# [Pd(CBDCA-*O,O'*)$(NH_3)_2$]: the $Pd^{II}$ Analogue of a Platinum Anticancer Drug (CBDCA = cyclobutane-1,1-dicarboxylate)

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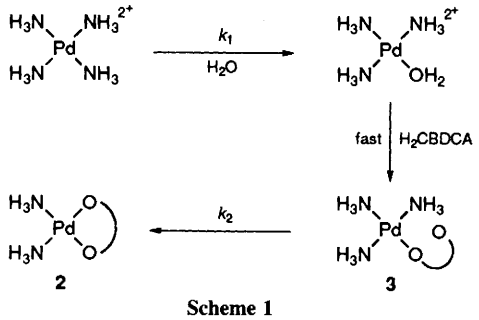
The X-ray crystal structure of [Pd(CBDCA-*O,O'*)$(NH_3)_2$] shows that it is isostructural with the anticancer drug carboplatin 'Paraplatin'; the mechanism of formation of this complex from reaction of $[Pd(NH_3)_4]^{2+}$ with $H_2$CBDCA has been elucidated by NMR spectroscopy.

Carboplatin, [Pt(CBDCA-*O,O'*)$(NH_3)_2$] **1**, is a square-planar $Pt^{II}$ complex[1,2] widely used as the drug 'Paraplatin' in cancer chemotherapy,[3] but the preparation of the $Pd^{II}$ analogue **2** does not appear to have been reported. For related malonate and oxalate derivatives, Nakayama *et al.*[4] reported a preparative route similar to that used for $Pt^{II}$: removal of the chloride ligands from *cis*-$[PdCl_2(NH_3)_2]$ with $Ag^+$ in aqueous solution (which has been reported to lead to *cis*-$[Pd(NH_3)_2(H_2O)_2]^{2+}$ as the preferred isomer),[5] followed by reaction with the chelating biscarboxylate ligand. In our hands, attempts to prepare complex **2** in good yield by this method have not been successful. The reasons for this are apparent from studies of $^{15}N$-edited $^1H$ NMR and [$^1H$, $^{15}N$] 2D heteronuclear multiple quantum coherence (HMQC) spectra of $^{15}N$-labelled *cis*- and *trans*-$[PdCl_2(NH_3)_2]$ (prepared by standard methods[6,7]) in water. Both complexes react rapidly (within minutes at ambient temperature) to give the same complicated mixture of products with about 12 different types of coordinated $NH_3$ [Fig. 1(a)]. The severe overlap of low-field peaks in the $^{15}N$ dimension illustrates the advantage of [$^1H$, $^{15}N$] NMR spectroscopy over observation of $^{15}N$ peaks only[5] for obtaining an accurate picture of such equilibria. Addition of *cis*-$[PdCl_2(NH_3)_2]$ to an aqueous solution of $H_2$CBDCA did produce **2**, but only as one product amongst several other species [Fig. 1(b)].

Since $Pd^{II}$–$NH_3$ bonds are much more kinetically labile than $Pt^{II}$–$NH_3$ bonds, we decided to use $[Pd(NH_3)_4]^{2+}$ as a starting material[8,9] for reaction with $H_2$CBDCA. We stirred $[Pd(NH_3)_4]Cl_2$ (0.527 g, 2 mmol) with $AgNO_3$ (0.68 g, 4 mmol) in water (5 ml) for 10 min. After removal of the precipitated AgCl, we added $H_2$CBDCA (0.288 g, 2 mmol) and left the solution to evaporate slowly at ambient temperature. Yellow crystals of **2** formed† (yield 0.4 g, 70%), which were washed with ethanol and dried in air.

The X-ray crystal structure of **2**‡ showed it to be isostructural with the $Pt^{II}$ complex carboplatin[1,2] with square-planar coordination geometry (O–Pd– 90.9, N–Pd–N 95.0, N–Pd–O 87.0) and similar metal–N and metal–O bond lengths of 2.020(7) (2.010 Å for the Pt complex) and 2.017(6) (2.029 Å), respectively [Fig. 2(*a*)]. Complex **2** has crystallographically-imposed mirror symmetry, with Pd and all four cyclobutane carbons in the mirror plane. The six-membered chelate ring has a boat conformation, but in solution there is rapid ring-flipping about O(1)–O(1′) such that H(4), H(4′) and H(6), H(6′) are magnetically equivalent (same chemical shifts).




Scheme 1

The mechanism of formation of **2** from $[Pd(NH_3)_4]^{2+}$ and $H_2$CBDCA was investigated by NMR spectroscopy. The chloride and nitrate salts of $[Pd(NH_3)_4]^{2+}$ in water (pH 8) both gave two $^1H\{^{15}N\}$ NMR peaks at δ 3.15 (80%) and 2.85 (20%) which correlated with the same $^{15}N$ shift, δ −58.15. The former is assignable to $[Pd(NH_3)_4]^{2+}$ and the latter to a species with N *trans* to N, perhaps to *trans*-$[Pd(OH)_2(NH_3)_2]$. $^1H$ NMR spectra of a $D_2O$ solution containing 10 mmol $dm^{-3}$ $[Pd(NH_3)_4]^{2+}$ and 1 mol equiv. $H_2$CBDCA (pH* 2.5, where pH* is the pH meter reading for a $D_2O$ solution) were monitored for 2.5 h at 295 K. Three sets of peaks were assignable to $H_2$CBDCA (δ 2.32 and 1.85), the product **2** (δ 2.96 and 1.91), and a ring-opened intermediate [Pd(CBDCA-*O*)$(NH_3)_3$] **3** (δ 2.44 and 1.85), [Fig. 2(b)]. The latter shifts are close to those of the ring-opened $Pt^{II}$ complex *cis*-$[PtCl(CBDCA\text{-}O)(NH_3)_2]^-$ (δ 2.32 and 1.82, pH* 7), as are those of **2** to carboplatin (δ 2.88 and 1.90).[15] Further evidence of **3** was obtained from the $^{15}N$ NMR spectrum of the reaction during the early stages which, as well as reasonances for $[Pd(NH_3)_4]^{2+}$ and **2**, contained peaks at δ −58.2 and −69.9 assignable to $NH_3$ *trans* to $NH_3$ and an oxygen ligand (monodentate CBDCA), respectively, as in **3**. The oxygen ligand was not water since the species $[Pd(NH_3)_3(H_2O)]^{2+}$ (obtained by dissolving $[Pd(NH_3)_4]^{2+}$ in nitric acid solution at pH 0.85) had different shifts (δ −59.5 and −73.5).

Reasonable fits to the time dependences of the concentrations of $H_2$CBDCA, the intermediate **3** and product **2** were

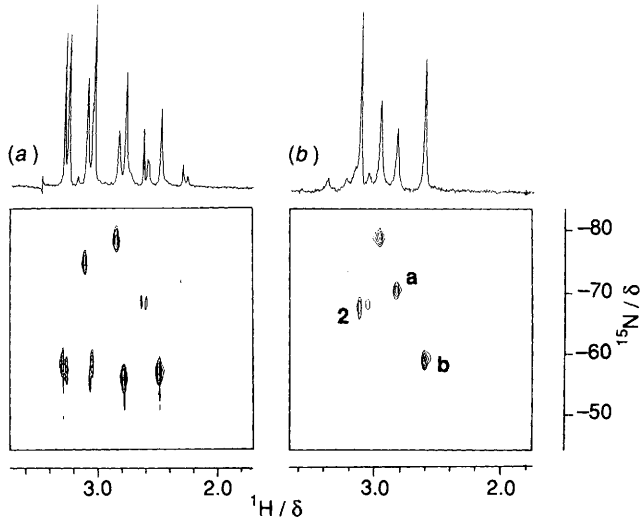



**Fig. 1** [$^1H$, $^{15}N$] HMQC NMR spectra of (*a*) *cis*-$[PdCl_2(NH_3)_2]$ in 90% $H_2O$/10% $D_2O$, and (*b*) a solution of $H_2$CBDCA (7 mmol $dm^{-3}$) in 90% $H_2O$/10% $D_2O$ to which 1 mol equiv. of *cis*-$[PdCl_2(NH_3)_2]$ had been added. The projections are $^{15}N$-edited $^1H\{^{15}N\}$ NMR spectra. Spectra were obtained as described previously;[19,20] the references are TSP (internal) for $^1H$ and 1.5 mol $dm^{-3}$ $NH_4Cl$ in 1 mol $dm^{-3}$ HCl (external) for $^{15}N$. *Trans*-$[PdCl_2(NH_3)_2]$ gives an identical spectrum to (*a*). Each type of coordinated $NH_3$ gives rise to a single cross-peak with characteristic $^{15}N$ shifts: $^{15}N$ *trans* to oxygen of $H_2O$ or OH *ca.* δ −70 to −80, *trans* to N ot Cl *ca.* δ −50 to −60. One of the products in (*b*) is **2**, δ $^{15}N$ −67.9, δ $^1H$ 3.12, and peaks **a** and **b** are assignable to $[Pd(NH_3)_3(X)]$ where X is an oxygen ligand ($H_2O$ or CBDCA).

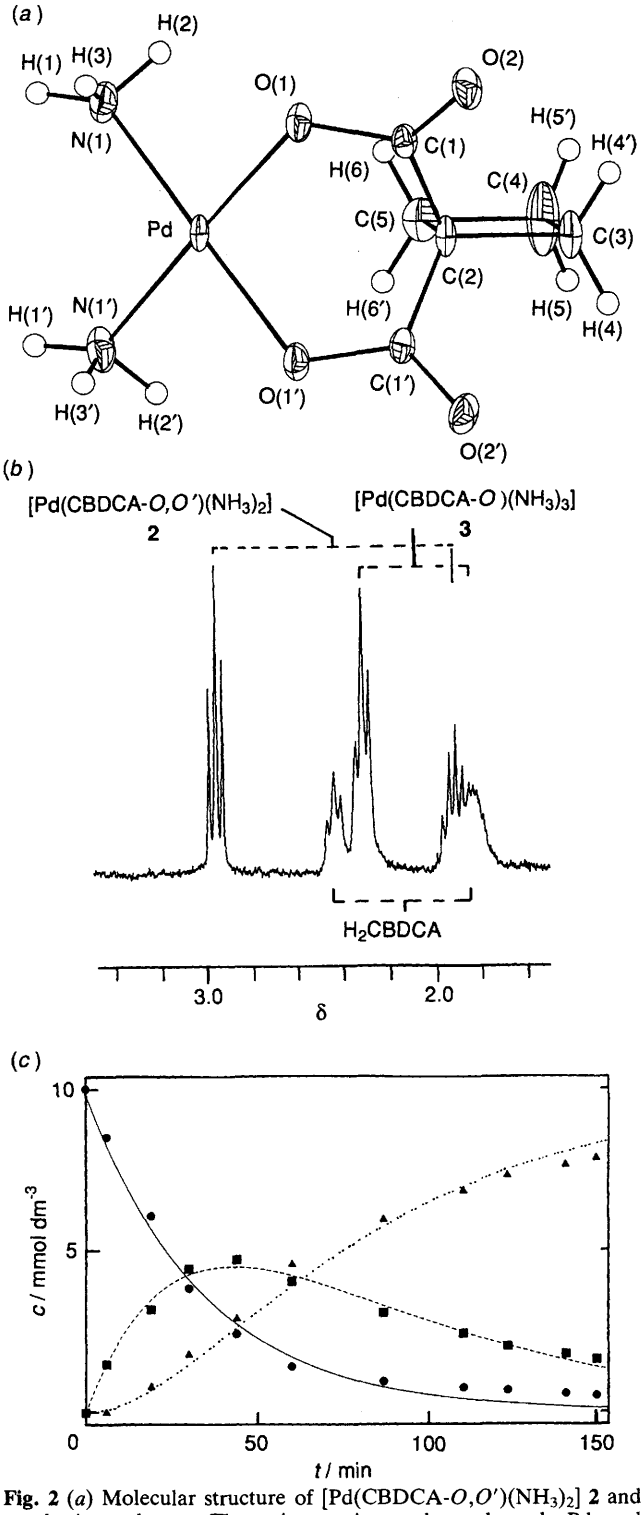



**Fig. 2** (*a*) Molecular structure of [Pd(CBDCA-*O*,*O'*)$(NH_3)_2$] **2** and numbering scheme. There is a mirror plane through Pd and C(2)–C(5); in this view the $PdO_2N_2$ plane has been tilted slightly so that all the atoms are visible. (*b*) 270 MHz $^1H$ NMR spectrum of [Pd$(NH_3)_4$]$(NO_3)_2$ in $D_2O$ 60 min after mixing at 295 K, showing peaks for unreacted $H_2$CBDCA, the intermediate [Pd(CBDCA-*O*)$(NH_3)_3$] **3** and product [Pd(CBDCA-*O*,*O'*)$(NH_3)_2$] **2**. (*c*) Plots of the concentrations of species detected during the reaction described in (*b*), and computer fits using the rate constants for the consecutive reactions given in the text. {● = $H_2$CBDCA; ▲ = [Pd(CBDCA-*O*,*O'*)$(NH_3)_2$] **2**; ■ = [Pd(CBDCA-*O*)$(NH_3)_3$] **3**}

obtained by assuming two consecutive first-order reactions and using standard equations,[16] [Fig. 2(*c*)]. This gave $k_{obs1}$ = (4.86 ± 0.15) × $10^{-4}$ $s^{-1}$ and $k_{obs2}$ = (3.04 ± 0.10) × $10^{-4}$ $s^{-1}$, and an initial concentration of $H_2$CBDCA of 9.81 ± 0.12 mmol $dm^{-3}$. These rates are close to those reported previously[9] for the hydrolysis of [Pd$(NH_3)_4$]$^{2+}$ in perchloric acid solutions (13.7 × $10^{-4}$ $s^{-1}$, 298 K), suggesting that the rate-determining steps in our reactions involve the release of the coordinated ammine ligands (Scheme 1). In contrast, [Pt$(NH_3)_4$]$^{2+}$ is a relatively inert species.

We find that complex **2** is stable towards hydrolysis and attack by chloride (50 mmol $dm^{-3}$) in water for several hours at 295 K. It might therefore exhibit interesting biological activity. Indeed, although relatively few data on the antitumour activity of $Pd^{II}$ complexes have been reported, those complexes with chelated ligands have given the most promising results.[17,18]

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## Footnotes

† Satisfactory elemental analysis was obtained.

‡ *Crystal data*: $C_6H_{12}N_2O_4Pd$, $M$ = 282.59, orthorhombic, $a$ = 7.804(1), $b$ = 10.407(1), $c$ = 11.033(1) Å, space group *Pnma*, $Z$ = 4. $U$ = 896.06 Å$^3$, $D_c$ 2.095 g $cm^{-3}$, $F(000)$ = 560, $\mu$(Mo-K$\alpha$) = 20.285 $cm^{-1}$. Unit cell dimensions and intensity data were obtained at 295 K using an Enraf-Nonius diffractometer and area detector with graphite monochromated Mo-K$\alpha$ radiation, following previously described procedures[10] (D = 40 mm, $2\theta_D$ = 18°). A total of 4741 reflections were measured, of which 1259 were unique and 1124 satisfied the condition $F_o > 3\sigma(F_o)$. The heavy method[11] was used and refined by full-matrix least-squares methods (SHELX-80).[12] Absorption corrections were applied at the isotropic refinement stage using the DIFABS procedure[13] adapted for FAST geometry.[14] All H atoms were allowed to ride on their parent carbon atoms in their calculated positions (C–H = 0.96 Å). The final $R$ and $R'$ values are 0.035 and 0.048, respectively. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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