtimox (11). The spectra presented the same hyperfine patterns to molecule 1 and 2.

Table 2

Experimental hyperfine splitting (Gauss) for the anion radicals investigate

Molecule	aN (NO_2)	aH (1)	aH (2)	aH (3)	aN (C=N)	aN (N=N)
1						
DMSO	8.80	5.38	3.66	1.29	0.54	-
DMF	7.75	5.04	2.52	1.20	0.32	-
ACN	8.70	5.28	3.50	1.25	0.48	-
2						
DMSO	7.65	5.17	2.48	0.2	1.59	0.74
DMF	7.50	4.76	2.38	0.2	1.50	0.62
ACN	7.60	5.10	2.40	0.2	1.55	0.70

CONCLUDING REMARKS

The nitrocompounds studied presented comparable voltammetric behaviors in both solvent used. The first wave corresponded to a reversible one-electron transfer in which the anion radicals were formed. The one electron addition product of Nifurtimox, has been suggested as the species responsible for the tripanocidal activity. From Table 2 it can be seen that Nifurtimox has more negative potential reduction than the new nitrocompounds, suggesting that its will be more effective than Nifurtimox.

The ESR spectra of the anion radical for molecules **1** and **2** were well resolved. The hyperfine splittings of molecule **2** indicate that the electron delocalization involves the side chain nitrogens. However, the ESR spectrum for molecule **1** indicates that in this case the delocalization was limited to the heterocyclic ring and to hydrogen 5 and

nitrogen 2. The hyperfine constants were not affected by the aprotic solvent used The second peak was attributed to the production of the hidroxylamine derivated.

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