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Dithiocarbazate complexes with the $[M(PPh_3)]^{2+}$ (M=Pd or Pt) moiety Synthesis, characterization and anti-*Tripanosoma cruzi* activity

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ABSTRACT

New neutral Pd(II) and Pt(II) complexes of the type $[M(L)(PPh_3)]$ (M Pd or Pt) were prepared in crystalline form in high-yield synthesis with the S-benzyldithiocarbazates and S-4-nitrobenzyldithiocarbazates derivatives from 2-hydroxyacetophenone, H_2L^{1a} and H_2L^{1b}, and benzoylacetone, H_2L^{2a} and H_2L^{2b}. The new complexes $[Pt(L^{1a})(PPh_3)]$ (**1**), $[Pd(L^{1a})(PPh_3)]$ (**2**), $[Pt(L^{1b})(PPh_3)]$ (**3**), $[Pd(L^{1b})(PPh_3)]$ (**4**), $[Pt(L^{2a})(PPh_3)]$ (**5**), $[Pd(L^{2a})(PPh_3)]$ (**6**), $[Pt(L^{2b})(PPh_3)]$ (**7**) and $[Pd(L^{2b})(PPh_3)]$ (**8**) were characterized on the basis of elemental analysis, conductivity measurements, UV–visible, IR, electrospray ionization mass spectrometry (ESI-MS), NMR (^1H and ^{31}P) and by X-ray diffraction studies. The studies showed that differently from what was observed for the H_2L^{1a} and H_2L^{1b} ligands, H_2L^{2a} and H_2L^{2b} assume cyclic forms as 5-hydroxypyrazolinic. Upon coordination, H_2L^{2a} and H_2L^{2b} suffer ring-opening reaction, coordinating in the same manner as H_2L^{1a} and H_2L^{1b}, deprotonated and in *O,N,S*-tridentate mode to the $(MPPh_3)^{2+}$ moiety. All complexes show a quite similar planar fourfold environment around the M(II) center. Furthermore, these complexes exhibited biological activity on extra and intracellular forms of *Trypanosoma cruzi* in a time- and concentration-dependent manner with IC_{50} values ranging from 7.8 to 18.7 μM, while the ligand H_2L^{2a} presented a trypanocidal activity on trypomastigote form better than the standard drug benznidazole.

1. Introduction

American Trypanosomiasis or Chagas disease is endemic in Latin America. Its etiological agent is the *Trypanosoma cruzi*, a hemoflagellate protozoan, whose life cycle involves vertebrate and invertebrate hosts [1]. According to the World Health Organization (WHO), 18 million people are infected with the *T. cruzi*, resulting in an annual death toll of 50,000 [2]. The current treatment of Chagas disease is unsatisfactory, depending on two nitroheterocycles, nifurtimox and benznidazole. Although effective for acute infections, they may cause undesirable side effects, frequently leading to the abandonment of the treatment [3]. Their efficacy during the chronic phase is still controversial, with poor indices of apparent cure and a lack of consensus regarding a parasitological cure in the future [3]. Thus, considerable efforts are being directed to developing new chemotherapeutical agents for chagasic patients, especially using inorganic complexes [4–7].

Metal chelates of dithiocarbazic acid, its S-alkyl/arylesters and their Schiff bases have been studied, mainly due to their potential anticancer, antibacterial, antifungal, antiamoebic and insecticidal activities [8–14]. Although the synthesis and complexation of S-benzyldithiocarbazate and its derivatives have been under study for many years, considerable attention continues to be given to these and related ligands and their metal complexes, since their properties can be greatly modified by introducing different substituents [10]. As reported for acylhydrazones and of 1,3-diketones [14], S-dithiocarbazate derivatives are also supposed to undergo cycle-chain equilibrium (Fig. 1) and can exist in several distinct isomeric forms. In contrast, thiosemicarbazone derivatives from 1,3-diketones were reported to suffer cyclization only in the presence of a metal substrate to form pyrazolate compounds, besides they were just found to act as bidentate ligands upon complexation with Pd(II) and Pt(II) [15].

On the other hand, transition metal-phosphine complexes, especially with the platinum group elements, are considerably important for both industrial and laboratory scale catalytic applications [16–18]. In the literature there is a number of complexes of Pd(II) and Pt(II)

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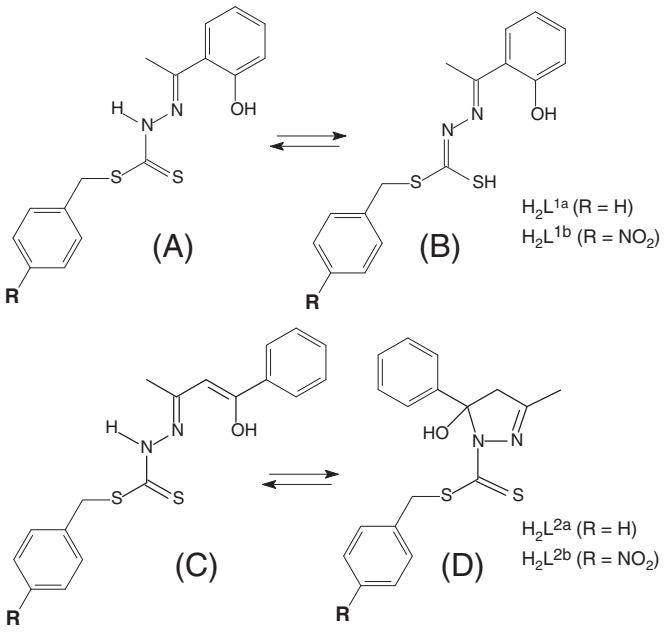

Fig. 1. Possible equilibrium in solution of the ligands used: (A) Thione tautomeric form of H_2L^{1a} and H_2L^{1b}; (B) thiol tautomeric form of H_2L^{1a} and H_2L^{1b}; (C) open-chain form of H_2L^{2a} and H_2L^{1b}; (D) cycle-chain form of H_2L^{2a} and H_2L^{2b}, 5-hydroxypyrazolic form.

with similar ligands, but few studies have been carried out on complexes having tridentate *O,N,S*-donor dithiocarbazate ligands and having triphenylphosphine in the fourth coordination site [19–23].

In the present work we describe the synthesis, spectral properties, crystal structures and the anti-trypanosomal activity of a series of dithiocarbazates derivatives (chart 1) and their complexes: [Pt(L^{1a})(PPh_3)] (**1**), [Pd(L^{1a})(PPh_3)] (**2**), [Pt(L^{1b})(PPh_3)] (**3**), [Pd(L^{1b})(PPh_3)] (**4**), [Pt(L^{2a})(PPh_3)] (**5**) and [Pd(L^{2a})(PPh_3)] (**6**), [Pt(L^{2b})(PPh_3)] (**7**) and [Pd(L^{2b})(PPh_3)] (**8**), where L^{1a}, L^{1b}, L^{2a} and L^{2b} represent the dianions of the ligands H_2L^{1a} = S-benzyl-β-N-(2-hydroxyphenylethylidine)dithiocarbazate, H_2L^{1b} = S-4-nitrobenzyl-β-N-(2-hydroxyphenylethylidine) dithiocarbazate, H_2L^{2a} = 5-hydroxy-3-methyl-5-phenyl-pyrazoline-1-(S-benzyldithiocarbazate) and H_2L^{2b} = 5-hydroxy-3-methyl-5-phenyl-pyrazoline-1-(S-4-nitrobenzyldithiocarbazate), respectively.

2. Experimental

2.1. Materials

[$PtCl_2(PPh_3)_2$], benzyl dithiocarbazate, H_2L^{1a} and H_2L^{2b} were all prepared according to literature procedures [13,17,24,25]. [$PdCl_2(PPh_3)_2$], 4-phenyl-2,4-butanedione, 2-hydroxyacetophenone and all solvents used were of reagent grade, purchased from commercial sources and used without further purification.

2.2. Physical measurements

IR spectra were measured as KBr pellets on a Shimadzu FTIR-spectrometer in the 4000–400 cm^{-1} region. The electronic spectra were recorded with a Shimadzu UV-1800 spectrophotometer. The conductivities of the complexes were measured in DMSO with a Orion Star Series conductimeter. Positive electrospray ionization mass spectrometry (ESI-MS) data were measured using an Agilent 6210 ESI-TOF (time of flight) spectrometer. All MS results are given in the following form: *m/z*, assignment. Elemental analyses (CHNS) were determined using a FISONS EA-1108 micro analyzer or a Heraeus vario EL elemental analyzer. NMR spectra for the complexes **1**, **2**, **5**, **6** and **8** were acquired on a Varian MERCURY plus spectrometer, 7.05 T, operating at 300.07 and 121.47 MHz for ^1H and ^{31}P, respectively. The $^{31}P\{^1H\}$ NMR spectra were externally referenced to H_3PO_4 (85%, δ = 0). The ^1H NMR spectra were internally referenced to TMS (tetramethylsilane). NMR spectra of the free ligands and of the complexes **3**, **4** and **7** were taken using a JEOL multinuclear spectrometer, operating at 399.65 and 161.70 MHz for ^1H and ^{31}P, respectively. Abbreviations used for the reported ^1H NMR spectra are as follows: s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets, m = multiplet.

2.3. X-ray structure determination

Single crystals suitable for X-ray data collections regarding **1**, **3**, **4**, **5**, **6** and **8** were grown by slow concentration of their solutions in a 1:2 mixture of MeCN/CH_2Cl_2. Suitable crystals of **2**·CH_2Cl_2 were obtained by recrystallization from CH_2Cl_2. The data collections were performed with Mo-Kα radiation (λ = 71.073 pm) on a BRUKER KAPPA APEX II CCD or on a STOE IPDS 2 T instrument. Standard procedures were applied for data reduction and absorption correction. The structures were solved by direct methods with SHELXS-97 and refined with SHELXL-97 [26]. The positions of the hydrogen atoms were calculated at idealized positions using the riding model option of SHELXL-97 [26]. Additional crystal data and more information about the X-ray structural analyses are shown in Table S1 as Supplementary data.

2.4. Preparation of the compounds

2.4.1. Preparation of 4-nitrobenzyldithiocarbazate

The previously reported method for preparing substituted dithiocarbazate [6] was modified by reaction with 4-nitrobenzylchloride.

Potassium hydroxide (11.4 g, 0.2 mol) was dissolved completely in 90% ethanol (70 mL) and the mixture was cooled in ice. To the cold solution, hydrazine hydrate (10 g, 0.2 mol) was added slowly, under stirring. Carbon disulfide (15.2 g, 0.2 mol) in ethanol (25 mL) was then added dropwise under vigorous stirring for about 1 h. The temperature of the reaction mixture was kept around −5 °C during the addition by adding nitrogen to the ice. Two layers formed at this time. The resulting yellow oil (lower layer) was separated using a separatory funnel, dissolved in 40% ethanol (40 mL) and cooled in ice. 4-nitrobenzylchloride (32.8 g, 0.2 mol) was partially dissolved in 100 mL of 80% ethanol and added slowly to the above solution under vigorous mechanical stirring. This solution was kept under stirring for 1 h. The resulting pale yellow product was separated by filtration, washed with water and dried. The product was used without further recrystallization. Yield: 85%. Anal. Calcd for $C_8H_9N_3O_2S_2$: (243.30 g mol^{-1}): C, 39.49; H, 3.73; N, 17.27; S, 26.35. Found: C, 40.25; H, 3.44; N, 16.95; S, 25.69%.

2.4.2. Preparation of H_2L^{1b}

4-nitrobenzyldithiocarbazate (4 mmol) dissolved in MeOH (10 mL) was added to a solution of the desired 2-hydroxyacetophenone (4.1 mmol) in MeOH (5 mL). The mixture was refluxed for 2 h. The solutions were cooled to room temperature, after which yellow precipitates were obtained. The solids were filtered off, washed with *n*-hexane and dried in air. Yield: 73%. Anal. Calcd for $C_{16}H_{15}N_3O_3S_2$: (361.43 g mol^{-1}): C, 53.17; H, 4.18; N, 11.63; S, 17.74. Found: C, 54.50; H, 4.43; N, 11.57; S, 17.28%. ^1H NMR (DMSO-d_6, ppm): 2.53 (s, 3H, CH_3), 4.74 (s, 2H, CH_2), 6.90–7.00 (m, 2H, Ph), 7.33–7.65 (m, 2H, Ph), 7.92 (d, J = 8.5 Hz, 2H, Ph), 8.22 (d, J = 8.5 Hz, 2H, Ph), 11.23 (s, 1H, NH), 12.89 (s, 1H, OH).

2.4.3. Preparation of H_2L^{2a}

A solution of 4-phenyl-2,4-butanedione (0.811 g, 5.0 mmol) in MeOH (10 mL) was added to a solution of the S-benzyldithiocarbazate (0.991 g, 5.0 mmol) in MeOH (10 mL). The mixture was refluxed for 2 h