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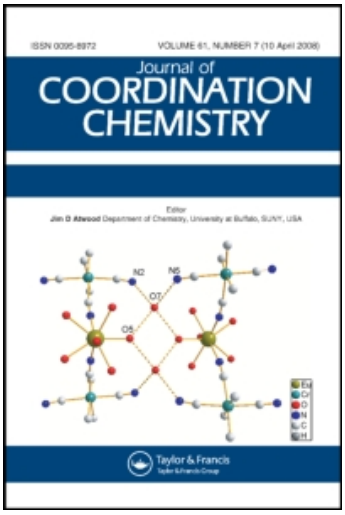

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Iron(III) complexes with N⁴-para-tolyl-thiosemicarbazones: spectral and electrochemical studies and toxicity to Artemia salina

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Iron(III) complexes with N^4-*para*-tolyl-thiosemicarbazones: spectral and electrochemical studies and toxicity to *Artemia salina*

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Iron(III) complexes [Fe(H2Fo4pT)Cl_3] (**1**), [Fe(H2Ac4pT)Cl_3] (**2**) and [Fe(H2Bz4pT)Cl_3] (**3**) with N^4-*para*-tolyl-thiosemicarbazones derived from 2-formyl (H2Fo4pT), 2-acetyl (H2Ac4pT) and 2-benzoylpyridine (H2Bz4pT) were prepared and characterized. EPR data for **1–3** reveal the presence of low-spin iron(III) with $d^2_{xz}d^2_{yz}d^1_{xy}$ ground state. Electrochemical studies of the complexes showed mostly metal-centered redox changes with a quasi-reversible Fe(III)/Fe(II) couple. H2Fo4pT and H2Ac4pT exhibited toxicity against *Artemia salina* at low doses ($LD_{50} = 27.5\,\mu M$ and $LD_{50} = 4.7\,\mu M$, respectively). Upon coordination the toxicity increased substantially in the case of [Fe(H2Fo4pT)Cl_3] ($LD_{50} = 1.9\,\mu M$) and did not change for [Fe(H2Ac4pT)Cl_3]. H2Bz4pT and its iron(III) complex were not soluble in water.

Keywords: N^4-*para*-tolyl-thiosemicarbazones; Iron(III) complexes; EPR spectra; Electrochemistry; *Artemia salina*

1. Introduction

Thiosemicarbazones have been the subject of numerous studies because of their chemical and biological properties [1]. Their transition metal complexes are more potent antimalarial, antibacterial, antileprotic and antitumoral agents than the parent thiosemicarbazones [1–3]. Structure-activity relationship studies revealed that the presence of a bulky group attached to the terminal nitrogen at the lateral chain strongly enhances the pharmacological activity of these compounds [4].

α(N)-heterocyclic thiosemicarbazones are believed to exercise their antitumor effects by inhibiting the activity of ribonucleoside diphosphate reductase (RDR), a key enzyme involved in the conversion of ribonucleotides into desoxiribonucleotides during DNA syntheses [1]. The active form of the drugs are their iron(II) complexes [5, 6].

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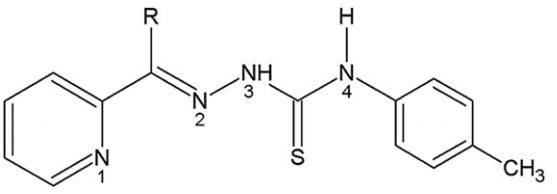

Figure 1. General structure of N^4-*para*-tolyl-derived thiosemicarbazones: R=H (H2Fo4pT); R=CH_3 (H2Ac4pT); R=C_6H_5 (H2Bz4pT).

In the proposed mechanism of action oxidation of the iron(II) complex occurs with release of one electron, which inactivates a tyrosyl free radical present in the structure of the enzyme [5, 6]. Our group suggested that reduction of the iron(III) to iron(II) complex by cellular thiols could be part of this pathway [7–10]. Another possible mode of action involves binding of the complex molecules at the minor groove of the DNA helical structure through intercalation, thus preventing the unwinding of DNA [11].

Several α(N)-heterocyclic thiosemicarbazones are effective for removing excess iron from iron-loaded mice, indicating this class of compounds as good chelators for applications in the therapy of metal intoxication [12].

In continuation of earlier reports on iron(III) complexes with *N*(4)-substituted α(N)-heterocyclic thiosemicarbazones [13], the present work deals with the synthesis and structural characterization of three new iron(III) complexes with N^4-*para*-tolyl-thiosemicarbazones derived from 2-formyl (H2Fo4pT), 2-acetyl (H2Ac4pT) and 2-benzoylpyridine (H2Bz4pT) (figure 1). The toxicity of the thiosemicarbazones and their metal complexes against *Artemia salina* was assayed as a prescreening of antitumoral action.

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2. Experimental

All reagents were of AR grade, obtained from commercial sources and used without purification. Spectrograde solvents were used for spectral, electrochemical and conductance measurements.

2.1. *Apparatus*

Partial elemental analyses were performed on a CE Instruments CHN-O EA 1110. Infrared spectra were recorded on a Bomem-Michelson MB – 102 spectrometer using KBr pellets; a Tecnopon MCA 150 conductivity bridge was employed for molar conductivity measurements. Magnetic susceptibility measurements were carried out on a Johnson Matthey MSB/AUTO balance. Electron paramagnetic resonance (EPR) spectra were obtained on a Bruker ESP300E with modulation frequency of 100 kHz and modulation amplitude of 1 mT. Frozen ethanol solutions of the complexes (1 mM) were measured at liquid N_2 temperature (77 K) in Teflon® tubes of 3 mm internal diameter. Ambient temperature spectra of samples in the solid state and ethanol solution were obtained in glass capillaries of 1.2 mm internal diameter. Spectral simulations were performed using EasySpin [14].

Electrochemical experiments were carried out at room temperature in dichloromethane containing 0.1 mol L^{-1} tetrabutylammonium perchlorate (TBAP, Fluka Purum) using an electrochemical analyzer from Bioanalytical Systems Inc. (BAS), model 100BW. The working and auxiliary electrodes were stationary Pt foils, and the reference electrode was Ag/AgCl, a medium in which ferrocene is oxidized at 0.48 V (Fc^+/Fc).

2.2. *Synthesis of complexes*

The thiosemicarbazones were obtained as reported in the literature [15]. Iron(III) complexes were obtained by mixing the desired thiosemicarbazone with $FeCl_3 \cdot 6H_2O$ in acetone at room temperature in 1 : 1 metal-to-ligand molar ratio. The precipitates were filtered off and washed with diethyl ether.

2.3. *Assay of toxicity against* Artemia salina

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The *A. salina* (brine shrimp) lethality test was employed as an antitumor prescreen. Lethality towards brine shrimp was assayed using literature procedures [16, 17]. Lethal dose (LD_{50}) is the amount of a substance which causes the death of 50% of a group of test animals. Determination of LD_{50} is an indication of the short-term poisoning potential (acute toxicity) of a compound.

Artemia salina encysted eggs (10 mg) were incubated in 100 mL of seawater under artificial light at 28°C, pH 7–8. After incubation for 24 h, nauplii were collected with a Pasteur pipette and kept for an additional 24 h under the same conditions to reach the metanauplii stage. The samples to be assayed were dissolved in 1% DMSO (dimethylsulfoxide) and diluted in five different concentrations in seawater. About 10 nauplii were added to each set of tubes containing the samples. Controls containing 1% DMSO in seawater were included in each experiment. Forty eight hours later, the number of survivors was counted, recorded and the lethal dose 50% (LD_{50} value) and 95% confidence intervals were calculated by Probit analysis [18]. The repeatability of the method was evaluated using at least three replicates of each concentration.

3. Results and discussion

Microanalyses suggest the formation of [Fe(H2Fo4pT)Cl_3] (**1**), [Fe(H2Ac4pT)Cl_3] (**2**) and [Fe(H2Bz4pT)Cl_3] (**3**). The conductivity values of **1**–**3** measured in CH_2Cl_2 at 1.0×10^{-3} mol L^{-1} are in the range 7–17 μS cm^{-1}. The low values indicate non-electrolytes. Magnetic moments in the 1.53–1.78 BM range are close to the calculated value of 1.73 BM, characteristic of one unpaired electron in low-spin iron(III) complexes (table 1).

3.1. *Infrared spectra*

Characteristic IR bands (4000–200 cm^{-1}) for the free thiosemicarbazones, when compared with those of its Fe(III) complexes, provide information regarding the bonding sites of the primary ligand molecules. The ν(C=C) + ν(C=N) composed

Table 1. Analytical data and some physical properties for **1**–**3**.

Complex	Analytical data[a]			Conductivity[b]	μ_{eff} (BM)
	% C	% H	% N		
[Fe(H2Fo4pT)Cl_3] (**1**)	43.8 (43.6)	4.2 (4.1)	11.5 (11.4)	12	1.54
[Fe(H2Ac4pT)Cl_3] (**2**)	42.9 (42.8)	4.5 (4.4)	11.3 (11.1)	17	1.78
[Fe(H2Bz4pT)Cl_3] (**3**)	47.4 (47.2)	3.6 (3.6)	11.1 (11.0)	7	1.53

Notes: [a]Values in the parentheses are the calculated ones.
[b]$\mu S\,cm^{-1}$.

mode observed at 1582–1595 cm^{-1} in the spectra of the thiosemicarbazones shifts to 1538–1548 cm^{-1} in the spectra of the complexes, indicating coordination of the azomethine nitrogen N_2 [15, 19–21].

Absorption at 796–777 cm^{-1} in the spectra of the uncomplexed thiosemicarbazones, attributed to the ν(C=S) vibration, shifts to 763–788 cm^{-1} (8–14 cm^{-1}) in those of the complexes, in accordance with coordination through a thione sulfur [19, 22]. The shift observed upon complexation is compatible with coordination of a neutral thiosemicarbazone. The pyridine in-plane deformation modes at 599–612 cm^{-1} in the spectra of the free bases shift to 612–613 cm^{-1} in the complexes, suggesting coordination of the heteroaromatic nitrogen [15, 19, 20].

Infrared data for the complexes indicate coordination of the thiosemicarbazones through the N_{py}–N–S chelating system.

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3.2. *EPR spectra*

EPR spectra of the complexes in ethanol solutions frozen at 77 K, depicted in figure 2(a), exhibit a spectrum with three different g values (orthorhombic g tensor) characteristic of low-spin Fe^{III} in an octahedral environment with rhombic distortion. The small deviation of the g values from the free-electron value 2.0023 suggests a $d^2_{xz}d^2_{yz}d^1_{xy}$ (in fact, t^5_{2g}) ground state configuration [23]. Similarity of the EPR spectra indicates similar coordination spheres of Fe^{III} in ethanol. Complexes **1** and **3** [figure 2(a)] also show a very broad spectrum superimposed to the main spectrum, probably due to insoluble material at 1 mM concentration. At room temperature the anisotropy of the complexes in ethanol solution is completely averaged out due to fast rotation, and the spectra (not shown) are isotropic with $g_{iso} \approx 2.11$ and linewidths of 4.1 to 4.7 mT.

Polycrystalline samples of the three compounds exhibit different EPR spectra [figure 2(b)]. The broad lines of **1** and **2** completely hide the anisotropy of the Fe(III) site, so that the spectra are mainly isotropic. Complex **3** presents much narrower intense lines [the original spectrum of **3** was divided by 80 to fit the same scale as **1** and **2** in figure 2(b)], allowing determination of the three principal values of the g tensor.

Spectral simulations were performed for a simple orthorhombic system, a single low-spin Fe^{III} ($S = 1/2$) with given g_1, g_2, and g_3 values (principal values of the g tensor), Lorentzian or Gaussian line-shapes, and magnetic field strain, to account for orientation dependent linewidths. Simulated spectra are displayed as dotted lines superimposed to the experimental ones in figure 2(c). The g values and linewidth parameters are presented in table 2.

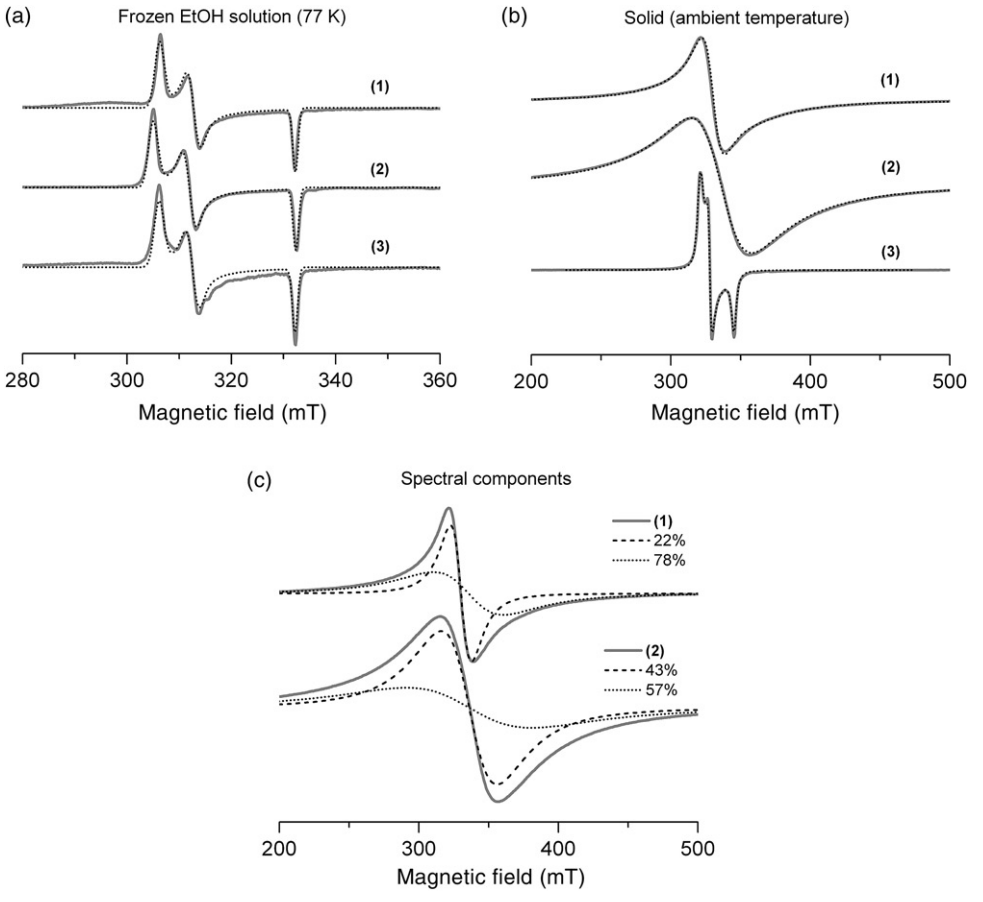

Figure 2. EPR spectra of (**1**)–(**3**) (a) in ethanol at 77 K and (b) in the polycrystalline state at ambient temperature (dotted lines). The simulated spectra appear in gray. (c) Simulated EPR spectral components (dashed and dotted lines) of (**1**) and (**2**), and their sum (gray).

Table 2. EPR spectral parameters for **1**–**3** obtained by spectral simulations using the software EasySpin (ΔB_{fwhm} is the full width at half height linewidth).

Complex in EtOH 77 K	ΔB_{fwhm} (mT) Gaussian	B_{strain} (mT)	g_1	g_2	g_3	g_{iso}
1	1.0	0, 2.3, 1.9	2.010	2.135	2.181	2.109
2	1.05	0, 2.3, 1.9	2.008	2.139	2.188	2.111
3	1.0	0, 2.3, 2.0	2.009	2.135	2.180	2.108
Solid ambient temperature	ΔB_{fwhm} (mT) lorentzian	B_{strain} (mT)	g_1	g_2	g_3	g_{iso}
1 Compound 1 22%	15					2.108
1 Compound 2 78%	50					2.075
2 Compound 1 43%	40					2.070
2 Compound 2 57%	90					2.070
3	2.0	1.4, 0.0, 1.8	2.016	2.123	2.168	2.102

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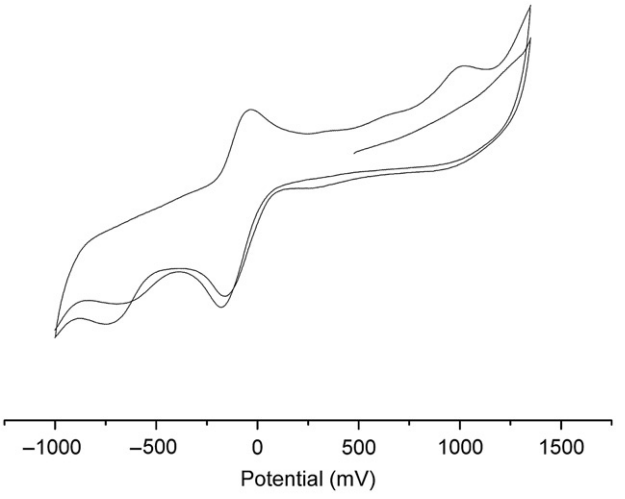

Figure 3. Cyclic voltammogramm of [Fe(H2Ac4pT)Cl_3] (0.100 V s^{-1}, CH_2Cl_2, 0.1 mol L^{-1} TBPA).

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Table 2 shows that the complexes dissolved in ethanol (77 K) have very similar EPR parameters. The spectral shapes were simulated using a Gaussian uniform broadening of 1.0 mT full width at half maximum and B_{strain} broadening components of about 2.3 and 2 mT for g_2 and g_3, respectively.

Contrary to the frozen ethanol solutions, the spectral shapes of the polycrystalline samples are simulated using Lorentzian lineshapes, characteristic of homogeneous broadening. This suggests that the paramagnetism of Fe^{3+} ions produces strong but fluctuating local fields even in the solid state. The polycrystalline spectra of **1** and **2** could not be simulated using a single spectral component because of their wide wings. They are simulated using two components with different linewidths (see table 2). Figure 2(c) shows the individual spectral components and their occurrence in the compounds. Note that the more intense components correspond to 22% and 43% of the paramagnetic species in **1** and **2**, respectively, mainly due to the different linewidths. Complex **3** presents a single anisotropic ($g_1 \neq g_2 \neq g_3$) spectral component with much narrower peaks.

The linewidths of the polycrystalline samples are much larger than in ethanol (table 2) from the small distance between the Fe^{3+} ions leading to strong magnetic dipolar interactions. The linewidth of solid **3** is only twice that of the frozen ethanol solution, due to the bulk substituent of **3**, which maintains the Fe^{3+} ions apart in the crystal.

3.3. *Electrochemical studies*

The cyclic voltammograms of **1**–**3** (see figure 3) show one quasi-reversible process in the −0.053 to −0.174 V range, attributed to Fe^{II}/Fe^{III} oxidation, followed by the corresponding reduction at −0.002 to 0.073 V. Quasi-reversibility of this wave was inferred from the cathodic to anodic current intensity ratio (table 3). Two consecutive reduction waves were observed in the −0.80 to −1.20 V range, assigned to redox processes of the thiosemicarbazone. These two reduction signals could be assigned to

Table 3. Cyclic voltammetry data for **1**–**3** ($0.100\,V\,s^{-1}$, CH_2Cl_2, $0.1\,mol\,L^{-1}$ TBAP).

	Fe^{II}/Fe^{III}	Fe^{III}/Fe^{II}	Reversibility (i_{pa}/i_{pc})
[Fe(H2Fo4pT)Cl_3] (**1**)	−0.053	0.073	0.7
[Fe(H2Ac4pT)Cl_3] (**2**)	−0.174	−0.002	0.7
[Fe(H2Bz4pT)Cl_3] (**3**)	−0.076	0.045	0.8

Table 4. LD_{50} average values for the N^4-*para*-tolyl-thiosemicarbazones and their iron(III) complexes.

Compound	LD_{50} ($\mu mol\,L^{-1}$)
H2Fo4pT	22.7
	29.2
	30.6
Average $LD_{50} \pm$ SD	**28 ± 4**
CV (%)	1.28
[Fe(H2Fo4pT)Cl_3]·C_3H_6O (**1**)	1.50
	1.90
	2.30
Average $LD_{50} \pm$ SD	**1.9 ± 0.4**
CV (%)	3.67
H2Ac4pT	5.10
	4.60
	4.60
Average $LD_{50} \pm$ SD	**4.7 ± 0.3**
CV (%)	0.01
[Fe(H2Ac4pT)Cl_3]·C_3H_6O (**2**)	5.20
	4.60
	4.40
Average $LD_{50} \pm$ SD	**4.8 ± 0.4**
CV (%)	4.12

Notes: LD_{50} = Lethal dose which causes the death of 50% of a group of test animals; SD = Standard deviation; CV = Covariance.

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a two-step, two-electron reduction involving cleavage of the N–N single bond by reduction with two electrons and then reduction by two electrons at the imine formed, as suggested for pyridine-derived thiosemicarbazones and semicarbazones [19, 24–26].

3.4. *Toxicity against* Artemia salina

LD_{50} average values for the thiosemicarbazones and their iron(III) complexes are reported in table 4. We obtained $LD_{50} = 27.5\,\mu M$ and $4.7\,\mu M$ for H2Fo4pT and H2Ac4pT, respectively. H2Bz4pT is not soluble in aqueous media due to the presence of two hydrophobic phenyl groups. For **1** and **2** we found $LD_{50} = 1.9\,\mu M$ and $4.8\,\mu M$, respectively. Complex **3** was insoluble. Upon complexation the value of LD_{50} decreases, indicating higher toxicity. Moreover, the LD_{50} value for **1** was the lowest, suggesting that it is the most promising compound. The thiosemicarbazones and their complexes were found to be more active than lapachol ($LD_{50} = 68\,\mu g\,mL^{-1} = 281\,\mu M$), a known reference [27]. In previous work we tested 2-pyridineformamide-derived

thiosemicarbazones and their iron(III) complexes with LD_{50} values for the thiosemicarbazones in the 26.09–35.24 μM range and in the 14.12–30.14 μM range for their complexes [13]. Therefore, the presently studied compounds are more toxic to *A. salina*, suggesting a higher cytotoxic activity.

4. Conclusions

The toxicity against *A. salina* bioassay has a good correlation with cytotoxic activity in some human tumors [27]. The low values of LD_{50} obtained for the studied compounds in this assay indicate they could have antineoplastic properties. The values of Fe^{III}/Fe^{II} redox potentials for **1**–**3** fall in the range of cellular reductants [28]. Therefore, if the complexes have antitumoral activity, their biochemical pathway could involve Fe^{III}–Fe^{II} reduction by cellular thiols, as suggested previously for iron complexes of other thiosemicarbazones [7–10].

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