Co-ordination of Amides to *cis*-$[Pt^{II}(NH_3)_2(H_2O)_2]^{2+}$

By S. JOHN S. KERRISON and PETER J. SADLER*
(*Department of Chemistry, Birkbeck College, Malet Street, London* WC1E 7HX)

Summary ^{15}N and ^{195}Pt N.m.r. studies show that when acetamide is added to aqueous solutions of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ and $[Pt(en)(H_2O)_2]^{2+}$ (en = ethylenediamine), equilibria are rapidly established with species in which H_2O is substituted by the amide carbonyl oxygen atom without NH_2 deprotonation; the relevance to platinum blue formation is discussed.

THE coordination of acetamide to Pt has fascinated workers ever since the report[1] in 1908 of an intensely blue-coloured compound ('Platinblau'), formulated then as $Pt(CH_3CONH).H_2O$. Although later revised[2] to $Pt^{IV}(CH_3CONH)_2(OH)_2$, it seems more likely to be a mixed oxidation state, oligomeric compound.[3] Interest in this area has been stimulated further by the finding[4] that blue complexes can be prepared by reaction of *cis*-diamminediaqua platinum(II) complexes with a variety of amides including pyrimidines, and that these are antitumour agents and useful stains for electron microscopy. We show here by a combination of ^{15}N and ^{195}Pt n.m.r. studies that the first (and relatively rapid) step in the reaction of acetamide with *cis*-$[Pt^{II}(NH_3)_2(H_2O)_2]^{2+}$, (**1**), and its ethylenediamine analogue (**2**), involves Pt co-ordination to the acetamide carbonyl group without NH_2 deprotonation.

The $\{^1H\}$-^{15}N n.m.r. spectrum of a 0·8 M solution of ^{15}N-enriched (>95%) (**1**)† in H_2O at 30 °C shows a 1:4:1 triplet centred at −446 p.p.m.‡ with $^1J(^{15}N$–$^{195}Pt)$ 386 Hz. On addition of 1 equiv. of [^{15}N]acetamide two peaks are seen in the acetamide region at −256 and −268 p.p.m. (relative intensity 1:2·5) within 5 min of mixing, and whilst the solution was still colourless. We assign the first peak to bound and the second to unbound acetamide, since we measured a shift of −270 p.p.m. for acetamide alone in D_2O in good agreement with the reported value.[5] In the *cis*-$Pt(NH_3)_2$ region of the spectrum a new peak appeared at −444 p.p.m. suggesting that *ca.* 18% of Pt had reacted compared with 29% of the acetamide. However T_1 and n.O.e. differences may introduce large errors into these figures. Little change in the percentages of reacted and unreacted species occurred over the next hour, suggesting that equilibrium was rapidly established. By then the colour of the solution was beginning to turn blue.

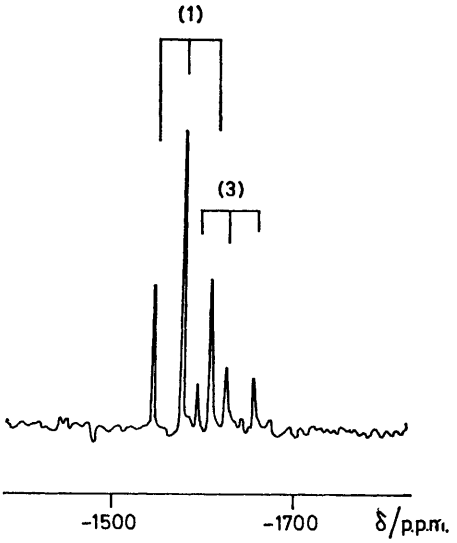


FIGURE 1. 12·8 MHz $\{^1H\}$–^{195}Pt n.m.r. spectrum of 0·8 M *cis*-$[Pt(^{15}NH_3)_2(H_2O)_2]^{2+}$ in the presence of 1 equiv. of MeCO-$^{15}NH_2$, within 1 h of mixing.

The $\{^1H\}$-^{195}Pt n.m.r. spectrum of (**1**) in H_2O is a 1:2:1 triplet at −1574 p.p.m. with $^1J(^{15}N$–$^{195}Pt)$ 387 Hz. On addition of 1 equiv. of [^{15}N]acetamide, a new triplet appears at −1621 p.p.m. with coupling $^1J(^{15}N$–$^{195}Pt)$ 384 Hz, Figure 1. This spectrum was accumulated 15—45

† ^{15}N-Labelled Pt complexes were prepared by standard methods [S. C. Dhara, *Indian J. Chem.*, 1970, **8**, 193; V. V. Lebedinskii and V. A. Golovnya, *Neorg. Khim. Acad. Nauk. SSSR*, 1947, **20**, 95 (*Chem. Abs.*, 1947, **44**, 5257)]. Aqueous solutions of the diaqua-complexes were obtained by stirring these halide complexes with $AgClO_4$ and removing the precipitate. The resulting pH is *ca.* 1·5. pK_a Values are *ca.* 5·5 and 7·2.

‡ ^{15}N N.m.r. shifts are relative to $MeNO_2$ (external); most associated J-values are accurate to ± 3 Hz. ^{195}Pt N.m.r. shifts are relative to Na_2PtCl_6 in D_2O (external); most associated J-values are accurate to ± 6 Hz.

min after mixing, again whilst the solution was colourless. After 75 min *ca.* 40% is in this new form. The formation of a 1:1 rather than a 2:1 complex seems to be indicated from this when combined with the above (^{15}N) results. Addition of a second equiv. of acetamide raises the proportion of reacted Pt to *ca.* 55%, in a solution which has already turned bluish-green. The overall decrease in signal-to-noise ratio suggests that some of the Pt is now reacting to produce another species which is not spectrally observable, perhaps because it is polymeric or paramagnetic. The linewidths of the new triplet (*ca.* 46 Hz) are considerably greater than those due to (**1**) (*ca.* 22 Hz), and a 15 h accumulation with 3 Hz resolution revealed fine structure of *ca.* 8 Hz separation. We attribute this to a 3-bond ^{15}N–^{195}Pt coupling, the value being similar to others reported,[6] and no such fine structure exists when [^{14}N]acetamide is used. The centre peak is broader than the outer peaks of the triplet (see Figure 1), suggesting that the two ammine ligands are no longer equivalent in this new species, and that a 1:1 complex is formed.

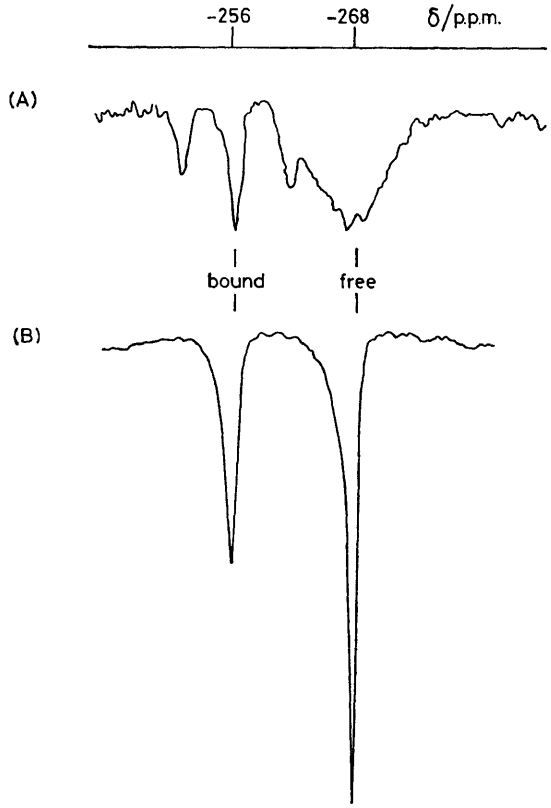
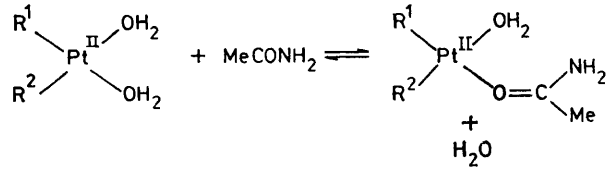


FIGURE 2. The acetamide region of an 18·24 MHz ^{15}N n.m.r. spectrum of an aqueous solution of 0·8 M *cis*-[Pt(^{15}N-en)$_2$(H$_2$O)$_2$]$^{2+}$ accumulated between 10 and 70 min after the addition of [^{15}N]acetamide (1:1). (A) ^1H-Coupled with irradiation gated to retain the (negative) n.O.e. (B) ^1H-Decoupled.

The experiment was repeated using ^{15}N-labelled [Pt(en)(H$_2$O)$_2$]$_2^{+}$ (**2**) (en = ethylenediamine). The results were similar. With 1 equiv. of [^{15}N]acetamide, the new acetamide ^{15}N resonance is again at −256 p.p.m. whilst the Pt(en) peak shifts by 2 p.p.m. from −408 (^1J 426 Hz) to −406 p.p.m. (^1J 414 Hz). The ^1H-coupled spectrum, Figure 2, shows clearly that the NH_2 hydrogens on Pt-bound acetamide are in slow exchange with solvent protons. The ^{195}Pt n.m.r. resonance for (**2**) at −1914 p.p.m. (^1J 421 Hz) shifts to −1975 p.p.m. (^1J 421 Hz), although the extent of reaction (*ca.* 10%) is less than that for (**1**).



(1) $R^1 = R^2 = NH_3$
(2) R^1, R^2 = en
(3) $R^1 = R^2 = NH_3$
(4) R^1, R^2 = en

These data point to the rapid establishment of an equilibrium between the diamminodiaquaplatinum(II) complex (**1**) and the monoacetamido complex (**3**) [and analogous species (**2**) and (**4**)]. The replacement of one oxygen (H$_2$O) by another (C=O) leads to relatively small changes in the ^{195}Pt n.m.r. chemical shift (47—61 p.p.m.) and ^{15}N–^{195}Pt coupling constant. Co-ordination of the acetamide N on the other hand would have resulted in an additional large ^{15}N–^{195}Pt coupling (*ca.* 300 Hz for N *trans* to N)[7] and a larger shift of its ^{15}N resonance. (The co-ordination shift of 86 p.p.m. for NH_3, for example, can be compared with the 12 p.p.m. shift observed here). Complex (**3**) has the required 3-bond coupling path between Pt and the acetamide N, which still has two attached protons. Co-ordination of C=O rather than NH_2 (as opposed to NH^-) avoids loss of the stabilisation energy associated with the planar amide structure.

Blue species appear to result from simultaneous oxidation and attack of a second Pt at the NH_2 group of co-ordinated acetamide with proton displacement, giving the bridging acetamidato arrangement observed in the crystalline α-pyridone blue.[8] Since aqua- and hydroxo-*cis*-diammineplatinum(II) species have been implicated in the mechanism of action of Pt anti-cancer drugs, the possibility must be considered that attack occurs at amide carbonyl groups of proteins or nucleotides.

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