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Preparation and characterization of palladium(II) complexes with *N*-arylalkyliminodiacetic acids. Catalytic activity of complexes in methoxycarbonylation of iodobenzene

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ABSTRACT

The reactions of *N*-arylalkyl derivatives of iminodiacetic acid (H_2Bnida, H_2Peida, H_2Ppida, *o*-H_2Cbida; Bn = benzyl, Pe = 2-phenylethyl; Pp = 3-phenylprop-1-yl; *o*-Cb = *o*-chlorobenzyl) with sodium tetrachloropalladate(II) in aqueous solutions were investigated. Five new palladium(II) complexes [Pd(HBnida)$_2$]·2H_2O (**1a**), [Pd(HBnida)$_2$] (**1b**), [Pd(HPeida)$_2$] (**2**), [Pd(HPpida)$_2$] (**3**) and [Pd(*o*-HCbida)$_2$] (**4**) were prepared and characterized by infrared spectroscopy, ^{1}H, ^{13}C and ^{15}N NMR spectroscopy and thermal analysis (TGA/DTA). The crystal structure of **1a** was determined by single-crystal X-ray structural analysis. The palladium(II) ion in the molecule of **1a** adopts a square planar coordination with two *N*,*O*-bidentate *N*-benzyl-hydrogeniminodiacetate ions. Complex **1a** is a *trans*-isomer. Antitumor properties of the complexes were tested on three human cell lines. The compounds did not significantly inhibit the growth of colon (HCT 116), breast (MCF-7) and lung (H 460) tumor cell lines. All prepared palladium(II) complexes exhibit the acceptable activities towards the methoxycarbonylation of iodobenzene.

1. Introduction

The design of multidentate ligands which have the potential to bind metals in a variety of modes is of great interest to us as we attempt to gain a clear understanding of how the nature of the metal, solvent and also the pH of the reaction mixture combine to give a variety of structures. Using experimental methods for the preparation of various *N*-arylalkyliminodiacetate ligands reported previously [1], we have prepared five palladium(II) complexes due to their possible catalytic and pharmacological properties. Carbonylation represents an important method for transforming bulk and fine chemicals into a diverse set of useful products [2–5], in which CO acts as a most useful C1 building block to introduce carbonyl group into the parent molecules. In the last decades, palladium-catalyzed carbonylation of aryl halides in the presence of nucleophiles has attracted much attention and become a promising tool for the synthesis of aromatic carbonyl compounds such as esters, acids, amides, ketones, alkynones, due to the increasing consciousness of the environmentally benign and efficient methodology in organic synthesis [6–13]. Among the aromatic carbonyl compounds, aromatic esters are conventionally synthesized with the involvement of carboxylic acid precursors. Alternatively, aryl carboxylic acid derivatives can be prepared through palladium-catalyzed carbonylation of the corresponding aryl halides with alcohols, which is defined as alkoxycarbonylation of aryl halides [3,14–17]. The advantages of this method include the broad availability of substrates and the high tolerance of palladium catalysts against a variety of functional groups. Therefore, this route has become a useful tool for the preparation of substituted aromatic esters.

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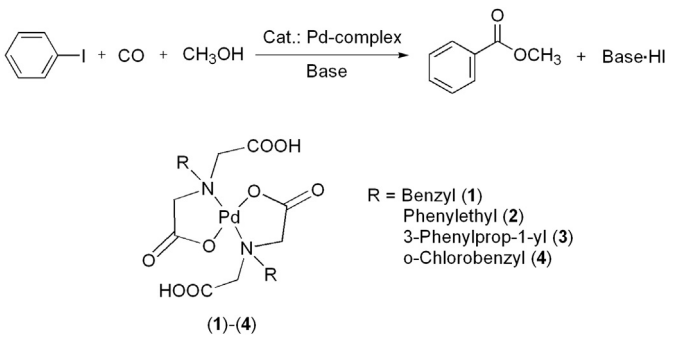
Besides their catalytic aspects, palladium(II) compounds exhibit inherent cytotoxic behavior. On the basis of the structural analogy (d^8 ions in a square-planar geometry) and the thermodynamic difference with platinum(II) complexes, there is much interest in the study of palladium(II) complexes as potential anticancer drugs, especially those bearing the chelating ligands [18–22].

Here we report the preparation, spectroscopic (IR and NMR) and thermal characterization of five new palladium(II) complexes with *N*-arylalkyliminodiacetate ligands as well as their antitumor properties and catalytic activity (Scheme 1). The crystal structure of the complex **1a** is also reported.

2. Experimental

2.1. Materials and physical measurements

Sodium hydroxide and $Na_2PdCl_4 \cdot xH_2O$ ($x \approx 3$), containing 30% Pd by weight, were purchased from Alfa Aesar and used as received without further purification. The ligands were prepared as reported earlier [1]. CHN analyses were performed on Perkin–Elmer 2400 Series II CHNS analyzer in the Analytical Services Laboratories of the Ruđer Bošković Institute, Zagreb, Croatia. The IR spectra were obtained from KBr pellets in the range 4000–450 cm^{-1} with Perkin–Elmer Spectrum RXI FTIR-spectrometer. TGA/DTA measurements were performed at heating rate of 10 °C min^{-1} in the temperature range of 25 – 600 °C, under nitrogen or oxygen flow of 20 mL min^{-1} on instrument Mettler-Toledo TGA/SDTA 851^e. Approximately 10 mg of sample were placed in standard aluminum crucible (40 μL). All NMR measurements were performed on a Bruker DRX AVANCE 500 spectrometer equipped with a 5 mm triple broadband inverse probe (TBI) with a z-gradient coil, and a Varian-NMR-vnmrs 600 spectrometer equipped with a 600 MHz PFG Auto XID ($^1H/^{15}N–^{31}P$ 5 mm) indirect probe. The measurements were carried out in DMSO-d_6 solutions, at the room temperature (303 K), using typical parameter values. Residual solvent signals were used as the secondary references, assuming 2.49 ppm (^1H) and 39.5 ppm (^{13}C) with respect to the TMS signal (0 ppm). Typically, a set of ^1H NMR, ^{13}C NMR, and $^{13}C,^1H$ g-HSQC and HMBC spectra were obtained. The nitrogen-15 chemical shifts were obtained from $^{15}N,^1H$ g-HMBC spectra, optimized for $^nJ(^1H,^{15}N)$ of 3, 6, or 8 Hz, depending on the sample. The nitrogen chemical shifts were given with respect to CH_3NO_2 (0 ppm). The $^1H(^{13}C)$ and ^{15}N NMR chemical shifts of starting ligands (ppm) are given below: H_2Bnida: $^1H(^{13}C)$ [ppm]: 3.41(53.6) $\underline{CH_2}CO_2H$; (172.3) $\underline{C}O_2H$; 3.83(57.1) $\underline{CH_2}Ar$; (138.7) C^i, 7.35(128.7, 128.2) *ortho*, *meta*, 7.26(127.1) *para* Ar; ^{15}N: −349.1 ppm; H_2Peida: $^1H(^{13}C)$ [ppm]: 3.49(54.6) $\underline{CH_2}CO_2H$; (172.4) $\underline{C}O_2H$; 2.88(55.8) $N\underline{CH_2}CH_2Ar$; 2.72(33.7) $NCH_2\underline{CH_2}Ar$; (139.9) C^i, 7.21(128.2) *ortho*, 7.27(128.6) *meta*, 7.18(129.9) *para* Ar; ^{15}N: −350.1 ppm; H_2Ppida: $^1H(^{13}C)$ [ppm]: 3.43(54.8) $\underline{CH_2}CO_2H$; (172.4) $\underline{C}O_2H$; 2.67(53.5) $N\underline{CH_2}CH_2CH_2Ar$; 1.68(29.2) $NCH_2\underline{CH_2}CH_2Ar$; 2.57(32.6) $NCH_2CH_2\underline{CH_2}Ar$; (142.0) C^i, 7.19(128.2) *ortho*, 7.26(128.2) *meta*, 7.16(125.6) *para*, Ar; ^{15}N: −353.1 ppm; *o*-H_2Cbida: $^1H(^{13}C)$ [ppm]: 3.46(53.9) $\underline{CH_2}CO_2H$; (172.3) $\underline{C}O_2H$; 3.96(54.2) $\underline{CH_2}Ar$; (132.9) C^i, 7.63(130.5), (136.4) *ortho*, 7.28(127.1), 7.41(129.1) *meta*, 7.23(128.6) para Ar; ^{15}N: −353.1 ppm. The samples have been measured about one hour after dissolution. In a few days, the samples slowly decomposed in DMSO solutions.



Scheme 1. Methoxycarbonylation of iodobenzene with methanol catalyzed by the palladium(II) complexes **1**–**4**.

2.2. Synthesis of the complexes

An aqueous solution of $Na_2PdCl_4 \cdot xH_2O$ ($x \approx 3$), (0.18 g; 0.5 mmol in 20 mL) was added to a hot solution containing 1 mmol of the appropriate ligands H_2Bnida, H_2Peida, H_2Ppida and *o*-H_2Cbida (Bn = benzyl, Pe = 2-phenylethyl; Pp = 3-phenylprop-1-yl; *o*-Cb = *o*-chlorobenzyl) and 0.04 g (1 mmol) NaOH in 25 mL of water. The resulting yellow solution was left to stand at room temperature for 48 h in case of complex **1a** (the crystallization starts few hours after mixing of the reactants) or overnight in case of the complexes **2**–**4** (**2** crystallizes after few minutes, while **3** and **4** precipitate immediately). The complexes were filtered off by suction, washed with water (5 mL for **1a**, 15 mL for **2**–**4**) and dried. Complex **1a** was dried by standing in air for a few hours, while **2**–**4** were dried first by standing in air for a few days and then in a desiccator over anhydrous $CaCl_2$. Drying the sample of **1a** in a desiccator over solid KOH at room temperature for one week gave $[Pd(HBnida)_2]$ (**1b**). The complexes are soluble in dimethyl sulfoxide and *N*,*N*-dimethylformamide but almost insoluble in water and pyridine.

$[Pd(HBnida)_2] \cdot 2H_2O$ (**1a**). From 0.23 g H_2Bnida. Yellow crystals; yield: 0.19 g (64%). After ~2 weeks, yellow prismatic crystals of **1a** (0.05 g; 17%), suitable for X-ray structural analysis, were obtained by the slow evaporation of the filtrate. Total yield 82%. Anal. Calc. for $C_{22}H_{28}N_2O_{10}Pd$ (586.89): C, 45.02; H, 4.81; N, 4.77%. Found: C, 46.02; H, 4.84; N, 5.08%. The assigned IR data (cm^{-1}): 3586(s) (ν(OH) of H_2O); ~3370(m, broad), 1718(s), 1231(m), 709(w) (ν(OH), ν(C=O), δ(OH) and π(OH) of COOH); 1628(vs) and 1358(m) (ν_{as} and ν_s of COO^-). Other IR data (cm^{-1}): 2932(w), 2711(w), 2602(w), 2515(w), 2365(w), 1942(w, br), 1494(w), 1459(w), 1434(w), 1418(w), 1319(m), 1288(w), 1114(w), 1084(w), 1065(w), 994(w), 964(w), 949(w), 921(m), 898(w), 871(w), 779(w), 751(w), 669(w), 636(w), 598(w), 571(w), 573(w).

$[Pd(HBnida)_2]$ (**1b**). The assigned IR data (cm^{-1}): ~3450 (m, broad), 1736(vs), 1216(s), 698(m) (ν(OH), ν(C=O), δ(OH) and π(OH) of COOH); 1612(vs) and 1380(vs) (ν_{as} and ν_s of COO^-). Other IR data (cm^{-1}): 2928(m), 2744(m), 2674(m), 2598(m), 2534(m), 1494(w), 1456(w), 1416(m), 1326(m), 1260(m), 1112(m), 1084(w), 1050(w), 1026(m), 964(m), 932(m), 892(m), 872(m), 748(m), 636(w), 588(w), 558(w), 524(w), 502(w). $^1H(^{13}C)$ NMR (δ, ppm; *J*, Hz): 3.15, 3.66 (56.1), ^2J 17.6 Hz CH_2 (het. ring); (168.9) (het. ring); 3.37, 4.36 (63.3), ^2J 15.9 $\underline{CH_2}CO_2H$; (176.7) $\underline{C}O_2H$; 3.80, 4.03 (64.0), ^2J 12.5 $N\underline{CH_2}Ar$; (132.3) C^i, 8.21(132.4) *ortho*, 7.49(128.5) *meta*, 7.43(129.1) *para*, Ar. The main to secondary product molar ratio: 1:0.16.

$[Pd(HPeida)_2]$ (**2**). From 0.24 g H_2Peida. Yellow crystals; yield: 0.27 g (93%). Anal. Calc. for $C_{24}H_{28}N_2O_8Pd$ (578.88): C, 49.79; H, 4.88; N, 4.84%. Found: C, 49.87; H, 5.06; N, 4.82%. The assigned IR data (cm^{-1}): ~3450(w, broad), 1731(vs), 1216(s), 701(m) (ν(OH), ν(C=O), δ(OH) and π(OH) of COOH); 1604(vs) and 1370(s) (ν_{as} and ν_s of COO^-). Other IR data (cm^{-1}): 3026(w), 2930(m), 2870(m), 2534(w), 2367(w), 1496(w), 1456(m), 1436(w), 1416(w), 1327(m), 1259(m), 1114(m), 1076(w), 1033(w), 996(w), 884(broad, m), 826(w), 754(m), 625(w), 584(w), 546(w), 522(w), 500(w), 481(w). $^1H(^{13}C)$ NMR (δ, ppm; *J*, Hz): 3.33, 3.72 (58.2), ^2J 17.3 Hz CH_2 (het. ring); (169.3) (het. ring); 3.31, 4.07 (62.7), ^2J 16.5 $\underline{CH_2}CO_2H$; (178.2) $\underline{C}O_2H$; 2.89 (63.5) $N\underline{CH_2}CH_2Ar$; 3.49, 3.92 (32.7) $NCH_2\underline{CH_2}Ar$; (138.1) C^i, 7.48(129.1) *ortho*, 7.33 (128.6) *meta*, 7.28 (126.5) *para*, Ar.