

Platinum Cytidine Blue

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Although several platinum complexes of cytosine and its N(1) derivatives have been reported [1], 'platinum blues' containing these ligands do not appear to have been described previously.

Reaction of aqueous equimolar K_2PtCl_4 and cytidine (Cyd) in the presence of air yields acidic dark green solutions*. Addition of alkali up to amounts near to one equivalent causes the band at 607 nm apparent in the visible spectrum of the mixture to increase slowly and the solution to turn blue in color. By addition of excess of alkali the absorption maximum is shifted and the solution becomes violet. When K_2PtCl_4 and Cyd are reacted under an Ar atmosphere an orange color develops instead of green. These observations indicate metal oxidation and proton release as necessary conditions for formation of platinum blues from Cyd.

The chemical and spectroscopic behaviour of the $[PtCl_4]^{2-}$ -Cyd system is fairly reproducible. However, a variety of platinum-containing species is probably formed in solution, similarly to the case of other platinum blues [1, 2], and the obtained blue solids cannot be definitely considered as simple compounds. Hereafter data are reported on the platinum cytidine blue (PCB) prepared by reacting K_2PtCl_4 , Cyd and KOH in the molar ratio 1:1:0.8 under air. In a typical experiment a solution of 0.25 M K_2PtCl_4 and 0.25 M Cyd in water is allowed to stand for 5 d and then treated with 0.8 equiv. of KOH. Evaporation of the solution after 5 d and repeated reprecipitation of the residue from water-ethanol give an amorphous blue product whose elemental analysis is consistent with the composition $K_{0.2}Pt(Cyd)Cl_{1.5}(OH)_x(OH_2)_y$, where the degree of hydration is variable and the possible hydroxide content not determined. The presence of potassium as a counterion is inferred from elemental analysis of the precipitate obtained by treating aqueous PCB

with Ph_4AsCl . This compound and PCB display close absorbances per mol of Cyd in the range 340–860 nm (Me_2SO).

The visible spectrum of Solid PCB [λ_{max} 620 nm] is similar to the spectrum of water solutions [λ_{max} 607 nm, ϵ 1700 per mol of Cyd (0.1 M chloride added)]; the visible absorption is decreased by addition of concentrated acids. The compound is stable, very soluble in water and diamagnetic. The magnetic susceptibility, $\chi = -0.43 \times 10^{-6} \text{ cm}^3 \text{ g}^{-1}$ (20 °C), indicates that the fraction of unpaired electrons per platinum atom should be small, if any.

The 1H NMR spectrum of PCB in D_2O displays broad base and ribose resonances, with maxima in the H(6)–H(5)–H(1') region at $\delta = 7.3$ and $\delta = 5.9$. When aqueous PCB is treated with $NaBH_4$ the blue color is immediately discharged; the NMR spectrum of the resulting orange solution in the H(6)–H(5)–H(1') region shows, besides minor sharp resonances, broad signals at $\delta = 7.0$ and $\delta = 5.9$. NMR spectra of the system $[PdCl_4]^{2-}$ -Cyd have been examined for comparison. In the palladium(II) system blue species are not formed and the question of possible shift and broadening of resonances due to the presence of paramagnetic species does not arise. Spectra of equimolar $[PdCl_4]^{2-}$ -Cyd solutions in Me_2SO-d_6 show ribose hydroxyl resonances at $\delta = 5.4$ and $\delta = 5.1$ with relative intensities 1 and 2. The spectrum of PCB in the same solvent exhibits in addition to the signals apparent from D_2O solutions a broad resonance at $\delta = 5.1$ and a less intense one at $\delta = 5.4$; this rules out extensive deprotonation at ribose hydroxyls. Metallation at C(5) is excluded by integral intensity in the H(6)–H(5)–H(1') region. Signals from amino protons in Me_2SO-d_6 solutions of PCB could not be identified.

Spectra of N(3) bound Cyd complexes of the type $[Pd(Cyd)_nCl_{4-n}]^{n-2}$ ($n = 1-4$) in D_2O exhibit H(6) and H(5) doublets with chemical shifts in the narrow ranges $\delta = 7.84-7.96$ [H(6)] and $\delta = 5.99-6.12$ [H(5)]; these values are slightly different from chemical shifts of uncomplexed Cyd ($\delta = 7.88$ and $\delta = 6.11$) [3]. When one equivalent of KOH is added to an equimolar solution of $[PdCl_4]^{2-}$ and Cyd a quite different NMR pattern is formed: besides signals ascribed to free Cyd, a H(6) doublet at $\delta = 7.05$ is observed with rather broad unsymmetrical lines. Corresponding H(5) doublets are observed at $\delta = 5.77$ and $\delta = 5.60$, other H(5) resonances possibly overlapping with H(1') signals. Addition of excess alkali gives rise to broadening of all resonances of the palladium complexes (both base and ribose); maxima in the H(6)–H(5)–H(1') region are observed at $\delta = 7.1$ and $\delta = 5.9^{**}$. The similarity of this spec-

*For example, a mixture of 0.25 M K_2PtCl_4 and 0.25 M Cyd gives pH = 1.8 after 5 d at room temperature.

**Please, for footnote, see overleaf.

trum and of the spectrum of PCB indicates that shift and broadening of resonances for the latter compound are not related to the presence of paramagnetic species. The broad nature of these spectra can be accounted for instead by the presence of a mixture of different complexes and/or by polynuclear complex formation.

The large upfield shift of base proton resonances observed in the system $[\text{PdCl}_4]^{2-}\text{-Cyd-OH}^-$ and in PCB relative to free Cyd cannot be accounted for by simple metal coordination of the nucleoside through N(3) and by magnetic anisotropy of neighboring groups. Changes of chemical shifts observed upon formation of the complexes $[\text{Pd}(\text{Cyd})_n\text{Cl}_{4-n}]^{n-2}$, $[\text{enPtCyd}(\text{OH}_2)_2]^{2+}$ and $[\text{enPt}(\text{Cyd})_2]^{2+}$ [1] are considerably smaller. Moreover, base stacking of the nucleoside is known to produce little effect on Cyd resonances [4]. The NMR pattern of PCB can be accounted for by deprotonation of the nucleoside at C(4)NH₂ and metal binding of CydH_{-1} as a chelating or bridging group through N(3) and N(4) or O(2) atoms. It is pertinent to note that appreciable upfield shifts of H(6) and H(5) base resonances are observed when the isoelectronic nucleoside uridine is coordinated to platinum(II) after deprotonation [1]. Metal for proton substitution at the amino group of Cyd has been found to occur in the system $\text{CH}_3\text{-Hg}^{\text{II}}\text{-Cyd}$ [5]. Deprotonation at C(4)NH₂ does not occur in the systems $(\text{H}_3\text{N})_2\text{Pt}^{\text{II}}\text{-Cyd}$ and $\text{enPt}^{\text{II}}\text{-Cyd}$, where platinum blues are not formed [1]. Other possible deprotonation sites in the PCB forming reaction are metal bound water molecules from hydrolysis of Pt-Cl bonds. Therefore, an alternative explanation of the observed NMR pattern would be bifunctional metal binding of undissociated Cyd through N(3) and O(2) forced by the formation of hydroxo complexes, possibly involving Pt(OH)Pt bridges.

The constitution of platinum blues is still not well established apart from few cases. Mixed oxidation state, amidate bridges and stacked polymeric structures with Pt-Pt bonds have been proposed to

**The acid-base reaction is reversible: by addition of excess D_2SO_4 the spectrum is changed to that of the mixture $[\text{PdCydCl}_3]^- \text{-Cyd}^+$.

be common features of the entire class of these compounds [6].

The NMR spectra of equimolar $[\text{PtCl}_4]^{2-}\text{-Cyd}$ solutions in D_2O equilibrated under air show rather sharp doublets at $\delta = 7.84$ [H(6)] and $\delta = 6.10$ [H(5)] characteristic of 'usual' N(3) bound Cyd complexes of Pt^{II} and a broad signal at $\delta = 7.3$ due to the blue species. Higher field broad signals overlap with the more intense H(5) and H(1') doublets; partial deuteration of Cyd at C(5) is also shown to occur. The NMR spectra of the reacting mixtures at intermediate stages show, besides the above signals, a broad resonance at $\delta = 7.0$ assigned to platinum(II) deprotonated complexes by comparison with the spectra of the system $[\text{PdCl}_4]^{2-}\text{-Cyd-OH}^-$ and of the PCB-NaBH₄ reaction mixture. Addition of D_2SO_4 to the equilibrated solutions gives rise slowly to a decrease in the relative intensity of the signal at $\delta = 7.3$ and to the appearance of signals from CydD^+ , whereas addition of KOH causes the spectrum to become slowly similar to that of PCB, the H(6) and H(5) doublets being reduced to broad shoulders. The spectra of equilibrated solutions of $[\text{PtCl}_4]^{2-}$ and Cyd in the molar ratio 1:2 show signals from CydD^+ and PCB and doublets at $\delta = 7.84$ and $\delta = 6.10$. These results suggest that the mechanism of formation of PCB involves complexation of Cyd with platinum(II) through N(3) as the first step, followed by the deprotonation process and polyfunctional coordination of the nucleoside, and eventually by metal oxidation.

References

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