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Synthesis of Some Palladium(II) Complexes of 1,2-Diaminocyclohexane and Dicarboxylates as Cisplatin Analogues of Palladium Series

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Abstract □ Ten [Pd^{II}(dicarboxylato)(1,2-diaminocyclohexane)] complexes were prepared after the antitumor-active Pt(II)-1,2-diaminocyclohexane complexes as the cisplatin analogues of palladium series. They were characterized by means of elemental analysis, IR and NMR spectroscopy. As a result, the dicarboxylate ligands were confirmed to be chelated with Pd(II) within the scope studied. The stability differences between the dicarboxylato complexes according to the chelate ring size could not be differentiated due to generally lower thermodynamic stability of the dicarboxylato Pd(II) complexes.

Keywords □ Pd(II)-dach complexes, Pd(II)-dicarboxylato complexes, cisplatin analogues.

The discovery of *cis*-diamminedichloroplatinum (II) (cisplatin) as an antitumor agent has stimulated much interest in the search for more potential and less toxic antitumor platinum and other metal complexes,[1-3] thus having better therapeutic indices. In the earlier development of analogous Pt(II) complexes of cisplatin, it was observed that for the antitumor activity charge neutrality and ligands of moderate stability were essential, namely, the charged complexes or complexes having ligands with fast leaving rates were shown to be inactive and toxic[4]. Although recent studies revealed that some charged Pt(II) complexes and/or the complexes having ligands with fast leaving rates showed good antitumor activity,[5] some of cisplatin analogues developed meeting the above requirements are considered to be potential second-generation antitumor agents.[6] Like cisplatin, however, they still have drawbacks such as high nephrotoxicity, low water solubility, and relative inactivity against gastrointestinal tumors.[7]

The structurally analogous palladium complexes showed either little or marginal activity[1]. However, Gill[8] reported several palladium complexes having bidentate amine ligands which showed antitumor activity comparable to or greater than cisplatin. The little or marginal antitumor activities of the former palladium complexes were explained on the basis of fast reactivities of the leaving groups as the reactivity of Pd(II) complexes is approximately 10^5 times higher compared to Pt(II) complexes.[9] Thus, in order to develop active antitumor palladium complexes, it seems to be imperative to moderate the lability of the leaving groups. Gill adopted the use of dicarboxylates as chelating agents for the purpose as one of approaches to the goal. He, however, reported the preparation, without any characterization, of only three Pd(II) complexes having 1,2-diaminocyclohexane and dicarboxylato ligands which showed the activity.[8]

In this paper, we report the synthesis and structural characterization of ten uncharged 1,2-diaminocyclohexane-dicarboxylato Pd(II) complexes prepared by procedures different from those of Gill, as the palladium series of cisplatin analogues.

The following abbreviations are used for some ligands and others: dach, *trans-dl*-1,2-diaminocyclohexane; cbdc, 1,1-cyclobutanedicarboxylato; phthalato, *o*-phthalato; DMSO, dimethyl sulfoxide. The abbreviations commonly used for some ligands are also used without full nomenclature.

EXPERIMENTAL METHODS

Materials and instruments

The reagents purchased were of analytical grade and used without further purification except dach which was recrystallized as the dihydrochloride. Ag_2O was used as a freshly prepared wet product. All the dicarboxylic acids used were L-forms where stereoisomers exist.

Decomposition points (dec.p.) were determined with an electrothermal micro melting point apparatus and uncorrected. FT-IR spectra were recorded on a Bomem Michelson 100 spectrophotometer. ^{1}H- and/or ^{13}C-NMR spectra were obtained with Brucker AM 300 spectrometer using trimethylsilane as an internal standard. Elemental analysis was performed on a W.C. Heraeus D 5450 elemental analyzer.

Syntheses

[PdCl$_2$(dach)] : Previously, dach dihydrochloride was 6prepared by a modification of the published procedure for ethylenediamine dihydrochloride,[10] and K_2PdCl_4, essentially after the published procedure[11] starting from $PdCl_2$. [$PdCl_2$(dach)], a starting material for the products, was prepared by a modification of the procedure for [$PtCl_2$(en)][12] as follows: To a solution containing K_2PdCl_4 (3.264g, 10 mmole) in water (20 m*l*), a solution of dach dihydrochloride (1.872g, 10 mmole) in water (60 m*l*) was added portionwise with stirring. Then, 0.2 M NaOH was added portionwise to the stirred resulting solution mixture to precipitate a yellow solid until the pH of the reaction mixture was raised to *ca.* 7. After further stirring the mixture for several hrs, the precipitate was collected by filtration, washed with 0.01 N HCl, water, EtOH and ether. The crude product was further purified by treatment with Ag_2O in water and precipitation of the dichloro complex with 1 N HCl. After being washed with water and the above-mentioned other solvents, the product was dried *in vacuo*.

Yield: 97%, IR (KBr) cm^{-1}: 3274, 3194, 1557 (NH_2); ^{1}H-NMR (DMSO-d_6) δ: 0.85-1.30 (4H, m), 1.35-1.60 (2H, m), 1.75-1.90 (2H, m), 2.10-2.30 (2H, m), 4.50-4.72 (2H, m), 4.80-5.00 (2H, m); ^{13}C-NMR (DMSO-d_6) δ: 23.57 (γ-C[8]), 32.12 (β-C), 60.96 (α-C); Anal. calcd. for $C_6H_{14}N_2Cl_2Pd$: C, 24.72; H, 4.84; N, 9.61. Found: C, 24.83; H, 4.96; N, 9.55.

[Pd(dicarboxylato)(dach)] : The following complexes were prepared by one of two procedures described below each. [Pd(malonato)(dach)] **1**, [Pd(methylmalonato)(dach)] **2**, [Pd(dihydroxymalonato)(dach)] **3**, [Pd(cbdc)(dach)] **4**, [Pd(malato)(dach)] **5**, [Pd(tartrato)(dach)] **6**, [Pd(glutarato)(dach)] **7**, [Pd(diglycolato)(dach)] **8**, [Pd(phthalato)(dach)] **9**, [Pd(homophthallto)(dach)] **10**.

(a) *Via* the reaction of [$PdCl_2$(dach)] with Ag_2O. Complexes **1-8** were prepared by a modification of the published procedure for [Pd(malonato)(S-pn)] (S-pn=(S)-propylenediamine)[13] *via* the above reaction to yield an intermediate and subsequent reaction *in situ* with each dicarboxylic acid. For example, [Pd(malonato)(dach)], **1** was prepared as follows: A suspension of [$PdCl_2$(dach)] (292 mg, 1 mmole) and Ag_2O (slightly excessive than 1 mmole) in water (10 m*l*) was stirred in the dark at room temperature for 30 min. The AgCl precipitate formed was removed by centrifugation and the supernatant, a pale yellow intermediate solution, filtered to remove any AgCl precipitate left. To the stirred intermediate solution, a solution of malonic acid (104 mg, 1 mmole) dissolved in water (*ca.* 2 m*l*) was added dropwise and stirred further in the dark at room temperature for *ca.* 12 hrs. During the reaction, a precipitate formed after *ca.* 1 hr. This was filtered, recrystallized from water by dissolving at 40℃, washed with EtOH and ether, and dried *in vacuo*.

Grayish yellow powder, yield: 0.12g (38%), dec.p.: 222-229℃ (Not so correct due to very gradual discoloration. It is also the case with all the other complexes prepared.), IR (KBr) cm^{-1}: 3188, 3079 (NH_2), 1655, 1621, 1397 (COO^-); ^{1}H-NMR (DMSO-d_6, 50 ℃) δ: 0.80-1.20 (4H, m), 1.40-1.50 (2H, m), 1.72-1.83 (2H, m), 2.10-2.22 (2H, m), 3.21 (2H, s), 4.60-4.71 (2H, m), 5.05-5.18 (2H, m); Anal. calcd. for $C_9H_{16}N_2O_4Pd$: C, 33.51; H, 5.00; N, 8.68. Found: C, 33.54; H, 5.06; N, 8.74.

Except for **3**, the other complexes were prepared similarly. During each reaction of the intermediate with each dicarboxylic acid, a precipitate of each product formed within a few hours. **2**, **4** and **6-8** were recrystallized from water by dissolving them also at 40℃.

[Pd(methylmalonato)(dach)], ***2*** : Grayish yellow powder, yield: 0.12g (36%), dec.p.: 210-217℃, IR (KBr) cm^{-1}: 3193, 3105 (NH_2), 1649, 1621, 1408 (COO^-), ^{1}H-NMR (DMSO-d_6, 50℃) δ: 0.80-1.25 (4H, m), 1.07

(3H, d, J=6.9 Hz), 1.42-1.58 (2H, m), 1.70-1.82 (2H, m), 2.10-2.22 (2H, m), 3.67 (1H, q, J=6.9 Hz), 4.49-4.70 (2H, m), 4.95-5.15 (2H, m); Anal. calcd. for $C_{10}H_{18}N_2O_4Pd$: C, 35.68; H, 5.39; N, 8.32. Found: C, 35.91; H, 5.64; N, 8.46.

[***Pd(dihydroxymalonato)(dach)***], ***3*** : No precipitate formed in the reaction between the intermediate and the acid, and so the reaction solution was stirred for *ca.* 20 hrs. This was evaporated under reduced pressure to *ca.* 3 m*l* at 40℃ and refrigerated overnight at 0℃. The crystals obtained were filtered, recrystallized from water, washed with ether and dried *in vacuo*.

Yellow crystal, yield: 0.15g (43%), dec.p.: 178-185℃, IR (KBr) cm $^{-1}$: 3269, 3198 (OH, NH_2), 1637, 1619, 1441 (OH, CH_2), 1410 (COO^-); ^{1}H-NMR (D_2O, 50 ℃) δ: 1.06-1.30 (4H, m), 1.52-1.65 (2H, m), 1.90-2.05 (2H, m), 2.45-2.52 (2H, m); Anal. calcd. for $C_9H_{16}N_2O_6Pd$: C, 30.48; H, 4.55; N, 7.90. Found: C, 30.19; H, 4.69; N, 7.75.

[***Pd(cbdc)(dach)***], ***4*** : Pale yellow power, yield: 0.15g (42%), dec.p.: 228-236℃, IR (KBr) cm^{-1}: 3234, 3101 (NH_2), 1626, 1600, 1377 (COO^-); ^{1}H-NMR (DMSO-d_6, 40℃) δ: 0.90-1.25 (4H, m), 1.40-1.79 (6H, m), 2.05-2.22 (2H, m), 2.70-2.85 (4H, m), 4.50-4.57 (2H, m), 4.99-5.04 (2H, m); ^{13}C-NMR (DMSO-d_6, 40℃) δ: 20.02, 28.70, 36.08, 37.62, 61.83, 65.42, 182.15; Anal. calcd. for $C_{12}H_{20}N_2O_4Pd$: C, 39.74; H, 5.56; N, 7.72. Found: C, 39.71; H, 5.46; N, 7.87.

[***Pd(malato)(dach)***], ***5*** : Grayish yellow powder, yield: 0.14g (40%), dec.p.: 220-226℃, IR (KBr) cm^{-1}: 3266, 3198 (OH, NH_2), 1588 (COO^- NH_2), 1395 (COO^-); Anal. calcd. for $C_{10}H_{18}N_2O_5Pd$: C, 34.06; H, 5.14; N, 7.94. Found: C, 33.84; H, 5.35; N, 7.92.

[***Pd(tartrato)(dach)***], ***6*** : Grayish yellow powder, yield: 0.21g (57%), dec.p.: 180-187℃, IR (KBr) cm^{-1}: 3265, 3183 (OH, NH_2), 1620, 1585, 1398 (COO); Anal. calcd. for $C_{10}H_{18}N_2O_6Pd$: C, 32.58; H, 4.92; N, 7.60. Found: C, 32.83; H, 5.21; N, 7.59.

[***Pd(glutarato)(dach)***], ***7*** : Pale yellow powder, yield: 0.20g (56%), dec.p.: 208-213℃, IR (KBr) cm^{-1}: 3266, 3190 (NH_2), 1660 (COO), 1586 (COO^-, NH_2), 1400 (COO^-); Anal. calcd. for $C_{11}H_{20}N_2O_4Pd$: C, 37.68; H, 5.75; N, 7.99. Found: C, 37.88; H, 6.02; N, 8.10.

[***Pd(diglycolato)(dach)***], ***8*** : Pale yellow powder, yield: 0.13g (38%), dec.p.: 212-220℃, IR (KBr) cm^{-1}: 3268, 3197 (NH_2), 1669, 1602, 1407 (COO^-), 1129 (COC); Anal. calcd. for $C_{10}H_{18}N_2O_5Pd$: C, 34.06; H, 5.14; N, 7.94. Found: C, 34.18; H, 5.38; N, 8.04.

(b) *Via* the reaction of $[PdCl_2(dach)]$ with $AgNO_3$. Complexes **9** and **10** were prepared by a slight modification of the conventional procedure for analogous Pt(II) complexes[14] *via* the above reaction to yield another intermediate and subsequent reaction *in situ* with each dicarboxylic acid neutralized with NaOH. As an example, [Pd(phthalato)(dach)], **9** was prepared as follows: A suspension of $[PdCl_2(dach)]$ (292 mg, 1 mmole) and $AgNO_3$ (323 mg, 1.9 mmole) in water (10 m*l*) was stirred in the dark for 2 hrs. The AgCl precipitate formed was removed as described in (a). To the stirred pale yellow intermediate solution, a solution of *o*-phthalic acid (158 mg, 0.95 mmole) neutralized with 1 M NaOH (0.95 m*l*) was added dropwise and stirred further in the dark at room temperature for *ca.* 2 hrs. A precipitate formed soon after the addition of the phthalate solution. This was filtered, just washed in water at 40℃. After collection, the precipitate was washed with EtOH and ether, and then dried *in vacuo*.

Pale yellow powder, yield: 0.27g (75%), dec.p.: 226-233℃, IR (KBr) cm^{-1}: 3260, 3207 (NH_2), 1612 (COO), 1574 (NH_2, phenyl), 1388 (COO^-); Anal. calcd. for $C_{14}H_{18}N_2O_4Pd$: C, 43.71; H, 4.72; N, 7.28. Found: C, 43.98; H, 4.75; N, 7.41.

[***Pd(homophthalto)(dach)***], ***10 was prepared similarly*** : Pale yellow powder, yield: 0.29g (78%), dec.p.: 210-217℃, IR (KBr) cm^{-1}: 3253, 3192 (NH_2), 1612 (COO^-), 1586 (COO^-, phenyl), 1380 (COO^-); ^{1}H-NMR (DMSO-d_6, 50℃) δ: 0.90-1.30 (4H, m), 1.40-1.65 (2H, m), 1.75-1.95 (2H, m), 2.15-2.45 (2H, m), 3.54 (2H, s), 4.45-4.70 (2H, m), 5.05-5.25 (2H, m), 7.06-7.62 (4H, m); Anal. calcd. for $C_{15}H_{20}N_2O_4Pd$: C, 45.18; H, 5.06; N, 7.02. Found: C, 45.38; H, 5.10, N, 6.85.

Water solubilities of the complexes

In a water bath of 40℃, water was added portionwise with intervals to an appropriate amount of each complex with stirring until complete dissolution was effected except for three (malato, phthalato, and homophthalto) complexes which remained almost or practically undissolved even in 50 m*l* of water to 10 mg of each complex. The solutions were allowed to cool to room temperature (*ca.* 30℃), when no precipitation or crystallizing out was observed.

RESULTS AND DISCUSSION

Characterizatioin of the complexes

In the IR spectral data, the [Pd(dicarboxylato)-(dach)] complexes exhibit the two NH_2 absorption bands at 3270-3100 cm^{-1} compared to those at *ca.* 3390 and 3300 cm^{-1} for free dach[15] and three COO^- stretching bands at 1670-1585 cm^{-1} (two) and at 1410-1380 cm^{-1} (Only one is conspicuous.) compared to those at (*ca.* 1600 and) *ca.* 1560 cm^{-1} (namely, one or two), and *ca.* 1400 and *ca.* 1370 cm^{-1} in case of free malonate. When the malonato complex, for example, is compared to free malonate, the absorptions at 1655 and 1621 cm^{-1}, and 1397 cm^{-1} seem to correspond to those at 1600 and *ca.* 1560 cm^{-1}, and 1390 cm^{-1} in sodium malonate, respectively[16]. Thus, the prominant shift of the former antisymmetric COO^- stretching vibrations to higher frequencies verifies the complexation of malonate ion, which leads to the postulation that it is also the case with the other dicarboxylato complexes considering for the essentially similar properties of the dicarboxylates.

The NMR spectroscopy was also carried out to confirm the chelate formation by each dicarboxylato ligand for five among the ten complexes due to their solubility problem. Specifically, only the cbdc complex showed the bare solubility required in DMSO-d_6, the solvent usable for recording both ^{1}H- and ^{13}C-NMR spectra though at elevated temperature (*ca.* 40℃), and for the other three complexes (**1,2** and **10**), only ^{1}H-NMR spectra were obtained with difficulty even at 50℃. It is also the case for another complex **3** except for using D_2O.

Thus, the cbdc complex which is an analogue of the well-known Pt(II) complex, carboplatin, is more suitable as an example for elucidating the chelate structure directly. It has the molecular formula of $C_{12}H_{20}N_2O_4Pd$ and common distorted square-planar geometry for Pd(II) complexes of different donor atoms[17], and so postulated C_2 symmetry through the center of dach-Pd-dicarboxylato skeleton exhibited eight peaks in detail of 2H each and another one of 4H by ^{1}H-NMR indicating the expected symmetrical chelate structure formed with the dicarboxylato ligand as well as the dach ligand. The complex also gave seven carbon peaks attributable to the α- through θ-C atoms in the structural formula (Fig. 1), which is in accord with the above-mentioned chelate structure.

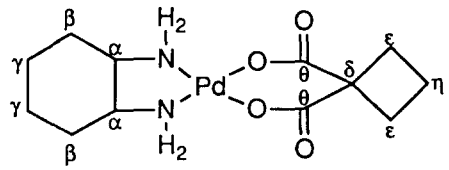

Fig. 1. Structure of [Pd(cbdc)(dach)] with labeling of C atoms.

A paper[18] appeared giving support to the above structure in which the absolute configuration of analogous [Pt(malonato)(dach)] was determined elucidating the chelate structure.

Consequently, in combination with the IR and elemental analysis data, and on the basis of the common nature of dicarboxylato ligands forming the bidentate chelate structures with metals, aside from the pmr data for complexes **1-3** and **10** which alone suggest the chelate structures of the complexes, it is reasonable to postulate that all the dicarboxylato complexes prepared have the chelate structures like the one shown in Fig. 1.

Preparative schemes

The conventional procedure for obtaining *cis*-$[MX_2A_2]$ (M=Pt, Pd; X=monoanion, X_2=dianion; A=monoamine, A_2=diamine)[8,14] has been treating the starting material *cis*-$[MX_2A_2]$ (X=Cl, I) with an amount slightly smaller than equivalent of $AgNO_3$ to obtain the intermediate *cis*-$[MA_2(H_2O)_2]^{2+}$ *in situ* and allowing it to react with anionic ligand(s) (Y=monoanion, Y_2=dianion) as shown by equations in Scheme 1.

$$cis\text{-}[MX_2A_2] + 2AgNO_3 + 2H_2O \longrightarrow cis\text{-}[MA_2(H_2O)_2]^{2+} + 2NO_3^- + 2AgX \quad \text{(Ia)}$$

$$cis\text{-}[MA_2(H_2O)_2]^{2+} + 2Y^- \text{ (or } Y_2^{2-}) \longrightarrow cis\text{-}[MY_2A_2] + 2H_2O$$

Scheme 1

Because of lack of water solubilities of *o*-phthalic and homophthalic acids themselves, complexes **9** and **10** were prepared according to Scheme 1.

Meanwhile, Nakayama *et al.*[13] introduced another procedure for the similar products (M=Pd, A_2=S-pn) in which the starting material was treated with

an equimolar amount of Ag_2O to obtain the intermediate *cis*-$[Pd(OH)_2A_2]$ *in situ*, and this was allowed to react with each acid itself as shown by equations in Scheme 2.

cis-$[PdCl_2A_2]$ + Ag_2O + H_2O
$\longrightarrow$*cis*-$[Pd(OH)_2A_2]$ + 2AgCl
(Ib)

cis-$[Pd(OH)_2A_2]$ + 2HY(or $(HY)_2$)
$\longrightarrow$*cis*-$[PdY_2A_2]$ + $2H_2O$

Scheme 2

In fact, they presumed the formation of dimeric complex base $[\{Pd(\mu\text{-}OH)A\}_2](OH)_2$ ($[\{Pd(\mu\text{-}OH)A\}_2]^{2+}$ (II)) as the intermediate instead of Ib by the reaction of an equimolar amount of each reactant without mentioning the pH of the intermediate solution. On the other hand, they confirmed the formation of Ib at pH *ca.* 12 and II at pH *ca.* 7 in the study of an equilibrium between them. This finding is similar to that found in the study of equilibria between the analogous Pt(II)-dach complexes of Ia, Ib and II by Gill *et al.*, *i.e.*, they observed almost exclusive presence of Ib form at pH>10[19]. In this respect, as the pH of the intermediate solution obtained in the present study was *ca.* 11.2, at least predominant formation of Ib, which would be also the case with the intermediate obtained by Nakayama *et al.*, is postulated from analogy with similar coordination chemistries of platinum and palladium.[8] This postulation is further supported by the preparation of $[M(OH)_2L]$ (M=Pt, Pd; L=bipy, phen) by Wimmer *et al.*[20] by the same reaction as shown above. The procedure shown in Scheme 2 has the advantages of full utilization of the starting material without possible contamination of the intermediate by Ag^+ and using the acid itself without neutralizing it. Thus, complexes **1-8**, having an anionic ligand from the dicarboxylic acid of considerable water solubility each, were prepared according to Scheme 2.

Nature of the dach-dicarboxylato complexes

The Pd(II)-dach complexes were chosen after the analogous Pt(II)-dach complexes which show relatively good antitumor activity without cross resistance with cisplatin.[21a] The dicarboxylato ligands were chosen also after the analogous antitumor active carboxylato Pt(II) complexes with reduced toxicity.[21b] They are the chelating leaving groups of moderate leaving capacity[21c], and the dicarboxylato complexes would be expected to show water solubility in some extent required for the expected antitumor activity through hydrogen bonding of water molecules to the uncoordinated carboxylate oxygen atoms.

In selecting the dicarboxylato ligands, mainly malonato derivatives, and succinate derivatives and their aromatic equivalents (with regard to the chelate ring members) were chosen on the basis of (a) the reported more potent antitumor activities exerted by the two parent and substituted malonato-Pd(II)-dach complexes compared to the oxalato complex[8] and (b) the interest in the size of chelate rings they form with Pd(II), which is closely related to the stability of metal complexes.[22] However, no apparent stability differences were observed between the three malonato complexes which have generally stable six-membered rings and glutarato, diglycolato and homophthalto complexes which have rather unstable eight-membered rings, and, on the whole, their instabilities were observed when their mixtures for the preparation were stirred at room temperature (*ca.* 30°C) for several-*ca.* 20 hrs., *i.e.*, a trace amount of fine black decomposition product (seemingly metallic palladium which adhered to the magnetic stirring bar) formed.[23] The instabilities shown are convincing based on the somewhat lower thermodynamic and kinetic stabilities of Pd(II) complexes compared to Pt(II) complexes.[24]

Water solubilities of the complexes

For the determination of water solubilities of the complexes, though rough, their recrystallization from a measured amount of water was attempted.

Among the complexes, only **3** showed considerable solubility (*ca.* 15 mg/ml), and those of the others were in the order: **4-7** (2.2-2.3 mg/ml)>**1** (*ca.* 1.4 mg/ml)>**2** (*ca.* 0.7 mg/ml)>**6** (*ca.* 0.6 mg/ml)>**8** (*ca.* 0.5 mg/ml). Thus, not to mention **3**, the solubilities of the former three complexes are higher than that (1 mg/ml in 5% dextrose solution[25]) of cisplatin. On the other hand, **5** was unexpectedly hardly soluble, and **9** and **10** seemed to be practically insoluble probably due to the greater nonpolar characteristic of the phenyl portion compared to the polar one of the dicarboxylate portion. Thus, the attempted

dissolution of the three complexes resulted in merely thorough washing of them with water.

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