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$[Pd(en)(H_2O)_2]^{2+}$ and $[Pd(pic)(H_2O)_2]^{2+}$ complexation by monohydroxamic acids: A solution equilibrium and solid state approach

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ABSTRACT

Complex formation between $[Pd(en/pic)(H_2O)_2]^{2+}$ (en = ethylenediamine, pic = pyridine-2-methylamine) and primary hydroxamic acids (ahaH = acetohydroxamic, bhaH = benzohydroxamic acid) or secondary hydroxamic acids (meahaH = *N*-methyl-acetohydroxamic, pheahaH = *N*-phenylacetohydroxamic and phebhaH = *N*-phenylbenzohydroxamic acid) was studied in aqueous solution by pH-potentiometry, ^1H NMR and ESI-TOF-MS. Secondary hydroxamates form 1:1 species with the $[Pd(N,N)(H_2O)_2]^{2+}$ ions via the [O,O] chelating sets. Unexpectedly, in the primary ligands deprotonation and coordination of the hydroxamate-NH starts as low as pH <2, where the $R_CC(O)N^-O^-$ ion is capable of linking two [Pd(diamine)]$^{2+}$ units via the coordination through the [O,O] chelate to one unit and through the monodentate hydroxymato-N^- atom to the another one. As a consequence, primary ligands can bind an excess of metal ion too. A trinuclear complex predominates in a wide pH-range (5–10 for en, 3–10 for pic) and the hydroxide ion starts to compete with the hydroxymato ligand only above pH 10. In the trinuclear species two [O,O] chelated Pd(II) units are bridged via a third palladium core that binds to the hydroximato-N donors of the two ligands. This binding mode was also proved by MS studies in solution and by revealing the molecular structure of $[(Pd(en))_3(bhaH_{-1})_2](BF_4)_2{\cdot}2H_2O$ (**2**), the first reported structure with a Pd(II)-hydroxymate-N^- monodentate coordination, characterized with single crystal X-ray diffraction in the solid state.

1. Introduction

Since the antitumor activity of *cis*-$[Pt(NH_3)_2Cl_2]$ (cisplatin) in 1964 was discovered, intensive research has been carrying out on various platinum complexes [1]. To find agents with high efficacy and especially with high selectivity, large number of platinum(II) complexes have been prepared and characterized both from chemical and biological aspects and, in addition to cisplatin, a few other complexes of this metal ion (*e.g.* carboplatin, oxaliplatin) are already applied in the chemotherapy [2]. Investigation of the complexation between platinum(II) and various ligands in solution is hindered by the inertness of these compounds [2]. At the same time, the lighter congener, palladium(II), that shows very similar coordination chemical properties to platinum(II), forms much more labile complexes therefore solution equilibrium studies on its complexes are possible [3]. Although this fact has initiated plenty of works on palladium(II)-containing complexes, several difficulties might also appear during solution equilibrium studies on Pd(II)-containing systems. For example, the unstable nature and its very high tendency for hydrolysis hinders the use of $[Pd(H_2O)_4]^{2+}$ in the investigations. Therefore, either $[PdCl_4]^{2-}$, or a rather stable and inert mono-complex formed between a diamine (*e.g.* ethylenediamine (en), 2-picolylamine (pic)) or a triamine (*e.g.* diethylenetriamine (dien), terpyridine (terpy)) and Pd(II) are generally used as metal ion sources. Investigation of the interaction of these latter complexes with different bioligands revealed the high preference of the metal core toward soft donor atoms (N- or S-donors) over the hard one(s) [3–12].

Although, the importance of hydroxamate-based compounds in various bio-relevant processes is well-known [13], their interaction with Pt(II) and Pd(II) has been studied quite rarely [14–18]. Perhaps, the reason of this previous slight interest has originated

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from the knowledge that a hydroxamate function coordinates to a metal ion typically via its two hard oxygens donors (carbonyl oxygen atom and deprotonated hydroxyl oxygen), and, as mentioned, hard donors are not preferred by the soft Pt(II) and Pd(II) metals [14,19]. However, the results obtained in the few previous studies, show quite high diversity of the coordination modes of hydroxamic acid based molecules in their Pt(II) and Pd(II) complexes. For example, synthesis of a series of Pt(II) and Pd(II) complexes with salicylhydroxamate revealed that not only the expected [O,O] coordination but an "atypical" [N,O]-type one was also found where the phenolate-*O* and hydroxamate-*N* donors form a six-membered chelate [16]. In another case, an organometallic dinuclear Pt(II) complex was found to form with benzohydroxamic acid. In this complex, two Pt(II)-diamine cores are bridged via a triply deprotonated benzohydroxamate ligand. The ligand is coordinated through the two hydroxamate-*O* donors to a Pt(II) core, while a [N,C] chelate to another one. The Pt(II)-*C* bond is formed from the deprotonation of the ortho carbon of the phenyl ring [15]. In the complex, *cis*-[$Pt^{II}Cl_2$(*x*-pyhaH)$_2$] (where *x* = 3 or 4, the pyridinehydroxamic acid ligand (pyrhaH) is coordinated to the platinum ion via the pyridine nitrogen only, leaving the hydroxamic acid function free for the potential release of cytotoxic nitric monooxide (NO) [20]. In the dinuclear complex, [{cis-Pt$(NH_3)_2$}$_2$(μ-2-pyhaH$_{-1}$)]$(ClO_4)_2{\cdot}H_2O$, the two Pt(II) centers are bridged via an [O,O] and an [N,N] chelate. The latter one involves hydroximato-*N* and pyridine-*N* donor atoms [21].

Although equilibrium studies might be possible with Pd(II)-containing systems (unlike Pt(II)), only a very limited number of papers deal with Pd(II)-hydroxamate complexes in solution [17,22]. In one of the few studies, stability constants were published for the bis and ternary complexes formed in the Pd(II)-methioninehydroxamic acid and Pd(II)-methioninehydroxamic acid-glycylglycine systems, respectively. In the same work, precipitation hindered the solution equilibrium study with several other aminohydroxamic acids [22]. The first examples for the existence of di- and trinuclear Pd(II) complexes between $[Pd(en)]^{2+}$ and a dihydroxamic acid (2,5-pyridinedihydroxamic acid) in solution were described in one of our previous papers [17].

To get a deeper insight into the interaction of hydroxamic acids with Pd(II), complexation between $[Pd(diamine)(H_2O)_2]^{2+}$ (diamine = en or pic) and various monohydroxamic acids ($R_CCO(R_N)NOH$) in solution has been studied (see Scheme 1 for the formulae of the monohydroxamic acids and bonding mode in the Pd(II) amine cores).

Scheme 1 indicates that monohydroxamic acids bearing different R_C and R_N substituents were studied providing also the possibility to gain information about sterical and electronic effects of substituents on the Pd(II)-binding ability of a hydroxamate function. To support the solution equilibrium results and to explore the stoichiometry and binding features of the complexes synthesis and characterization of some Pd(en)-monohydroxamates have also been carried out in the solid state. The results, obtained both from solution and solid state studies, might even be interesting in the development of new strategies for the removal of Pd catalysts [17,23], in the development of new catalysts [24], or modeling analogous but kinetically more inert Pt(II)-containing compounds.

2. Experimental

2.1. Materials and methods

$K_2[PdCl_4]$, ethylenediamine (en), 2-picolylamine (pic), acetohydroxamic acid (ahaH), benzohydroxamic acid (bhaH), *N*-methylhydroxylamine hydrochloride, KPF_6, $NaBF_4$ and $AgNO_3$ were commercially available chemicals of highest purity supplied by Aldrich, Fluka or Merck. *N*-phenylhydroxylamine hydrochloride was synthesized from nitrobenzene according to a reported procedure [25]. *N*-Phenyl-benzohydroxamic acid (phebhaH), *N*-methyl-benzohydroxamic acid (mebhaH) and *N*-methyl-acetohydroxamic acid (meahaH) were prepared from the appropriate acid chlorides and *N*-phenylhydroxylamine or *N*-methylhydroxylamine using a previously published procedure [26]. Identity and purity of the ligands were checked by NMR and MS methods. The concentrations of the ligand stock solutions were determined by pH-potentiometric titrations [27]. The palladium(II) complexes, $[Pd(en)Cl_2]$, $[Pd(en)(H_2O)_2](NO_3)_2$ and $[Pd(pic)(H_2O)_2](NO_3)_2$ (the complex cations abbreviated later as $[Pd(en)]^{2+}$ and $[Pd(pic)]^{2+}$) were prepared from $K_2[PdCl_4]$ by the procedure detailed in Ref. [5]. ^{1}H NMR spectra were acquired on a Bruker WP 360 SY instrument at room temperature in D_2O or DMSO-d^6 and referenced to sodium 3-(trimethylsilyl)-propionate (TSP). ESI-TOF-MS spectra were registered on a Bruker micrOTOF-Q 9 instrument in the positive and/or negative mode. IR spectra were recorded on a Jasco FT/IR-4100 instrument while elemental analyses were conducted on Elementar Vario MICRO CUBE instrument at the Department of Organic Chemistry, University of Debrecen, Hungary.

2.2. Crystal structure analysis

The diffraction intensity data collection was carried out at 293 K on a SuperNova diffractometer equipped with an Atlas detector using Mo K_α radiation (λ = 0.71073 Å). The structure was solved by SIR-92 program [28] and refined by full-matrix least-squares method on F^2, with all non-hydrogen atoms refined with anisotropic thermal parameters using the SHELX package [29]. Publication material was prepared with the WINGX-suite [30]. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were treated with a mixture of independent and constrained refinement. Hydrogen atoms of the methylene and NH_2 groups in 2 were refined using a riding model. Hydrogen atoms of water molecules were found at the difference electron density map but the distances of hydrogen and oxygen atoms should be restrained in the final stage of the refinement. Some disorder was observed at the tetrafluoroborate anions resulting in a few abnormal hydrogen-acceptor distances in hydrogen bonds with the participation of fluorine atoms. Crystallographic and experimental details are summarized in Table 1.

2.3. [Pd(en)phebha]PF_6 (**1**)

To $[Pd(en)Cl_2]$ (40.0 mg, 0.168 mmol) dissolved in water (4 mL) $AgNO_3$ (57.36 mg, 0.336 mmol) was added and the reaction mixture was stirred for 2 h in the dark. AgCl was filtered off and to the resulting solution phebhaH (35.78 mg, 0.168 mmol) was added. pH of the reaction mixture was set to 8.0 with the aid of 0.2 M KOH solution and five drops of MeOH was used to enhance dissolution of the ligand. KPF_6 (40.0 mg, 0.217 mmol) was added to the clear solution and after dissolution the reaction mixture was stored at 4 °C overnight. The yellow microcrystalline complex was collected by filtration washed with a small amount of water and diethyl ether and dried under vacuum, yield 34.9 mg (69%). $C_{15}H_{18}F_6N_3O_2PPd$ (523.71): calcd. C 34.40, H 3.46, N 8.02; found C 34.41, H 3.44, N 7.97. ^{1}H NMR: (360 MHz, DMSO, 298 K): δ = 2.45 (s, 4 H, –CH_2 en), 5.35 (s, 2 H, –NH_2), 5.44 (s, 2 H, –NH_2), 7.24–7.40 (m, 10 H, ArH) ppm. IR (KBr): $\nu_{max.}$ = 839 (P–F), 1419 (C–N), 2899 (C–H), 2966 (C–H), 3133 (C–H), 3301 (N–H), 3352 (N–H) cm^{-1}.