Unusual 16-Membered Ring System in a Dimeric Platinum(II) Glutarate Complex: $[Pt(NH_3)_2\{O_2C(CH_2)_3CO_2\}]_2 \cdot 4H_2O$

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Since the initial discovery of the antitumor activity of *cis*-$Pr(NH_3)_2Cl_2$ a large number of related platinum complexes have been prepared and tested in order to find analogues which are more active, less toxic, or more selective than the original dichloro-complex [1]. Prominent among the currently favoured 'second-generation' complexes are various $PtL_2(DCA)$ complexes, where L represents ammonia or a primary amine donor group and DCA is a dicarboxylate moiety.

During our studies on the behaviour of such DCA complexes, we have attempted to extend the known range of compounds of type $[Pt(NH_3)_2\{O_2C(CH_2)_n-CO_2\}]$ involving some naturally occurring dicarboxylic acids. We report here the hydrates formed by succinate (n = 2) and glutarate (n = 3) and the results of an X-ray diffraction study on the latter compound.

Both complexes were obtained by the same general method, detailed as follows for the glutarate. To a solution of glutaric acid (1.32 g, 10 mmol) and barium hydroxide (3.09 g, 9.8 mmol) in water (50 cm^3) was added one of freshly prepared *cis*-$[Pt(NH_3)_2(OH_2)_2]SO_4$ (10 mmol in 80 cm^3; obtained in the standard way from *cis*-$Pt(NH_3)_2I_2$ and silver sulphate). The solutions were mixed with rapid stirring and after *ca.* 30 mins. the precipitated barium sulphate was filtered off. The pale yellow filtrate was warmed to 60 °C for 3 hours, during which time a white precipitate formed. After overnight storage in a refrigerator, the solid product was collected and recrystallised from hot (70 °C) water to give white crystals of stoichiometry $Pt(NH_3)_2\{O_2C(CH_2)_3CO_2\} \cdot 2H_2O$ (*Anal.* Found: C, 15.11; H, 3.98; N, 6.89; Calc.: C, 15.19; H, 4.08; N, 7.08%).

The succinate was obtained as a white solid of stoichiometry $Pt(NH_3)_2\{O_2C(CH_2)_2CO_2\} \cdot H_2O$ (*Anal.* Found: C, 13.46; H, 3.26; N, 7.52; Calc.: C, 13.23; H, 3.33; N, 7.71%) but was too insoluble in water for recrystallisation.

As these compounds are much less soluble in water than the malonate derivatives [2], which, as far as is known [1, 3], contain a chelate DCA unit, it seemed worthwhile to explore the effect of the increase in DCA chain length on the coordination mode adopted by the succinate and/or glutarate. Good crystals of the succinate could not be obtained but the glutarate gave colourless crystals suitable for X-ray diffraction studies.

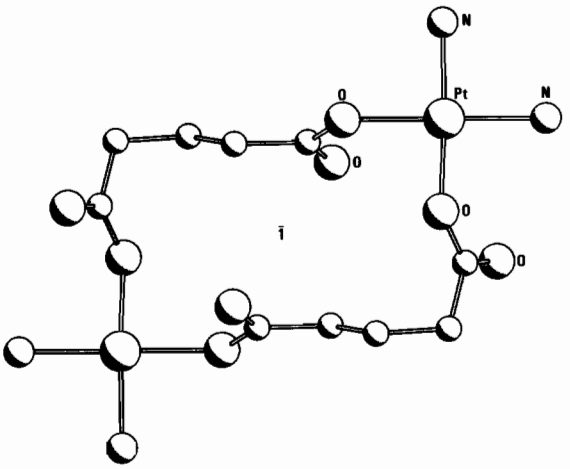

Fig. 1. Molecular Structure of the centrosymmetric $[Pt(NH_3)_2\{O_2C(CH_2)_3CO_2\}]_2$ dimer.

These elongated prisms are triclinic with a = 6.965(1), b = 8.941(1), c = 9.215(1) Å, α = 102.55(1), β = 107.72(1), γ = 96.89(1)°, U = 522.8(1) Å^3. X-ray intensity data were collected on a Nicolet R3m/Eclipse S140 diffractometer system. A total of 1319 independent reflections (to θ = 55°) were measured, using graphite-monochromated Cu-Kα radiation and an ω scan technique, of which 37 were judged to be 'unobserved'. The structure was solved by Patterson and Fourier methods, and least-squares refinement has now reached R = 0.0266. The program system SHELXTL [4] was used throughout the calculations.

The $[Pt_2(NH_3)_4(glutarate)_2]$ molecule (Fig. 1) is a centrosymmetric dimer in which the two *cis*-square-planar arrays about each platinum atom are bridged by the glutarate ligands to give a 16-atom ring system. The coordination about platinum is planar, with the Pt atom *ca.* 0.06 Å out of the coordination plane. Of the two independent carboxylate groups, one is almost normal to the coordination plane (87.8°), while the other makes an angle of 58.8° to this plane.

The mean Pt–N distance is 2.032 Å, while the mean Pt–O is 2.023 Å. These means can be compared to 2.022 and 2.029 Å in *cis*-Pt(dimethyldiaminopropane)(malonato) [5], 2.010 and 2.029 Å in *cis*-$[Pt(NH_3)_2$(cyclobutenedicarboxylato)] [3], 2.054 and 2.025 Å in $[Pt_2(NH_3)_4$(methyl-

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iminato)$_2$]$^{2+}$ [6], and 2.05 and 2.05 Å in [Pt$_2$-(NH$_3$)$_4$(methyluracilato)$_2$]$^{2+}$ [7].

The water molecules are not coordinated, but take part in hydrogen bonding of the type N–H··O and O–H··O involving carboxylate oxygen atoms and the NH_3 groups. There are also direct hydrogen bond links between the dimers of the type N–H··O.

The lower aqueous solubility found for the platinum glutarate complex compared with the malonate derivatives is understandable from its dimeric structure. In view of this, and because of the anti-tumour activity of several of the monomeric lower DCA complexes, we have examined the possibility of cleaving the bridge with ligands of biological relevance.

There was no apparent reaction when the solid complex was stirred with inosine or with $Na_2$5′-GMP in water at room temperature. However, when the solid compound was warmed with an aqueous solution of inosine to *ca.* 45 °C a clear solution was obtained. Evaporation of this to dryness gave a solid which, in contrast to the original dimer, was very soluble in water. Proton NMR studies of such a solution in D_2O showed the presence of coordinated inosine (δ H(8) 8.66; H(2) 8.22 ppm with respect to DSS) and methylene resonances identical to those of sodium glutarate. Similar results were obtained when the dimer was warmed (*ca.* 45 °C) with $Na_2$5′-GMP.

With the sodium salt of β-D-thioglucose, however, there was a reaction even at room temperature, with the formation of Pt(thioglucose)$_2$ in solution, though this reaction occurred much more slowly than with the related monomeric platinum DCA complexes. This raises the interesting possibility that such a bridged complex could undergo selective bridge cleavage under biological conditions, with the slow release of active platinum species.

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