Platinum Complexes of Uracil. Multiplicity and Interconversion of Binding Sites

BERNHARD LIPPERT

The complex-forming properties of uracil with $(NH_3)_3Pt^{II}$, $enPt^{II}$, and *cis*-$(NH_3)_2Pt^{II}$ have been studied with the use of ^1H NMR, Raman and infrared spectroscopy. A series of crystalline compounds were isolated and examined with regard to the various ways of uracil binding possible, and their respective spectral properties. Reaction between uracil and Pt(II) occurs over a wide pH range (ca. 2–9), with uracil acting as dianion, monoanion, and neutral ligand. As a neutral ligand, uracil takes a rare tautomeric structure with Pt binding through ring nitrogen atoms and one of the two acidic protons located at an exocyclic oxygen atom. Three important differences between complexes containing N-1- and N-3-bound uracil have been deduced from ^1H NMR spectra: the coupling constants of H-5 and H-6 with ^{195}Pt are different (N-1, $^3J_{^{195}Pt-^1H-6} \simeq 40$ Hz, $^4J_{^{195}Pt-^1H-5} \simeq 4$ Hz; N-3, $^4J_{^{195}Pt-^1H-5} \simeq 15$ Hz), the stabilities of the complexes in strongly acidic medium are different (Pt–N-3 bond is cleaved, Pt–N-1 bond is stable), and the two types of complexes show quite different tendencies to undergo isotopic $^1H/^2D$ exchange at the C-5 position in acidic medium (N-1 complexes exchange fast, N-3 complexes do not). Platinum complexes containing a single uracil ligand and an aquo ligand in their first coordination sphere show a remarkable tendency to undergo condensation reactions with uracil acting as bridging ligand *and* to form complexes with the Pt coordination site completely changed. For example, both $enPt(HU-N1)H_2O^+$ and *cis*-$(NH_3)_2Pt(HU-N1)H_2O^+$ readily form the respective (HU-N3) complex besides several bridged complexes. The same phenomenon is observed for coordinatively saturated complexes such as $enPt(HU)_2$, *cis*-$(NH_3)_2Pt(HU)_2$, $(NH_3)_3Pt(HU-N1)^+$, and $(NH_3)_3Pt(HU-N3)^+$ in the presence of aquo complexes such as $enPt(H_2O)_2^{2+}$, *cis*-$(NH_3)_2Pt(H_2O)_2^{2+}$, and $(NH_3)_3Pt(H_2O)^{2+}$. For the $(NH_3)_3Pt^{II}$ complexes of the uracil monoanions, a mutual interconversion of (HU-N1) $\rightleftharpoons$ (HU-N3) tautomer complexes has unambiguously been demonstrated. The heterogeneity of platinum uracil "tans" and "blues" results from the coexistence of complexes with different ways of uracil coordination and the possibility of oligomer formation involving identical or different ways of coordination. The distribution of the various complexes strongly depends upon the solvent, the pH, the temperature, and the Pt:uracil ratio.

Introduction

The majority of articles dealing with structural aspects of blue platinum complexes of pyrimidine-2,4-diones and related ligands, that appeared following the original report of Rosenberg and co-workers,[1] have been concerned with the nature of the blue color, the heterogeneous character of the products, the platinum oxidation state, and the possible platinum–platinum interactions.[2–10] Relatively few results dealing with the sites of platinum coordination have been reported.[11–14] Only in one case, with α-pyridone as ligand, this question has been solved unambiguously by X-ray structural analysis: Lippard and co-workers[15] showed that Pt coordination occurs through adjacent ring nitrogen and exocyclic oxygen in this system. With N-1-substituted pyrimidine-2,4-diones, this binding pattern has been confirmed since then,[16–19] and there are now two more examples with α-pyridone.[20] With unsubstituted pyrimidones, however, the question concerning the platinum coordination sites is still open for debate.

The present study has been undertaken for two main reasons: first, to get a better understanding of the complex forming properties of unsubstituted uracil with Pt(II), and, second, to evaluate the usefulness of Raman spectroscopy for the differentiation of metal coordination sites at typical multisite ligands such as uracil.

It has recently been demonstrated by the author that Raman spectroscopy permits a differentiation of uracil and thymine monoanion tautomers in solution[21] and, though less straightforward, also in the solid state.[22] Moreover, it has been shown that Raman spectroscopy is able to distinguish metal complexes of tautomers with metal binding occurring in a monodentate fashion.[23] Simultaneously and independently, Itoh and co-workers also showed the applicability of Raman spectroscopy for the study of tautomerism[24] and metal coordination to different tautomers.[25]

Herewith more detailed evidence is presented, demonstrating that Raman spectroscopy is a valuable tool for the differentiation of metal complexes of individual tautomers. On the other hand, a comparison with ^1H NMR spectroscopy shows the limitations of this method in a system being as complex as the Pt/uracil system. Infrared spectroscopy and poten-

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Pt Complexes of Uracil

tiometric studies have been performed to complete Raman and ¹H NMR results.

Abbreviations used: H₃U = uracil monocation; H₂U = neutral uracil; HU = uracil monoanion; U = uracil dianion; HU-N1 = uracil monoanion coordinated to Pt via N-1; HU-N1,O4 = uracil monoanion bridging two Pt atoms via N-1 and O-4; U-N3 = uracil dianion coordinated to Pt via N-3; etc.; DMF = dimethylformamide; en = ethylenediamine.

Experimental Section

Spectroscopy. ¹H NMR spectra were recorded on a JEOL JNM-FX 60 Fourier-transform spectrometer. Dependent upon the concentration, usually 200–1500 transients were accumulated into 8-K points of memory. Ambient temperature was 30 ± 1 °C. Chemical shifts are given in ppm and were measured by means of an internal [N(CH₃)₄]BF₄ reference and calculated relative to TSP (sodium 3-(trimethylsilyl)propanesulfonate), which was found to be 3.1869 ppm upfield of the [N(CH₃)₄]⁺ signal. Occasionally spectra were also recorded on a Varian EM 360 (60 MHz) in order to evaluate the effects of spectral changes due to condensation reactions and accumulation of a large number of transients. Since the spectral changes were slow (in the order of hours), the spectra obtained with the Fourier transform spectrometer reflect reasonably well the actual distribution of the various species in solution.

The reported pD values were obtained by adding 0.4 to the pH meter reading.

Infrared spectra were recorded on a Perkin-Elmer 580 grating spectrometer from KBr pellets and Nujol mulls (CsJ windows). Intensities: vs = very strong, s = strong, m = medium, w = weak, vw = very weak, sh = shoulder.

Raman spectra were recorded on a Coderg PH 1 with krypton laser excitation (647.1 nm, 50–400 mW power, depending upon the stability of the compounds in the laser beam). Decomposition was frequently observed with powder samples. Wavenumber calibration was achieved by means of indene. Spectral slit widths were as indicated; scan rates were usually 10 cm⁻¹ min⁻¹. Given Raman intensities refer to peak heights. If intensities of band intensities of different compounds are compared, weighted amounts of the respective compounds were dissolved and relative intensities were taken from the spectra of the mixtures. Potentiometric titrations were carried out under nitrogen.

Materials and Preparation of the Compounds. [(NH₃)₃PtNO₃]N-O₃,[26] enPtCl₂,[27] [(NH₃)₃Pt(HU-N1)]NO₃,[28] [(NH₃)₃Pt(HU-N3)]-NO₃,[28] enPt(HU-N1)Cl·H₅O₂⁺Cl⁻,[14] "platinum uracil tans",[14] and "platinum uracil blues"[1,4] were prepared according to the published procedures. K₂PtCl₄ and cis-Pt(NH₃)₂Cl₂ were purchased from Degussa and recrystallized; uracil from Fluka. The other compounds were prepared as subsequently described. No attempts were made to optimize the yields.

(a) K(HU). It was obtained in a way analogous to that of the corresponding thymine salt[29] from water with subsequent DMF treatment. In contrast to the thymine salt, K(HU) was not obtained in anhydrous form by this method. Solid-state Raman spectra indicate the presence of different tautomers in the product. Anal. Calcd for K(C₄H₃N₂O₂)·0.5H₂O: C, 30.18; H, 2.54; N, 17.60. Found: C, 30.58; H, 3.09; N, 17.53.

(b) [(NH₃)₃Pt(HU-N1)]Cl and [(NH₃)₃Pt(HU-N1)]NO₃. A 2-mmol sample of cis-(NH₃)₂Pt(HU-N1)Cl·0.5H₂O (**1**) was heated in 20 mL of 25% NH₃/H₂O to 85 °C until the solution became clear (ca. 10 min). The pH was lowered by means of HCl to 6 and the solution filtered and concentrated to 10-mL volume by rotary evaporation. Cooling for 2 h at 3 °C gave 450 mg of [(NH₃)₃Pt(HU-N1)]Cl. Further concentration gave a second crop which was contaminated with NH₄Cl. Brief treatment with MeOH removed NH₄Cl. Recrystallization was from water; 370 mg; colorless microneedles. Anal. Calcd for [(NH₃)₃Pt(C₄H₃N₂O₂)]Cl·2H₂O: C, 11.0; H, 3.7; N, 16.04. Found: C, 11.11; H, 3.98; N, 16.70.

Reaction of stoichiometric amounts of the chloride salt and AgNO₃ in aqueous 0.01 N HNO₃, filtration of AgCl, concentration, and precipitation with EtOH gave [(NH₃)₃Pt(C₄H₃N₂O₂)]NO₃·H₂O: 85%

yield; white powder. Anal. Calcd: C, 10.98; H, 3.23; N, 19.22; Pt, 44.61. Found: C, 11.22; H, 3.24; N, 18.80; Pt, 44.30.

(c) (NH₃)₃Pt(U-N1). A 100-mg sample of [(NH₃)₃Pt(HU-N1)]Cl or [(NH₃)₃Pt(HU-N1)]NO₃ was heated to 90 °C in 2 mL of 2 N NaOH in a stoppered flask until the solution became clear. Upon slow cooling, bright colorless needles precipitated. They were filtered, washed with a small volume of 0.1 N NaOH, and dried with methanol and ether; yield 30 mg. Anal. Calcd for (NH₃)₃Pt(C₄H₂N₂O₂)·2H₂O: C, 12.24; H, 3.86; N, 17.85; Pt, 49.73. Found: C, 12.72; H, 3.85; N, 18.05; Pt, 50.2.

(d) (NH₃)₃Pt(U-N3). A 150-mg sample of [(NH₃)₃Pt(HU-N3)]NO₃[28] was dissolved in 1.5 mL of 2 N NaOH at room temperature and the solution concentrated to 0.5-mL volume. Within 10 days at 3 °C very small colorless needles had precipitated. They were filtered and washed with methanol; yield 25 mg. Anal. Calcd for (NH₃)₃Pt(C₄H₂N₂O₂)·1.5H₂O: C, 12.53; H, 3.69; N, 18.28; Pt, 50.89. Found: C, 12.84; H, 3.53; N, 17.88; Pt, 51.0.

(e) enPt(HU-N1)Cl·DMF was obtained in two ways: (1) by 20 h of stirring of enPt(HU-N1)Cl·H₅O₂⁺Cl⁻ in excess DMF at 22 °C and filtration of the precipitate; (2) by stirring enPtCl₂ and AgNO₃ (5 mmol each) for 40 h at 22 °C in 80 mL of DMF in a stoppered flask. After filtration of AgCl, 800 mg of K(HU)·0.5H₂O was added and the suspension stirred for 3 days at 22 °C. The white precipitate was then filtered, washed with DMF, and dried; yield 1.80 g (76%). Anal. Calcd for (C₂H₈N₂)Pt(C₄H₃N₂O₂)Cl·C₃H₇NO: C, 22.76; H, 3.83; N, 14.75; Pt, 41.08. Found: C, 22.45; H, 3.88; N, 14.38; Pt, 40.69.

(f) enPt(HU-N1)Cl·H₂O was obtained in the following ways: (1) by 30 min of stirring of the DMF adduct, of part e, in excess 0.01 N HCl at 22 °C or 80 °C and filtration of the white precipitate (yield 90%) (slow evaporation of the filtrate gave a second crop as colorless to slightly tan needles of the monohydrate); (2) by treatment of the H₅O₂⁺Cl⁻ adduct[14] with excess water (yield 90%); (3) by a way which is analogous to the preparation of enPt(HU-N1)Cl·H₂O₂⁺Cl⁻ [14] by treatment of a "platinum uracil tan" with 0.1 N HCl instead of 1 N HCl as in the case of the former. Anal. Calcd for (C₂H₈N₂)Pt(C₄H₃N₂O₂)Cl·H₂O: C, 17.17; H, 3.13; N, 13.35; Pt, 46.48. Found: C, 17.52; H, 3.15; N, 12.85; Pt, 46.6.

(g) enPt(HU-N1)₂. enPtCl₂ (5 mmol) and AgNO₃ (10 mmol) were stirred for 24 h in 70 mL of DMF at room temperature. AgCl was filtered off, and 800 mg K(HU)·0.5H₂O was added. After 2 days, 280 mg of a white precipitate was filtered off, redissolved in H₂O, filtered again, and cooled to 3 °C. After 3 days, a white precipitate was filtered, washed with cold water and acetone; yield 90 mg. Another 30 mg were obtained as small, colorless needles upon slow evaporation of the remaining solution. Anal. Calcd for (C₂H₈N₂)Pt-(C₄H₃N₂O₂)₂·3H₂O: C, 22.60; H, 3.80; N, 15.82; Pt, 36.7. Found: C, 23.08; H, 3.86; N, 14.94; Pt, 36.9.

(h) [enPt(HU)]ₙ(NO₃)ₙ·0.5nH₂O (n = 2?) (Compound A). A 1-mmol sample of enPt(HU-N1)Cl·H₂O and 1 mmol of AgNO₃ were stirred in 100 mL of water for 24 h in a stoppered flask at room temperature. AgCl was filtered off and the solution concentrated to 4 mL by rotary evaporation at 30 °C. The solution was then kept at 3 °C for 6 days, filtered from some precipitate, and brought to pH ~0 by means of 6 N HNO₃. Within 1 day at room temperature, colorless, transparent crystals had formed. Filtration after 5 days, washing with water, and drying on air gave 100 mg. Anal. Calcd for (C₂H₈N₂)Pt(C₄H₃N₂O₂)NO₃·0.5H₂O: C, 16.48; H, 2.77; N, 16.02; Pt, 44.61. Found: C, 16.38; H, 2.99; N, 16.13; Pt, 44.5.

(i) [enPt(HU)]ₙ(NO₃)ₙ·2nH₂O (Compound B). enPt(HU-N1)-Cl·H₂O (1 mmol) and AgNO₃ (1 mmol) were stirred in 100 mL of water for 24 h in a stoppered flask at room temperature. AgCl was filtered off and the solution concentrated to 5-mL volume and kept at room temperature. pH of the solution was 2. Within 1 days, small, colorless cubes had formed. The precipitate seemed to redissolve with time, thus giving rise to greatly varying yields ranging from 5–80 mg, depending on the time of reaction. Attempts to recrystallize the compound failed and resulted in the formation of a yellow glass with an IR spectrum different from that of the starting compound (very broad bands). Anal. Calcd for (C₂H₈N₂)Pt(C₄H₃N₂O₂)NO₃·2H₂O: C, 15.52; H, 3.26; N, 15.09; Pt, 42.01. Found: C, 15.30; H, 3.08; N, 15.15; Pt, 42.0.

(k) Product from Reaction of (en)Pt(H₂O)²⁺ with Compound A. A 100-mg sample of [enPt(HU)]ₙ(NO₃)ₙ·0.5nH₂O was dissolved in a freshly prepared solution of [enPt(H₂O)₂](NO₃)₂ (1 mmol in 15

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mL of H_2O), concentrated to 5-mL volume by rotary evaporation, and then kept at 40 °C for 1–2 days (stoppered flask). By that time yellow crystals had formed which were collected, washed with water, and air-dried. The crystals lost transparency when kept in air; yield 40 mg.

Anal. Found: C, 12.72; H, 2.77; N, 14.67; Pt, 49.37. This leads to a formulation $Pt_1C_5H_{10.8}N_{4.1}O_x$. The compound contains nitrate, and from the IR spectrum (intense bands at 1610, 1550, 1395, and 1370 cm^{-1}), it is suspected that the compound consists of a Pt cluster with bridging uracil ligands.

(l) *cis*-(NH$_3$)$_2$Pt(HU-N1)Cl·0.5H$_2$O was obtained by decomposition of a "platinum uracil blue" (HCl, 70–80 °C) in a way analogous to the corresponding thymine complex.[4,13] It was also prepared by addition of K(HU)·0.5H$_2$O to a solution of *cis*-[(NH$_3$)$_2$Pt(DMF)-Cl]NO$_3$ in DMF (cf. preparation e), and subsequent treatment of the obtained DMF adduct with water; yield 70%. From the H$_2$O filtrate (pH ≃9), upon concentration and cooling, a small amount (2%) of *cis*-(NH$_3$)$_2$Pt(HU-N1)$_2$·2H$_2$O, (m), was obtained.

Anal. Calcd for (NH$_3$)$_2$Pt(C$_4$H$_3$N$_2$O$_2$)Cl·0.5H$_2$O: C, 12.52; H, 2.63; N, 14.60; O, 10.42; Pt, 50.84. Found: C, 12.90; H, 2.59; N, 14.12; O, 10.65; Pt, 50.90.

(m) *cis*-(NH$_3$)$_2$Pt(HU-N1)$_2$·2H$_2$O. *cis*-[(NH$_3$)$_2$Pt(DMF)$_2$](NO$_3$)$_2$, obtained from reaction of *cis*-(NH$_3$)$_2$PtCl$_2$ with 2 mol of AgNO$_3$ in DMF (600 mg of *cis*-(NH$_3$)$_2$PtCl$_2$ in 20 mL of DMF; filtration of AgCl after 24 h), was reacted with 2 equiv of K(HU)·0.5H$_2$O (3 days, 22 °C, stoppered flask). Then 900 mg of a white precipitate was filtered and treated with 40 mL of water for 30 min at 22 °C (pH of the slurry ≃10); 110 mg of a white powder was filtered. Concentration of the alkaline solution to 10-mL volume gave another 200 mg of this product. The combined precipitates were then treated with excess 0.01 N HNO$_3$ (10 min, 70 °C), filtered from undissolved residue, and finally cooled; yield 100 mg.

Anal. Calcd for (NH$_3$)$_2$Pt(C$_4$H$_3$N$_2$O$_2$)$_2$·2H$_2$O: C, 19.71; H, 3.32; N, 17.25; Pt, 40.03. Found: C, 19.70; H, 3.47; N, 17.25; Pt, 40.2.

(n) Na$_2$[(NH$_3$)$_2$Pt(U-N1)$_2$]. A 0.25-mmol sample of *cis*-(NH$_3$)$_2$Pt(HU-N1)$_2$·2H$_2$O was dissolved in excess aqueous NaOH (5 mL of 0.2 N NaOH), and the clear yellow solution was concentrated to 0.5-mL volume. Cooling at 3 °C (stoppered flask) gave large, colorless cubes which were briefly washed with water and air-dried; yield 40 mg. Anal. Calcd for Na$_2$[(NH$_3$)$_2$Pt(C$_4$H$_2$N$_2$O$_2$)$_2$]·6H$_2$O: C, 15.87; H, 4.0; N, 13.88. Found: C, 15.63; H, 4.04; N, 13.34.

Results and Discussion

Triammineplatinum(II) Complexes. (A) ^{1}H NMR Spectra and Reaction with H$^+$ and Additional (NH$_3$)$_3$Pt^{II}. Inagaki and Kidani have isolated both N-1- and N-3-coordinated uracil anion complexes of the triammineplatinum(II) moiety.[28] The authors differentiated between the two kinds of isolated complexes on the basis of UV, IR, and ^{1}H NMR spectroscopy. Their results are herewith confirmed and extended. In the present study, reactions of the two complexes with H$^+$ and additional (NH$_3$)$_3$Pt(H$_2$O)$^{2+}$ were studied. The complexity of the system is readily recognized when considering relevant pH-dependent equilibria of the various products possible (Figure 1). It is further increased if platinum–carbon, platinum–oxygen (exclusively) binding or binding of more than two platinum atoms per uracil ligand are included.

HU-N1 Complex. (a) Protonation. The ^{1}H NMR resonances of the uracilato ligand consist of a well-resolved sextet for H-6 and a badly resolved sextet of H-5, which almost looks like a doublet somewhat broadened at its basis. The multiplet structures of both signals arise from coupling between H-5 and H-6 ($^3J_{H-H}$ ≃ 7.3 Hz) and from coupling between the ^{195}Pt isotope (33.8% natural abundance, spin $^1/_2$) and the ^{1}H nucleus. The ^{195}Pt–^{1}H coupling constant for the H-6 resonance (38.3 Hz) is considerably larger than that of the H-5 resonance (4.3 Hz).[30] This finding is consistent with the platinum coordination site being closer to H-6 than to H-5, hence N-1 being the site of Pt binding. The spectrum of the (HU-N1) complex remains unchanged over the pH range 1–8. In strongly alkaline medium, the N-3 position becomes depro-
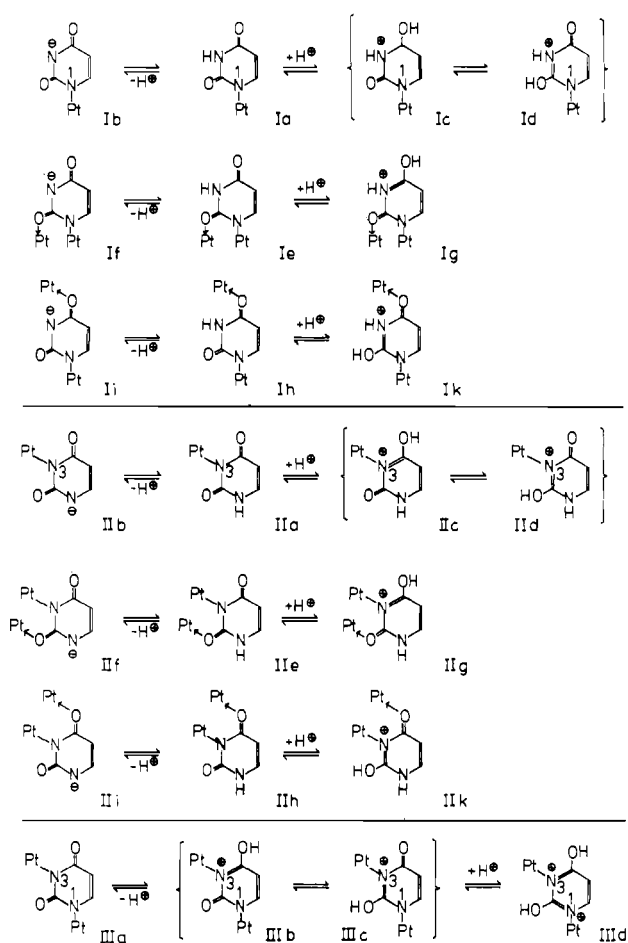
Figure 1. Relevant acid–base equilibria for different ways of coordination of 1 or 2 platinum atoms to the uracil ring. Only a single mesomeric structure is given for each example. So that excessive use of formal charges in the ring could be avoided, binding of a second platinum has been denoted by an arrow, except with N-1,N-3 binding.

tonated;[28] in strongly acidic solution (pH <0) the uracil ligand is protonated. Because of the similar effects expected for protonation and binding of a second Pt atom to the HU ligand, the low pH spectra were of particular interest. Protonation of the HU ligand according to

$$\text{Ia} \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} \{\text{Ic} \overset{?}{\rightleftharpoons} \text{Id}\}$$
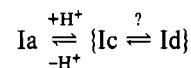
is evident from the downfield shift of the H-6 signal (Table I). This process is accompanied by a rapid collapse of the original signal structures, which indicates replacement of the proton at the C-5 position for a deuterium. The original H-5 signal disappears and the H-6 sextet is reduced to a triplet. The relative intensities of this triplet are 1:4:1 and correspond to the expected distribution according to the natural abundance of ^{195}Pt, and the coupling constant of 39.3 Hz indicates that platinum remains bound to the uracil ring. For the line in the center of the H-6 triplet, splitting due to coupling with the deuterium nucleus (spin 1) at C-5 might be expected. However, the small magnetic moment and the possibility of quadrupole relaxation of the ^{2}H nucleus can account for the fact that it is not observed.[31]

In contrast to HU-N3 complexes of platinum(II), (UH-N1) complexes are very stable toward acid treatment. For example, complexes with N-1-coordinated uracil and thymine have been isolated from aqueous HCl solutions at a pH ≤0.[14] Only

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(30) Cf. similar coupling in Figure 13d.

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Table I. Chemical Shifts (ppm) of Uracil Complexes of $(NH_3)_3Pt^{II}$

symbol[a]	pD	H-5	H-6	assignt	stability[e]
A	8–1.5	5.676	7.718	$(NH_3)_3Pt(HU-N1)^+$	stable
	1.2	5.679	7.731		
	0.8	no[c]	7.743		
	0.4	no	7.788		
	<0[b]	no	7.890		
B	2.1	no	7.853	dimer	some dec to give A
	2.0	no	7.886		
	1.9	no	7.910		
	1.7	no	7.935		
	0.4	no	8.046		
C	7–3	5.712	7.383	$(NH_3)_3Pt(HU-N3)^+$	dec to give H_2U
	2.25	5.735	7.402		
	1.0	5.779	7.440		
	0.4	5.988	7.628		
	<0[b]	6.023	7.659		
D	1.8	no	7.861	?	?[d]
	1.7	no	7.861		
E	1.8	no	8.196	?	?[d]

[a] It is noted that the symbols used do not correspond to those used in Tables II and III. [b] pD ≥ -1, since H_2U is released upon heating and not H_3U^+. [c] Not observed because of isotopic D/H exchange at C(5). [d] Signal intensities not sufficient. [e] Conditions: pD 0.4; 10 min; 90 °C.
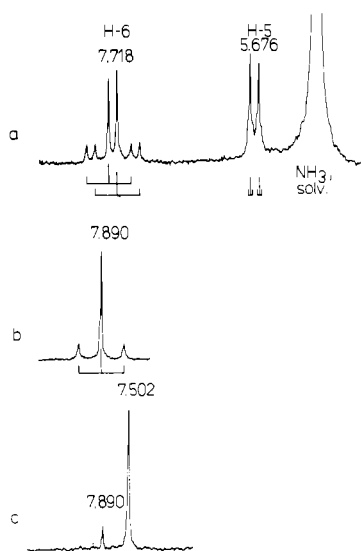

Figure 2. ^1H NMR spectrum of $[(NH_3)_3Pt(HU-N1)]^+$ in D_2O (0.15 M): (a) at pD 8 (identical at pD 1); (b) after addition of CF_3COOD (pD <0); (c) after 2 h at 95 °C (pD <0). The signal at 7.502 ppm is due to H_2U.

prolonged heating in a strongly acidic solution (2–5 h at 95 °C in D_2O/trifluoroacetic acid anhydrate (5:1 by volume)) results in the removal of the neutral uracil ligand, which is new deuterated at the C-5 position, from the platinum complex (Figure 2). The position of the H-6 singlet of the free uracil lies exactly in the center of the H-6 doublet of neutral uracil in its H-5, H-6 form. Thus it is possible to obtain uracil selectively deuterated (or tritiated) at the C-5 position via this route. Since there is a more facile route to obtain C-5 deuterated uracil (vide infra), this possibility will not be dealt with in more detail.

(b) Reaction with $(NH_3)_3Pt^{II}$. The presence of aquotriammineplatinum(II) nitrate also causes an exchange of the proton at the C-5 position of the uracilato ligand for deuterium. This leads, at an early stage of the reaction, to the nonet structure of the H-6 signal shown in Figure 3a, which actually is a superposition of the original sextet with the triplet of the
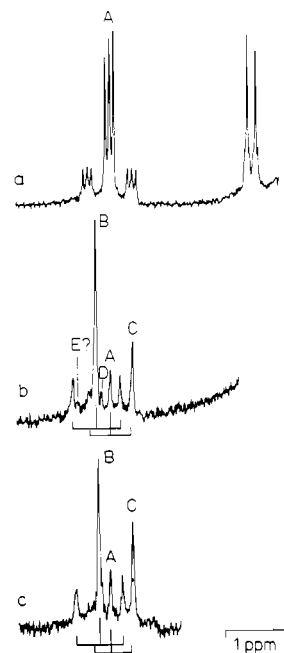

Figure 3. ^1H NMR spectra of a mixture of $[(NH_3)_3Pt(HU-N1)]NO_3$ (0.1 M) and $[(NH_3)_3Pt(D_2O)](NO_3)_2$ (0.2 M) in D_2O in the H-5, H-6 region: (a) after 3 h at 40 °C (pD 2.6); (b) after 43 h at 40 °C (pD 1.8); (c) after 10 days at 40 °C (pD 1.7). Due to isotopic exchange at C-5, no H-5 resonances are observed in (b) and (c).

complex deuterated at the C-5 position (signal A).

It is unclear, at present, whether this isotopic exchange is a consequence of coordination of a second Pt to the uracil ligand or caused by H^+ (pD of the solution is ca. 2.5). H^+ by itself causes slow exchange in this pH range. If it is due to a uracilato-bridged species, then this compound must be present in a low concentration only, since no NMR signal is detected at this stage of the reaction. In any case, once the isotopic exchange at the C-5 position is completed, all H-6 resonances of the starting compound and all newly formed products consist of singlets only or, with ^{195}Pt coupling, of triplets.

With time, the H-6 triplet of the HU-N1 complex decreases and new resonances appear. In sequence of their intensities, these are as follows.

Signal B. A triplet ($J \simeq 40$ Hz) occurs at lower field. Since its relative intensity increases with increasing Pt:uracil ratio, it is assigned to a uracil-bridged dimer. It must, at least in part, contain the doubly deprotonated uracil ligand U since its formation is accompanied by a decrease in pH. The position of this signal is clearly pH dependent, as shown in Table I, and indicates an equilibrium of the kind

$$U\text{-}X,Y + H^+ \rightleftharpoons HU\text{-}X,Y$$
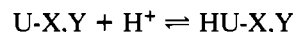
Signal C. A signal upfield of the H-6 signal of the starting compound grows, which does not exhibit satellites due to ^{195}Pt–^1H coupling. It is assigned to the complex with the N-3-coordinated uracil ligand $[(NH_3)_3Pt(HU-N3)]^+$ (IIa) for the following reasons. Its position corresponds exactly with the position of the center of the H-6 doublet of IIa (vide infra) at the same pH. Like IIa, it does not exhibit ^{195}Pt coupling satellites.[32] Addition of acid causes the same marked downfield shift as with the H-6 doublet of IIa. Brief warming of the acidified solution (pD 0.4; 15–30 min at 70–90 °C) removes the signal completely and shifts it upfield again to a position agreeing extremely well with that of the H-6 signal

(32) It is noted that this argument might be questioned, since ^{195}Pt–^1H coupling may not always be observed. Cf.: Lallemand, J. Y.; Soulié, J.; Chottard, J. C. *J. Chem. Soc., Chem. Commun.* **1980**, 436.
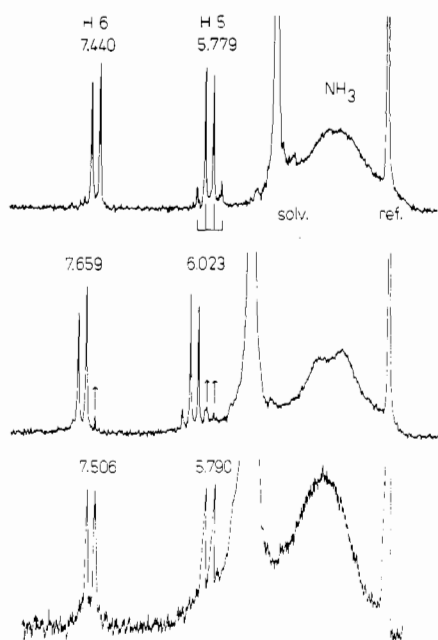
Figure 4. ^{1}H NMR spectrum of [(NH$_3$)$_3$Pt(HU-N3)]NO$_3$ (0.1 M) in D$_2$O/CF$_3$COOD: (a) at pD 1; (b) at $-1 < $ pD < 0; (c) at $-1 < $ pD < 0 after 30 min at 70 °C. The observed H-5 and H-6 signals correspond to H$_2$U (ref = N(CH$_3$)$_4^+$ resonance).

Figure 5. ^{1}H NMR spectra of a mixture of [(NH$_3$)$_3$Pt(HU-N3)]NO$_3$ (0.1 M) and [(NH$_3$)$_3$Pt(D$_2$O)](NO$_3$)$_2$ (0.2 M) in D$_2$O in the H-5, H-6 region: (a) after 6 h at 40 °C (pD 2.3); (b) after 4 days at 40 °C (pD 2.0); (c) after 7 days at 40 °C (pD 1.9).

of free uracil. Thus signal C exhibits the identical changes of IIa. The most convincing argument, however, in favor of this interpretation comes from the following experiment. When starting with [(NH$_3$)$_3$Pt(HU-N3)]$^+$ (IIa) and adding [(NH$_3$)$_3$Pt(H$_2$O)]$^{2+}$, the reaction eventually approaches the same equilibrium as does the reaction starting out with [(NH$_3$)$_3$Pt(HU-N1)]$^+$ (Ia).

Signal D. Another weak signal slightly downfield from the original one of Ia (signal A) appears to be constant in its intensity. It is observed only in the pD range above 2, otherwise it is hidden under the intense signal B. Because of its weakness, it is not possible to say whether there is any coupling with ^{195}Pt.

There appears to be yet another weak signal E close to the downfield ^{195}Pt satellite of signal B. Since it is not observed in all spectra, no further speculations are appropriate.

The observed disappearance of the H-5 resonances due to deuterium exchange represents a severe disadvantage for properly assigning the site of protonation and of binding of a second platinum atom, respectively. For example, if O-4 were the binding site, a larger downfield shift of H-5 as compared to H-6 might be expected. If it were O-2, H-6 might possibly be shifted more than H-5. If N-3 were the second site of platinum coordination, considerable coupling with H-5 might be expected.

The observed isotopic exchange at the C-5 position of N-1-platinated uracil is qualitatively different from a similar isotopic exchange observed by Lim and Martin[33] with N-3-platinated uridine at higher pH.

HU-N3 Complex. (a) Protonation. In Figure 4a the ^{1}H NMR spectrum of the (uracilato-*N3*)triammineplatinum(II) complex is shown. The H-5 signal of the uracil ligand exhibits ^{195}Pt satellites with $^4J_{^{195}\text{Pt}-^1\text{H}} \simeq 15$ Hz. This value is close to that reported before for a platinum complex of uridine.[28]

At a pH (or pD) below approximately 1, the uracilato ligand becomes protonated according to
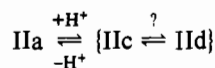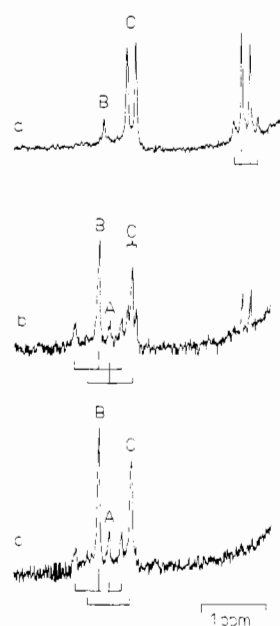
$$\text{IIa} \underset{-\text{H}^+}{\overset{+\text{H}^+}{\rightleftharpoons}} \{\text{IIc} \overset{?}{\rightleftharpoons} \text{IId}\}$$

as indicated by the downfield shifts of both H-5 and H-6 resonances. H-5 is shifted slightly more than H-6 (Table I). In contrast to the situation with the corresponding N-1 complex, no exchange of ^{1}H vs. ^{2}D at the C-5 position is occurring, not even at a pD below 0.

The platinum complex containing a neutral uracil ligand is, like the corresponding one with the N-1-bound ligand, qualitatively different from other metal complexes of neutral uracil with divalent Mn, Co, Ni, Cu, Zn, and Cd.[34] There oxygen coordination is assumed, whereas in the platinum complexes described here, N coordination is retained with the uracil ligand having the rare iminol tautomer structure. The protonated complex [(NH$_3$)$_3$Pt(H$_2$U)]$^{2+}$ is stable at room temperature or even at 40 °C but readily decomposes when briefly warmed above 70 °C with formation of free uracil:

$$[(\text{NH}_3)_3\text{Pt}(\text{H}_2\text{U-N3})]^{2+} \rightarrow [(\text{NH}_3)_3\text{Pt}]^{2+} + \text{H}_2\text{U}$$
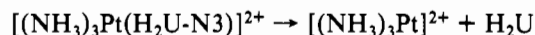
Thus the complex behaves very much like N-3-platinated 1-methylthymine complexes,[35] although protonation of the monouracilato complex is somewhat harder to achieve than protonation of the bis(1-methylthyminato-*N3*) complex of *cis*-Pt^{II} (p$K \simeq 2$). This may have something to do with the better stabilization of the protonated ligand in the bis complex due to favorable hydrogen bonding.[35] However, it is quite clear, that protonation of the N-3-platinated uracil monoanion occurs at a higher pH than that of N-1-platinated uracil.

No conclusions concerning the site of protonation of the HU-N3 complex are possible from the ^{1}H NMR spectra since any coupling between ^{2}D firmly bound to O-4 or O-2 with H-5, for reasons outlined above, may not be detected. However, with the lack of any significant differences in the observed downfield shifts of the H-5 and H-6 resonances of the protonated complex, it appears likely that O-4 is not favored over O-2 with respect to protonation. With free uracil, protonation to give the monocation is believed to predominantly occur at O-4, thus causing the larger downfield shift of H-5 as compared to H-6.[36]

(33) Lim, M. C.; Martin, R. B. *J. Inorg. Nucl. Chem.* **1976**, *38*, 1915.

(34) Goodgame, M.; Johns, K. W. *J. Chem. Soc., Dalton Trans.* **1977**, *17*, 1680.

(35) Lippert, B. *Inorg. Chim. Acta* **1981**, *55*, 5.

(b) Reaction with $(NH_3)_3Pt^{II}$. Addition of aquotriammineplatinum(II) nitrate to a solution of $[(NH_3)_3Pt(HU-N3)]^+$ (H-6 resonance corresponds to signal C in Figure 5) leads to changes in the NMR spectrum. These changes are accompanied by a decrease in pD from originally 2.7 to 1.8. In sequence of their intensities, the following new resonances are observed.

Signal B. This triplet occurs downfield relative to the original C signal. Only at higher concentrations of this species, the ^{195}Pt satellites ($J \simeq 40$ Hz) are well observable. The position of signal B is pD dependent in exactly the same way as is the corresponding signal in the $(NH_3)_3Pt(HU-N1)/$ $(NH_3)_3Pt(D_2O)$ system. It therefore is assigned to the uracil bridged dimer.

Signal A. This signal appears at a position agreeing perfectly with the position of the $[(NH_3)_3Pt(HU-N1)]^+$ complex. There is also a weak signal 20 Hz downfield from it which, from its relative intensity, should be the ^{195}Pt satellite. The upfield satellite is not observed since it is hidden under the intense H-6 signal of the starting compound. It is interesting to note that only after the appearance of the A signal one observes a singlet growing in the center of the original H-6 doublet of signal C. This change is accompanied by a gradual disappearance of the original H-5 and H-6 resonances, clearly indicating isotopic exchange at the C-5 position of the uracil ring. This finding is consistent with the observation on the easy isotopic exchange at the C-5 position of N-1-platinated uracil but not of the N-3-platinated one.

Signal D. This signal appears at a position identical with that in the $(NH_3)_3Pt(HU-N1)/(NH_3)_3Pt(D_2O)$ system. Again, there may be another weak signal (denoted E in the $(NH_3)_3Pt(HU-N1)/(NH_3)_3Pt(D_2O)$ system) close to the downfield ^{195}Pt satellite of signal B, but because of its insufficient intensity, no unambiguous identification is possible.

After approximately 4–5 days at 40 °C, the spectrum does not change any more under the experimental conditions. It then corresponds exactly with the spectrum obtained with the HU-N1 compound as starting material. This means that an equilibrium for the interconversion of N-1- into N-3-coordinated complex and vice versa is reached. The appearance of other signals (B, D, E (?)) besides those of the HU-N1 and HU-N3 complexes indicates that this interconversion proceeds via a relatively stable species (dimer B) and one or more (D, E (?)) less stable species. The equilibrium distribution of B:C:A:D is approximately 10:4:2:1 under the conditions of the experiment (0.1 M Pt(HU) complex; 0.2 M $(NH_3)_3Pt(D_2O)^{2+}$; 40 °C; final pD 1.7).

It is tempting to assume that the intermediate between monodentate N-1 and monodentate N-3 binding is a N-1,N-3-bridged dimer, which is in a pH-dependent equilibrium according to

$$IIIa \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} \{IIIb \overset{?}{\rightleftharpoons} IIIc\}$$
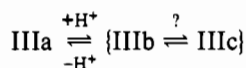
and that formation of this species either from monodentate N-1 or monodentate N-3 complexation proceeds via less stable N and O-complexed intermediates. At present there is no hard evidence for this assumption. Studies are under way to further clarify the question concerning the mechanism of this interconversion.

Equilibrium Mixture. Changes upon Acid Treatment. The discovery of the equilibration of species having different donor sites gets additional support by another experiment. When the equilibrium mixtures, obtained from starting with either the HU-N1 or the HU-N3 complex, are acidified and sub-
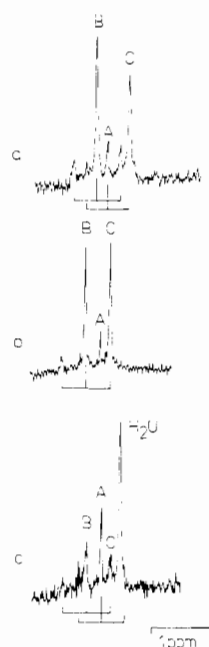
Figure 6. H-6 signals of a mixture of $[(NH_3)_3Pt(HU-N3)]^+/$ $[(NH_3)_3Pt(D_2O)]^{2+}$ in D_2O: (a) at pD 1.9 after 7 days at 40 °C (cf. Figure 5c); (b) after addition of CF_3COOD (pD 0.4); (c) at pD 0.4 after 20 min at 90 °C.

sequently warmed, they show identical behavior: addition of acid (CF_3COOD, pD 0.4) causes downfield shifts for A, B, and C resonances, indicating protonation of the complexes (Figure 6). Brief warming leads to the specific decomposition of the N-3-platinated complex as indicated by the formation of free uracil and the disappearance of the C signal. There is definitely no decrease in the signal intensity of A, the resonance of the N-1-platinated complex. On the contrary, there is a slight increase in intensity or this signal at the expense of B, which indicates some decomposition of this species.

Selective Deuteration of Uracil at C-5. With N-1 platination of uracil and additional H^+ (or Pt^{II}) binding at one of the two exocyclic oxygens causing rapid proton/deuterium exchange at the C-5 position, an attempt to achieve C-5 deuteration exclusively through protonation was undertaken. In a study on the isotopic distribution of tritiated pyrimidines, Fink had already suggested the preparation of C-5-tritiated uracil by heating uracil in acidic tritiated water.[37] For this purpose, uracil was dissolved in a mixture of D_2O and trifluoroacetic acid anhydride (2:1 by volume), and ^1H NMR spectra were taken after different periods of heating. At room temperature, shifts of the H-5 and H-6 resonances indicate that no measurable protonation of uracil occurs in this solvent mixture (the pK_a of H_3U^+ is about -3[38]). Heating to 90–95 °C leads to a gradual disappearance of the original H-5 and H-6 doublets and the simultaneous appearance of a H-6 singlet in the center of the original H-6 doublet. The isotopic exchange was complete within 5 h. Cooling, filtration, and recrystallization from H_2O gave uracil selectively deuterated at C-5 with 95% yield. Deuteration at the C-5 position was evident from the NMR spectrum of the product (singlet at 7.538 ppm) and the IR spectrum (e.g., C-5-D at 2320 cm^{-1}, C-6-H at 3090 cm^{-1}). From comparison with the published IR spectrum of C-5,C-6 dideutero uracil,[39] it can be ruled out that any measurable C-6 deuteration has occurred as well. The outlined method appears indeed to be a facile route to obtain C-5 deuterated or,

(36) (a) Wagner, R.; von Philipsborn, W. *Helv. Chim. Acta* **1970**, *53*, 299. (b) Poulter, C. D.; Anderson, R. B. *Tetrahedron Lett.* **1972**, *36*, 3823.

(37) Fink, R. M. *Arch. Biochem. Biophys.* **1964**, *107*, 493.
(38) Katritzky, A. R.; Waring, A. J. *J. Chem. Soc.* **1962**, 1540.
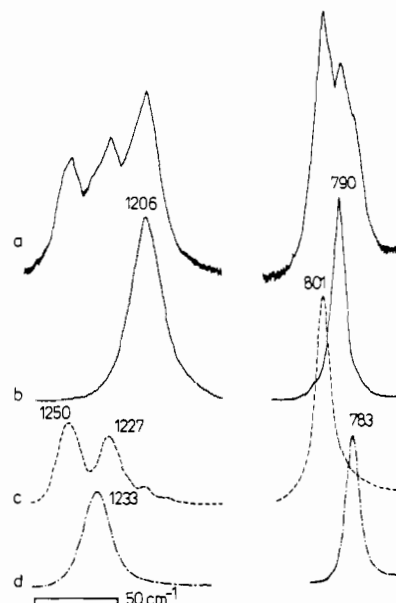(39) Susi, H.; Ard, J. S. *Spectrochim. Acta Part A* **1971**, *27A*, 1549.
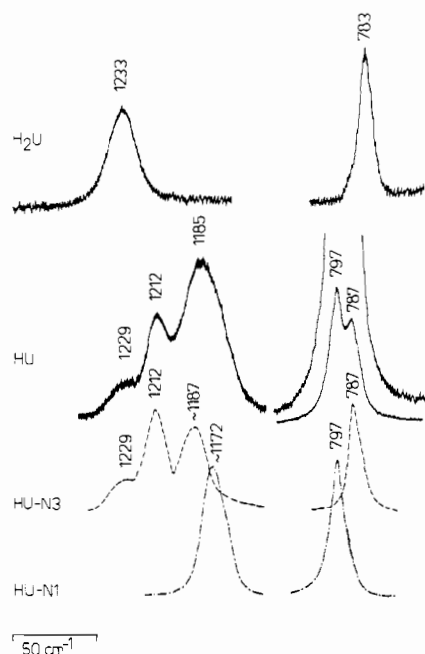
Figure 7. Raman-active ring-stretch and ring-breathing modes of uracil (H$_2$U) and sodium uracilate (NaHU) in H$_2$O. Assignment of HU-N1 and HU-N3 tautomers according to ref 21a. Relative intensities of 1187 and 1172 cm^{-1} bands are estimated only and may be reversed. Intensities of the ring-breathing modes are reduced by a factor of 6. Slit width was 4 cm^{-1}.

Figure 8. Raman solution (H$_2$O) spectra in the 1200–800-cm^{-1} range: (a) mixture of [(NH$_3$)$_3$Pt(H$_2$O)]$^{2+}$ and HU prior to isolation of individual components (preparation according to ref 28); (b) [(NH$_3$)$_3$Pt(HU-N1)]NO$_3$ after separation; (c) [(NH$_3$)$_3$Pt(HU-N3)]NO$_3$ after separation; (d) H$_2$U after separation. The slit width was 4 cm^{-1}.

analogously, C-5 tritium labeled uracil in high yield. Another way to prepare 5-deuterated uracil involves a much more complicated synthesis via 5-bromouracil.[40]

It should be mentioned that we recently reported on the isotopic exchange of 1-methylcytosine in acidic solution with *cis*-(NH$_3$)$_2$Pt^{II} coordinated at the N-3 position.[41]

(B) Raman and IR Spectroscopy. As has been shown by Tobias and co-workers, Raman spectroscopic changes of nucleobase vibrations as a consequence of metal coordination almost exclusively depend upon electronic changer in the ligand caused by the heavy-metal electrophile.[42] Therefore, a bound nucleobase has essentially the same Raman spectrum regardless of the other ligands bound to the metal as long as the donor atom of the nucleobase remains the same. Alternatively, if different absorptions of the same vibration are observed, this is a strong indication that different binding modes may occur.

Bands selected for the differentiation of binding sites in this present study were the ring-stretching mode of uracil around 1200 cm^{-1} and the ring-breathing mode around 800 cm^{-1}. Both modes are in-plane modes (A′) and polarized.[39,43] Although other differences in the spectra of the various uracil complexes were observed as well, these two modes were studied preferentially because of their high intensities and the absence of other Raman-active vibrations in these regions. It is noted that the position of the skeletal stretching mode of uracil appears to be somewhat sensitive toward hydrogen bonding, as has been shown for polyU.[44] However, since the magnitudes in shifts due to hydrogen bonding are considerably

smaller than those observed in the present study, it is fair to attribute the differences in band positions essentially to changes within the uracil ligand as a consequence of metal binding and ignore hydrogen bonding. With hydrogen bonding becoming more significant in the solid state, and also because of crystal effects that can cause band splitting, the interpretation of the solid-state spectra is less straightforward than that of solution spectra.[22]

In Figure 7, the respective Raman bands of uracil and monosodium uracilate in aqueous solution are shown. The assignment of the individual uracil monoanion tautomer bands is according to ref 21.

Reaction of (NH$_3$)$_3$Pt(H$_2$O)$^{2+}$ with HU, which leads to the formation of HU-N1 and HU-N3 complexes,[28] can be followed with Raman spectroscopy.[23] In Figure 8, the reaction mixture of (nitrato)triammineplatinum(II) nitrate and sodium uracilate in water prior to isolation of the components is shown. The spectrum represents a superposition of the N-1-coordinated uracil complex Ia, the N-3-coordinated one IIa, and unreacted uracil. The two tautomers were separated according to the published procedure.

As an alternative to the reported method, the N-1-coordinated uracil complex Ia (as Cl$^-$ and NO$_3^-$ salts) has now been prepared in a different way (cf. Experimental Section). A quantitative determination of the intensities of the respective Raman bands shows the complex with the N-1-coordinated tautomer to have a larger scattering coefficient than its N-3 counterpart. The following relative intensities were obtained in aqueous solution: [(NH$_3$)$_3$Pt(HU-N1)]$^+$ (Ia), 790 (10), 1206 (8.7); [(NH$_3$)$_3$Pt(HU-N3)]$^+$ (IIa), 801 (5.6), 1227 (1.8), 1250 (2.2) cm^{-1}. For comparison, the band intensities of free uracil H$_2$U are 783 (7) and 1233 (4) cm^{-1}.

It is noted that the 1206-cm^{-1} band of the N-1 tautomer complex is of considerable broadness and slightly asymmetric. Whether this is due to another unresolved band is unclear, since no band separation could be achieved even at 1-cm^{-1} slit width.

HU-N1 Complex. Deprotonation and Reaction with (NH$_3$)$_3$Pt(H$_2$O)$^{2+}$. In Figure 9a the Raman spectrum of [(NH$_3$)$_3$Pt(HU-N1)]$^+$ (Ia) in aqueous solution in the 1200–
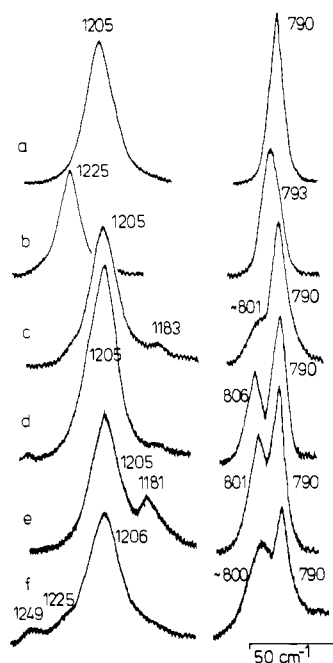
(40) Párkányi, C.; Šorm, F. *Collect. Czech. Chem. Commun.* **1963**, *28*, 2491.
(41) Lippert, B.; Lock, C. J. L.; Speranzini, R. A. *Inorg. Chem.* **1981**, *20*, 335.
(42) See, e.g.: (a) Mansy, S.; Wood, T. E.; Sprowles, J. C.; Tobias, R. S. *J. Am. Chem. Soc.* **1974**, *96*, 1762. (b) Mansy, S.; Tobias, R. S. *Inorg. Chem.* **1975**, *14*, 287.
(43) Lord, R. C.; Thomas, G. J., Jr. *Spectrochim. Acta, Part A* **1967**, *23A*, 2551.
(44) Mansy, S.; Douthart, R. J. *Procl. Int. Conf. Raman Spectrosc., 5th* **1976**, 190–191.

Figure 9. Raman solution (H₂O) spectra in the 1200–800-cm⁻¹ range: (a) [(NH₃)₅Pt(HU-N1)]⁺, 0.15 M, pH 4.7; (b) (NH₃)₃Pt(U-N1), 0.07 M, pH 13.5; (c) [(NH₃)₃Pt(HU-N1)]Cl (0.15 M) + [(N-H₃)₃Pt(H₂O)](NO₃)₂ (0.3 M), 2 h, 80 °C, pH 1.9; (d) [(NH₃)₃Pt(HU-N1)]Cl (0.15 M) + [(NH₃)₃Pt(H₂O)](NO₃)₂ (0.15 M) + NaOH, 3 days, 40 °C, pH 7.7; (e) sample d after addition of HNO₃, pH = 1.1; (f) [(NH₃)₃Pt(HU-N1)]Cl (0.15 M) + [(N-H₃)₃Pt(H₂O)](NO₃)₂ (0.3 M), 2.5 h, 90 °C, pH 2.9. The slit width in all cases was 4 cm⁻¹.

800-cm⁻¹ range is shown (cf. also Figure 8b). In strongly alkaline medium, the uracil ligand of Ia is deprotonated to give (NH₃)₃Pt(U-N1) (Ib). A crystalline compound of this composition has been isolated. Its Raman-active ring-breathing (793 cm⁻¹) and ring-stretching modes (1225 cm⁻¹) are depicted in Figure 9b.

When Ia is treated with [(NH₃)₃Pt(H₂O)]²⁺ at 40 °C, new bands gradually appear around 800 and 1185 cm⁻¹, indicating that bridge formation of the uracil ligand has occurred (Figure 9c). As mentioned before, the pH is dropping during the reaction. Thus a partial deprotonation of the uracil monoanion ligand must have taken place, leading to the uracil dianion. At higher pH (7–8), the complex with the uracil dianion bridge is formed in better yield (Figure 9d). Addition of acid to the solution containing the dianion bridge causes a rapid spectral change (Figure 9e): the 806-cm⁻¹ band shifts to 801 cm⁻¹, and a new band appears around 1180 cm⁻¹. Thus the spectrum is similar to (identical with (?)) that obtained upon reaction of Ia with [(NH₃)₃Pt(H₂O)]²⁺ at lower pH. The quickness of the spectroscopic change on addition of acid (Figure 9d → 9e) rules out any change in coordination site during this process. However, from the Raman spectra it is not possible to tell whether this refers to the equilibria Ic ⇌ Id or Ie ⇌ If or IIIa ⇌ {IIIb ⇌? IIIc}. Gradually, but faster upon brief warming, new bands around 1250 and 1225 cm⁻¹, appear, which are characteristic of the complex IIa with the N-3-coordinated uracil (Figure 9f).

HU-N3 Complex. Protonation, Deprotonation, and Reaction with [(NH₃)₃Pt(H₂O)]²⁺. In Figure 10a the most intense Raman bands of [(NH₃)₃Pt(HU-N3)]⁺ (IIa) in the 1200–800-cm⁻¹ range are shown. Addition of acid leads to formation of [(NH₃)₃Pt(H₂U-N3)]²⁺ (IIc and/or IId), as indicated by a marked intensity increase and a slight shift of the ring-stretching mode around 1225 cm⁻¹. The ring breathing mode is not affected (Figure 10a; dotted line). When briefly heated with acid (HCl, HClO₄, HNO₃) to 70–90 °C, complex IIc
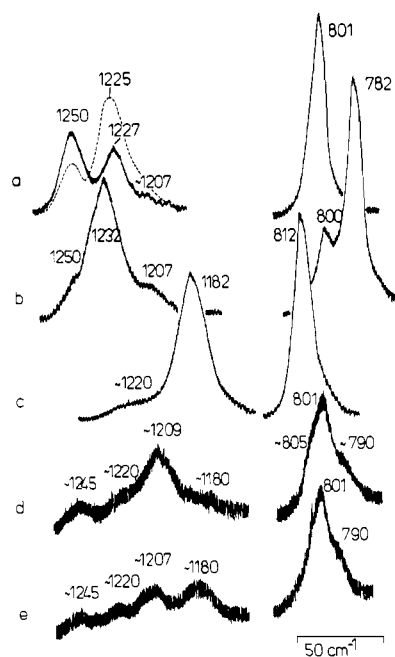
Figure 10. Raman solution (H₂O) spectra in the 1200–800-cm⁻¹ range: (a) [(NH₃)₃Pt(HU-N3)]NO₃, 0.15 M, pH 3.2 (solid line), pH 0 (dotted line); (b) [(NH₃)₃Pt(HU-N3)]NO₃ + HCl, 0.15 M Pt, pH 0.3, after 15 min at 80 °C; (c) (NH₃)₃Pt(U-N3), 0.15 M, pH 13.5; (d) [(NH₃)₃Pt(HU-N3)]NO₃ + [(NH₃)₃Pt(H₂O)](NO₃)₂, 0.15 M each, after 1 h at 80 °C, pH 1.7; (e) spectrum d after addition of HNO₃, pH 0.5. The slit width was 4 cm⁻¹ in spectra a–c and 6 cm⁻¹ in spectra d and e.

(and/or IId) is readily decomposed with formation of free uracil. The characteristic bands of neutral uracil at 1233 and 783 cm⁻¹ appear (Figure 10b) and, with the use of HCl, the Pt–Cl stretching mode of the formed [(NH₃)₃PtCl]⁺ species is observed around 320 cm⁻¹. This is in agreement with the ¹H NMR results mentioned above and similar results (UV, NMR) in the 1-methylthymine/cis-Ptᴵᴵ system.³⁵ The different stabilities of N-1 and N-3 tautomer complexes can be nicely demonstrated with the triammineplatinum(II) complexes: when a mixture of HU-N1 and HU-N3 complexes is treated with 1 N HCl and warmed, the signals of the N-3 complex disappear and signals of free uracil appear. The bands of the HU-N1 complex remain unchanged.

In strongly alkaline medium, the N-3-bound uracil monoanion is deprotonated (pK = 11.4²⁸). The spectrum of (NH₃)₃Pt(U-N3) (IIb), which has been isolated, is shown in Figure 10c. Reaction of IIa with additional [(NH₃)₃Pt-(H₂O)]²⁺ could not be followed at room temperature because of precipitation of IIa. On heating the reaction mixture, new Raman bands around 790 and above 801 cm⁻¹ as well as around 1200 and 1180 cm⁻¹ are observed (Figure 10d). As in the [(NH₃)₃Pt(HU-N1)]⁺ system, the pH is dropping while reaction occurs (from 3.1 after addition of the aquo species to 1.7 after 1 h at 80 °C). Addition of HNO₃ leads to an increase in intensity of the band around 1180 cm⁻¹ at the expense of the band around 1200 cm⁻¹ (Figure 10e). Addition of base restores the original spectrum, thus indicating that no change in coordination sites takes place during the addition of acid and base. The quality of spectra in Figure 10, d and e certainly is anything but satisfying. However, in combination with the NMR results and the spectra of the [(NH₃)₃Pt-(HU-N1)]⁺ system, they may be considered reliable enough to support the above mentioned conclusion on the existence of the following major components in mixtures of [(NH₃)₃Pt(HU)]²⁺ and [(NH₃)₃Pt(H₂O)]²⁺: [(NH₃)₃Pt-(HU-N1)]⁺, [(NH₃)₃Pt(HU-N3)]⁺, [(NH₃)₃Pt(HU-X,Y)-Pt(NH₃)₃]³⁺ with Raman bands around 800 and 1180 cm⁻¹,

and $[(NH_3)_3Pt(U\text{-}X,Y)Pt(NH_3)_3]^{2+}$ with Raman bands around 805 and 1200 cm^{-1}.

Solid-State Spectra. The differences in Raman solution spectra between the individual tautomer complexes outlined above can be observed in the solid-state spectra as well. The HU-N1 complex exhibits its strongest Raman lines at 1213 (6) and 794 (10) cm^{-1}, the HU-N3 complex at 1239 (6.2), 1228 (2.3), and 796 (10) cm^{-1}. The corresponding IR bands are observed at 1210 (w) and 790 (vw sh) cm^{-1} for the HU-N1 complex and at 1240 (w) and 1220 (m) cm^{-1} for the HU-N3 complex. The 796-cm^{-1} band is not observed for the latter since it is superimposed by two strong IR bands in this region. Apart from the double-bond stretching region of the IR spectrum, that has been dealt with for the HU-N1 and the HU-N3 complexes before,[28] the 900–1200-cm^{-1} range appears to be of some limited diagnostic value. The absence of any IR absorption in this region (except the weakly IR active ν_1 mode of NO_3^- salts around 1050 cm^{-1}) seems to be characteristic for a uracil monoanion bound to platinum through N-3 in a monodentate fashion. The HU-N1 complex (1054 (m), 1014 (m) cm^{-1}), the U-N1 complex (1120 (w), 1055 (s), 1015 (m), 982 (m), 948 (s) cm^{-1}), and the U-N3 complex (1104 (s), 1070 (s), 1018 (s), 978 (w) cm^{-1}) exhibit a series of bands in this region.

Clearly, solid-state spectra are much less suitable for a differentiation of tautomer complexes than solution spectra. In particular, the differences in the most intense Raman lines around 800 cm^{-1} of the tautomer complexes are too small to be considered significant. The corresponding IR bands are either of very low intensity or not observable at all. There are, however, distinct differences in both the number and the positions of bands of the ring-stretching modes of the HU-N1 and HU-N3 complexes. They are very observable in the Raman spectra and reasonably observable in the IR spectra.

(Ethylenediamine)platinum(II) Complexes. HU-N1 Complexes. Three chloro(uracilato)(ethylenediamine)platinum(II) complexes and a bis(uracilato)(ethylenediamine)platinum(II) complex have been isolated. Of the 1:1 complexes (a monohydrate, a dimethylformamide adduct, and a pentahydrodioxonium chloride adduct), an X-ray structure determination has been carried out for the latter.[13] From their preparative relationship with the compound characterized by X-ray analysis, as well as on the basis of solid-state Raman spectra, it is concluded that the donor atom of the two other 1:1 complexes is N-1 as well. Raman spectra also strongly indicate that the bis complex contains uracil bound through N-1. Mono(uracilato) complexes: DMF adduct, 791 (10), 1203 (10) cm^{-1}; monohydrate, 794 (10), 1209 (6) cm^{-1}; $H_5O_2^+Cl^-$ adduct, 791 (10), 1191 (4) cm^{-1}. Bis(uracilato) complex: 790 (10), 1210 (6) cm^{-1}. The position of the ring stretching mode of the pentahydrodioxonium chloride adduct deviates by approximately 20 cm^{-1} from the range usually observed with monodentate binding via N-1. This undoubtedly reflects the perturbation of the uracil ring as a consequence of the extremely short hydrogen bond between the O-4 atom of uracil and the $H_5O_2^+$ unit (2.47 (2) Å). This very strong hydrogen bond causes, for example, a lengthening of both N(3)–C(4) and C(4)–C(5) bonds compared to the corresponding thymine complex, which does not contain the $H_5O_2^+Cl^-$ unit.[13] The ^1H NMR resonances of enPt(HU-N1)$_2$ at pD 5 are observed at 7.596 ppm (H-6), 5.606 ppm (H-5, J_{H-H} = 7.3 Hz), and 2.689 ppm (C_2H_4, J_{195Pt-^1H} = 40 Hz). Addition of acid results in a rapid isotopic exchange at C-5 and the appearance of a H-6 triplet (J_{195Pt-^1H} = 40 Hz). As indicated by the downfield shift of the H-6 signal below pD $\simeq 1$, the bis(HU-N1) complex is more readily protonated than mono(HU-N1) complexes are. Again, this could be a consequence of a favorable intramolecular hydrogen bond which stabilizes the rare uracil tautomer

Table II. Chemical Shifts (ppm) of Uracil Resonances in enPt^{II} Complexes and Tentative Assignments

sym-bol[a]	D	H-5	H-6	assignt[e]	stability[f]
A'	11	5.320	7.769	[enPt(HU-N1,O2)]$_2$$^{2+}$	partial dec to give B'
	1.9	5.856	7.963		
	0.4	5.894	8.013		
B'	2.3	5.694	7.690	enPt(HU-N1)D$_2$O$^+$	stable
	0.4	no[b]	7.702		
C'	1.8	no	7.608	HU-N3,O4	gradual dec to give H_2U
	1.4	no	7.612		
	0.4	no	7.620		
D'	4–2.3[c]	5.716	7.387	enPt(HU-N3)D$_2$O$^+$	dec to give H_2U
	2.0[c]	5.726	7.395		
	1.8[d]	no	7.404		
	0.4[c]	5.992	7.641		
E'	1.8	no	7.914	?	
	0.4	no	7.9–8 (?)		
F'	4–2.3	7.367	5.890	HU-N3,X	dec
	2.0	7.375	5.890		
G'	2.3	7.326	6.002	HU-N3,Y	dec
H'	5	5.606	7.596	enPt(HU-N1)$_2$	stable
	1.4	no	7.612		
	0.4	no	7.735		
I'	1.4	no	7.4–8.2	?	
K'	1.4	no	7.477	?	

^{a} It is noted that the symbols used do not correspond to those used in Table I. ^{b} Not observed because of isotopic D/H exchange at C(5). ^{c} Data taken from spectra of reaction en enPt(D$_2$O)$_2$$^{2+}$ + HU. ^{d} Data taken from spectra of A, B, and enPt(HU-N1)Cl + AgNO$_3$. ^{e} Relevant acid–base equilibria omitted for clarity. ^{f} Conditions: pD 0.4; 15 min; 90 °C.

coordinated to Pt.[35] Other examples of a minor tautomer, 2-hydroxypyridine, coordinated to Pt have recently been reported for the 1:1 and 2:1 complexes of this ligand.[20]
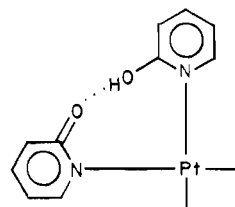
There is, however, a distinct differences between corresponding bis complexes of N-1 and N-3 tautomers: heating (10–20 min at 90 °C) does not decompose the N-1 complex in contrast to the N-3 complex (cf. Table II, signal H').

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(Uracilato-N1)(ethylenediamine)aquoplatinum(II) Nitrate. Solid-State Spectra and Reactivity in Solution. Removal of the halogen in chloro(uracilato-N1)(ethylenediamine)platinum(II) with silver nitrate yields a highly water soluble product. Both Raman and ^1H NMR spectra undergo changes with time, and both techniques indicate the formation of a variety of products. Two of these products have been isolated in crystalline form, both of which analyze as Pt:HU = 1:1 complexes. According to their ^{H} NMR spectra (vide infra), they are completely different species that are not in a pH-dependent equilibrium concerning the uracil ligand. However, they slowly equilibrate to a state identical with that reached when enPt(HU-N1)Cl and AgNO$_3$ are reacted in water. As a consequence, it proved impossible to recrystallize these two
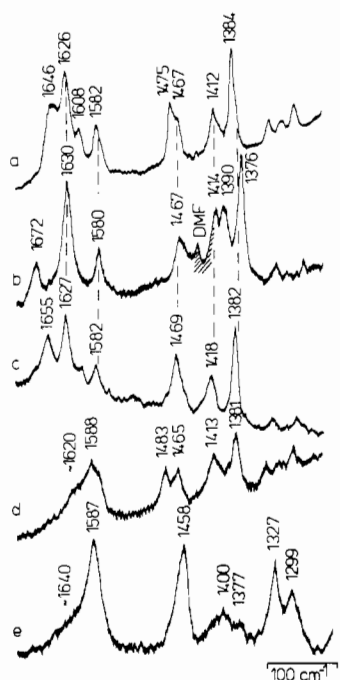
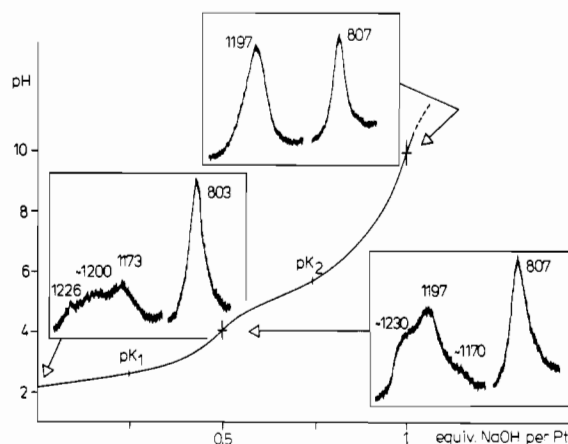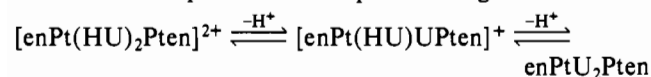**Figure 11.** Raman solid-state spectra between 1700 and 1300 cm^{-1}: (a) enPt(HU-N1)Cl·H$_2$O; (b) enPt(HU-N1)Cl·DMF; (c) enPt-(HU-N1)$_2$·3H$_2$O; (d) compound B; (e) compound A. The slit width was 4 cm^{-1} in spectra a–c, 6 cm^{-1} in spectrum e, and 8 cm^{-1} in spectrum d.

compounds with any chance of obtaining them in reasonable yields. It has also prevented the growth of crystals suitable for X-ray diffraction so far.

A third crystalline product, obtained by reaction of one of the two mentioned compounds with excess enPt(H$_2$O)$_2$$^{2+}$, has been isolated as well. These crystalline products will be dealt with first.

Compound A: A Dimer. A compound analyzing as (C$_2$-H$_8$N$_2$)Pt(C$_4$H$_3$N$_2$O$_2$)NO$_3$·0.5H$_2$O was isolated from a solution of the aquo complex at pH 0. From IR (Nujol) and Raman solid-state spectra it is evident that NO$_3$$^-$ is ionic, thus ruling out a monomeric structure with coordinated nitrate. Raman bands of the uracil ligand (solid state 805 (10), 1179 (4.8), 1227 (1) cm^{-1}; H$_2$O solution (pH 2) 803 (10), 1173 (2.3), 1200 (1), 1226 (1.5) cm^{-1}) are not consistent with monodentate binding through N-1 and therefore indicate bridge formation with N-1 being one donor atom (cf. ^{1}H NMR spectra). Spectroscopic differences between the HU-N1 complexes and the compound discussed here are also observed in the 1300–1700-cm^{-1} range of the Raman spectra (Figure 11): while the HU-N1 complexes exhibit similar band patterns around 1630, 1580, 1470, 1410, and 1380 cm^{-1}, compound A and also the second isolated compound B (vide infra) show marked deviations.

As evident from the ^{1}H NMR spectra, compound A is "stable" in solution for several hours before it undergoes re-arrangement reactions. This fact was used to carry out a combined Raman/potentiometric titration experiment. Titration with base shows the presence of two titratable protons in compound A, which are neutralized after addition of exactly 0.5 and 1 equiv of base per Pt. This, together with the simplicity of the Raman spectrum at pH 10, which strongly indicates the presence of a single type of ligand only at this pH, permits the conclusion of A being a head-to-tail dimer of composition [enPt(HU-N1,X)]$_2$(NO$_3$)$_2$·H$_2$O. Titration with base thus takes place in two steps according to

$$[enPt(HU)_2Pten]^{2+} \underset{-H^+}{\overset{-H^+}{\rightleftharpoons}} [enPt(HU)UPten]^+ \underset{-H^+}{\overset{-H^+}{\rightleftharpoons}}$$
$$enPtU_2Pten$$

Figure 12. Titration curve of dimer A and Raman solution (H$_2$O) spectra at pH 2.2, 4, and 10. The slit width was 4 cm^{-1}.
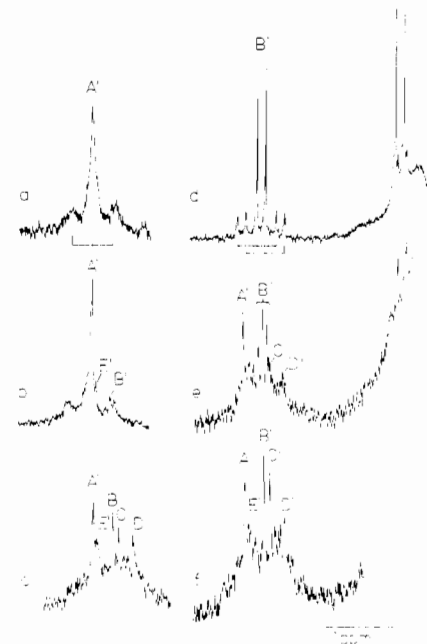
Figure 13. H-6 (compound A) and H-5, H-6 (compound B) resonances (0.1 M each, in D$_2$O) of (a) compound A after 15 min at 40 °C (pD 2.0), (b) compound A after 24 h at 40 °C, (c) compound A after 7 days at 40 °C (pD 1.8), (d) compound B immediately after dissolving (pD 2.3), (e) compound B after 3 h at 40 °C, and (f) compound B after 20 h at 40 °C (pD 1.8).

with pK_1 ≃ 2.6 and pK_2 ≃ 5.7 (Figure 12).

Deprotonation and protonation are reversible but limited by the slow rearrangement process in acidic medium (vide infra). The H-6 resonance of A at 7.963 ppm (triplet with $J_{^{195}Pt-^1H}$ = 37 Hz) is shown in Figure 13a. No H-5 signal is observed after 10–15 min at 40 °C as a consequence of rapid deuterium exchange. The C$_2$H$_4$ resonance around 2.7 ppm ($J_{^{195}Pt-^1H}$ = 40 Hz) and the NH$_2$ resonances around 5.3 ppm ($J_{^{195}Pt-^1H}$ = 60 Hz) are not shown. From the H-5 signal observed prior to complete isotopic exchange (5.856 ppm at pD 1.9), it is not possible to unambiguously say whether there are any ^{195}Pt coupling bands since this signal was superimposed with the broad NH$_2$ signal. However, the ^{1}H NMR spectrum of the titrated compound (enPtU)$_2$ (H-6 doublet at 7.769 ppm, ^{195}Pt coupling 38 Hz, and H-5 doublet at 5.320 ppm) does not show ^{195}Pt satellites for the H-5 signal. Although this does not necessarily rule out N-1,N-3 bridging,[32] such an arrangement seems highly unlikely for steric reasons as well: two N-1,N-3 bridges in a dimer would lead to an extremely strained molecule; two N-1,O-4 bridges in a dimer would also lead to very unfavorable bond angles around O-4, thus leaving

N-1,O-2 bridging as the most logical structure of A (head-to-head dimer).

Compound B: Another Nonmonomeric Complex. A compound, analyzing as $(C_2H_8N_2)Pt(C_4H_3N_2O_2)(NO_3)_2 \cdot 2H_2O$, has been isolated from a freshly prepared solution of (uracilato-*N1*)(ethylenediamine)aquoplatinum(II) nitrate at pH 2. IR (Nujol) and Raman solid-state spectra rule out a monomeric structure for the same reasons as for compound A: NO_3^- is of D_{3h} point symmetry, and the uracil ring modes at 801 (10), 1188 (1.3), and 1217 (8.4) cm^{-1} are distinctly different from those of the HU-N1 complexes. For differences in the 1300–1700-cm^{-1} Raman range, cf. Figure 11.

In Figure 13d, the ^1H NMR spectrum of B in the low-field region is shown. The sextet centered around 7.690 ppm is due to H-6 ($J_{H-H} = 7.3$ Hz, $J_{^{195}Pt-^1H} = 34$ Hz), the H-5 signal is observed at 5.694 ppm ($J_{^{195}Pt-^1H} = 4$ Hz). The en resonances occur at 5.4 (NH_2) and 2.65 ppm (C_2H_4). The ^{195}Pt coupling constants of both H-5 and H-6 are consistent with N-1 platinum binding, but it is not possible to say whether this refers strictly to a monodentate binding or some bridging as postulated for the solid state. The rapid change of B in solution suggests that if bridging is preserved in solution, it should be considerably weaker than that occurring in A.

Reaction of A with an Excess of $enPt(H_2O)_2^{2+}$. Compound A dissolves with yellow color in an excess of $enPt(H_2O)_2^{2+}$. Although a yellow, crystalline compound has been isolated from solution, elemental analysis so far has been inconclusive as to the composition of this species (cf. Experimental Section). In the ^1H NMR spectrum (A: $enPt(D_2O)_2^{2+} = 1:4$; pD = 1.9), a series of peaks ranging from approximately 7.4 to 8.2 ppm with an intensity maximum around 7.9 ppm are observed. It is suspected that these bands are due to different oligomers with identical binding modes since in the Raman spectrum only a single band around 820 cm^{-1} (ring-stretching modes at 1187 and 1231 cm^{-1}) is observed. The considerable displacement of the ring-breathing mode from the general 790–805-cm^{-1} range is noticeable. A similar band had been reported in the Pt/uridine system,[12] but the authors did not comment on the nature of this band (cf. Table II, signal I').

Equilibration of Complexes with Different Binding Sites in Solution. ^1H NMR Spectra. Both A and B undergo changes in aqueous solution, B much more rapidly than A (Figure 13). Since eventually the H-5 of the uracil ligand of B is exchanged as well, all observed resonances in the H-6 region of both spectra represent singlets (with the possibility of ^{195}Pt coupling).

As can be seen, after some time the ^1H NMR spectra of A and B are virtually identical with regard to the number of discernible signals (at least five A', B', C', D', E') and their positions and almost identical with regard to the relative intensities of these signals.[45]

Because of the slow time scale of the NMR experiment, the observed signals cannot be due to species being in an acid–base equilibrium but rather must be due to complexes with different donor sites, different stoichiometries, and/or different oligomeric size. In Table II the chemical shifts of the five most intense signals are listed and tentatively assigned. As with the simpler $(NH_3)_3Pt^{II}$ system, the signals of enPt(HU-N1) (B') and enPt(HU-N3) (D') are easily recognized by their different behavior upon acid treatment: B' is hardly shifted and quite stable when the pD is lowered to 0.4, whereas D' is quickly removed, and instead the signal of H_2U appears. The assignment of the C' signal represents a minor problem: although its position in the pD range 1.5–2 corresponds well with that of $enPt(HU-N1)_2$ (H'), there are two serious arguments against such an interpretation. First, the signal is shifted very

little when the pD is lowered, whereas the $enPt(HU-N1)_2$ signal is shifted markedly downfield. Second, the C' signal diminishes gradually at pD 0.4, whereas the HU-N1 complex is very stable even when heated. The C' signal is therefore assigned to a N-3,O-4-bridged species for the following reasons. (1) There is a similar downfield shift ($\sim$0.15 ppm) of the H-6 resonances in N-3,O-4-bridged complexes of 1-methylthymine and 1-methyluracil[16–19] relative to the H-6 resonances of the complexes with N-3 coordination only. (2) These N-3,O-4-bridged complexes show the same behavior in acidic medium: the H-6 resonances are hardly shifted, and there is a gradual decomposition of the complex with formation of the free ligand.

When looking at the H-6 signals of the uracil ligands in Figure 13c,d, it is immediately obvious that the mentioned signals sit on a broad resonance which, at its basis, is about 1.5 ppm wide.

A possible explanation for it could be the following: if a large number of oligomers of the various types of complexes with different donor sites are present, one might expect a broadening effect. With N-1,O-2 bridging, for example, formation of "closed" and "open" oligomers of different lengths could occur:
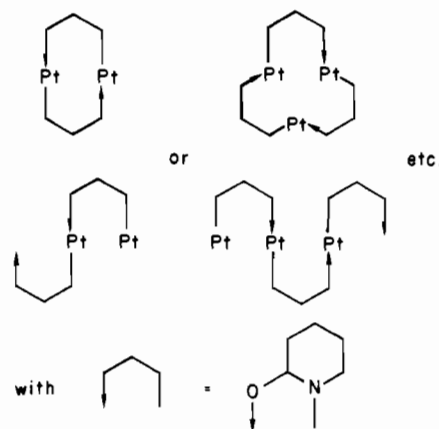
Oligomers with identical metal binding modes should thus have similar but not identical NMR resonances and hence lead to a signal broadening due to overlapping signals. To make things even more complicated, the combination of different metal binding modes in a single oligomer should further broaden the resonances. Consistent with this idea is the fact that in the $(NH_3)_3Pt$/uracil system, where only dimer formation is likely to occur,[46] no such broad underground is observed.

There is no indication from the Raman spectra (vide infra) that a single type of metal coordination might be responsible for the observed broad resonance as with the situation of compound A reacting with excess $enPt(H_2O)_2^{2+}$.

It cannot be ruled out completely that formation of paramagnetic species (cf. sections on uracil "tans" and "blues") may contribute to the observed resonance broadening, even though the samples were not exposed to oxygen. With platinum "blues", partial oxidation occurs even in a sealed tube.

"$[enPt(HU)H_2O]NO_3$". As briefly mentioned before, reaction of enPt(HU-N1)Cl with $AgNO_3$ in water yields a variety of products as concluded from ^1H NMR spectroscopy. From NMR spectra it also becomes evident that a product distribution is eventually obtained as with A and B as starting compounds. Raman spectroscopy fully confirms this.

In the following, the Raman spectroscopic changes observed during the "aging" process of a freshly prepared [enPt(HU-N1)$H_2O]^+$ solution will be considered. In Figure 14, Raman spectra in the ring-breathing and ring-stretching regions are

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(45) Within 2–3 weeks at 40 °C, one observes a slight increase in pD again (release of en?) and a decrease in intensity of signals A and E.

(46) Formation of higher oligomers with uracil acting as a bridge for three Pt atoms are theoretically possible.
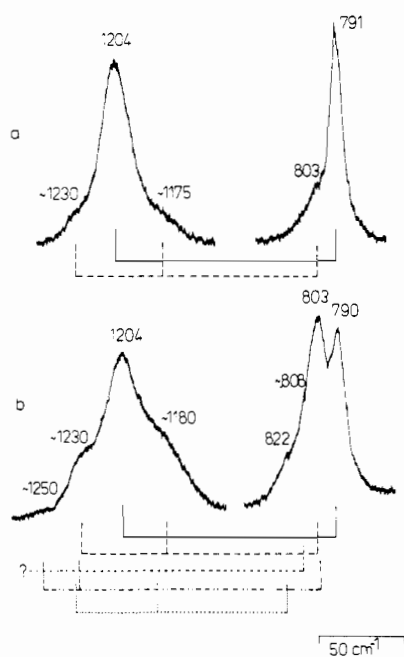
Figure 14. Raman solution spectra (H₂O) in the 1200–800-cm⁻¹ range obtained from reaction of enPt(HU-N1)Cl with 1 mol of AgNO₃ (0.25 M each): (a) 30 h after addition of AgNO₃, pH 2.05 (AgCl filtered off); (b) 2 days after spectrum a with sample kept at 22 °C and pH 1.4. The slit width was 4 cm⁻¹.

Figure 15. ¹H NMR spectra in the H-5, H-6 region of uracil of mixtures of [enPt(D₂O)₂](NO₃)₂ and KHU (0.15 M each): (a) after 6 h at 40 °C, pD has dropped to 2.25; (b) after 90 h at 40 °C, addition of CF₃COOD (pD 0.4), and 10 min at 80 °C. Unresolved, broad signal in H-6 region is shaded.

given at 30 h after mixing enPt(HU-N1)Cl and AgNO₃ and after 3 days at room temperature. It is found that, while the pH is dropping, a band at 803 cm⁻¹ is rapidly growing and eventually is the most intense band in the spectrum. The original 791-cm⁻¹ band is decreasing in intensity. Additional new bands appear around 808 and 822 cm⁻¹. Thus, in the ring-breathing region, four bands can be distinguished. Their counterparts in the ring-stretching region are, in particular for the minor components, not nearly as useful for a differentiation because they strongly overlap. Only the weak 1250-cm⁻¹ band is an indication for the existence of a N-3 complex. Its ring-breathing mode expected around 800 cm⁻¹ is superimposed by the strong 803-cm⁻¹ band. Thus the interpretation of the 1200-cm⁻¹ region results mainly from comparison with spectra of the (NH₃)₃Pt complexes (Figures 9 and 10) complex A (Figure 12) and complex B (not shown; 791, 1207 cm⁻¹). The 822-cm⁻¹ band has been dealt with before. The observed Raman bands are, in part, assigned as follows.

790	1204	N-1 monodentate or N-1, X bridging
(801)	(1227) 1250	N-3 monodentate
803	1173, 1226	N-1, O-2 bridging
808	?	?
822	1187, 1231	?

Addition of acid or base changes the spectra, but it does not increase the information obtainable from the Raman spectra greatly. It essentially supports the assignment of the two most intense signal sets and the N-3 coordination only.

"Platinum Uracil Tans". Reaction of the (ethylenediamine)diaquoplatinum(II) cation with uracil as well as other pyrimidine-2,4-diones gives yellow to tan products,[1,3,13] unless the concentrations of the starting materials are high. Then also green and purple solutions are obtained which, upon dilution, irreversibly become brown to tan.[47] The "platinum
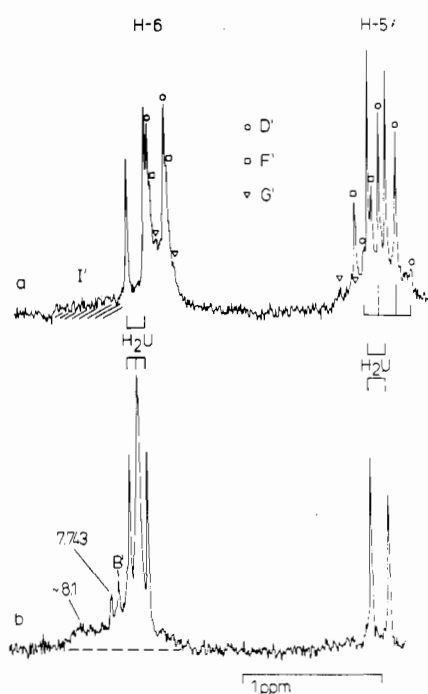
pyrimidine tans", very much like the "platinum pyrimidine blues" (vide infra), have interesting properties: for example, they show antitumor activity[48] and, if prepared in the presence of oxygen, they are mixed-valence state compounds and slightly paramagnetic.[49] It crucially depends upon the conditions of the preparation (Pt:ligand ratio, pH, reaction time, temperature) what product distribution is obtained. In the following, this will be exemplified for three cases with the use of ¹H NMR and Raman spectroscopy.

Preparation without pH Adjustment. Low pH. When [enPt(H₂O)₂]²⁺ and HU are combined in 1:1 ratio, the resulting mixture undergoes a fast decrease in pH. Within 5–6 h at 40 °C, the pH drops from 7–8 immediately after mixing of the compounds to 2–3 (0.15 M each). In the ¹H NMR spectrum, the formation of three distinct new sets of signals, D′, F′, and G′, and a broad, unresolved one (~0.5 ppm wide, I′) besides the H₂U signals is observed (Figure 15). Relative to the H-6 doublet of H₂U, the newly formed "distinct" signals appear upfield (at pD values >2), whereas the broad, unresolved one is situated downfield (Table II). With the H-5 resonances, the new signals appear both up- and downfield from the H₂U doublet. At least for the most intense newly formed H-5 signal, D′, ¹⁹⁵Pt satellites can be observed (J ≃ 14.6 Hz), thus indicating N-3 binding to Pt. This assignment gets additional support by the following arguments. (1) The almost identical chemical shift of the H-6 resonance of the Pt(HU-N3) complex in the "enPt(HU)NO₃" system (signal D′). (2) The missing tendency to undergo isotopic exchange at the C-5 position. It seems as though a measurable proton/deuterium exchange occurs only after the appearance of a weak singlet at 7.694 ppm which unambiguously can be assigned to the 1:1 complex enPt(HU-N1) or enPt(HU-N1,X),

(47) For example, enPt(H₂O)₂²⁺ and HU (0.4 M each) give a dark green solution within 5 min at 80 °C, and a purple-black solution is formed when a mixture of enPt(H₂O)₂²⁺ (0.5 M) and HU (0.25 M) is kept at 80 °C for 5–10 min.

(48) Rosenberg, B.; Van Camp, L., personal communication.
(49) The EPR spectrum of a "uracil tan" prepared at pH 7 is different from that of a "uracil blue" (ref 4), with the relative intensities of high- and low-field signals reversed. The low-field signal of a "tan" (g ≃ 2.4, hyperfine splitting due to ¹⁹⁵Pt) is less intense than its two high-field signals (g values slightly greater 2).
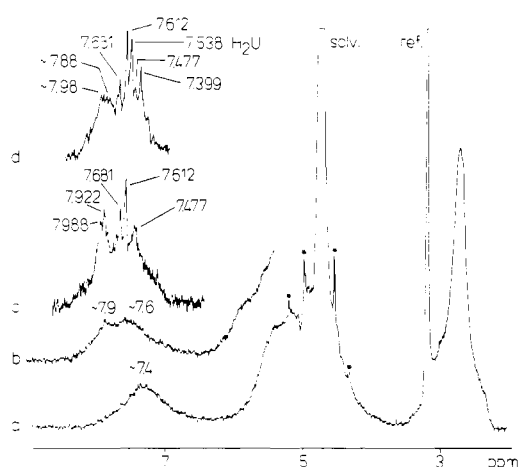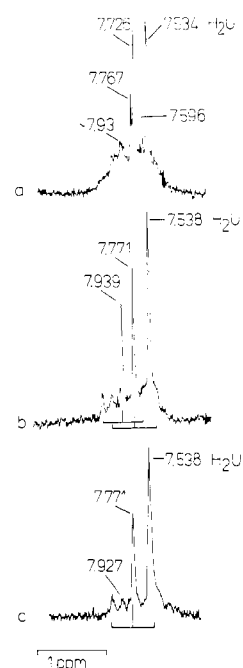
Figure 16. (a) ¹H NMR spectrum of "platinum uracil tan" prepared at pH 7, redissolved in D_2O (pD 6.9), (b) spectrum a after addition of CF_3COOD (pD 1.4), (c) spectrum b after 24 h at 22 °C, and (d) spectrum b after 24 h at 40 °C. Concentration was 60 mg of "uracil tan" in 0.4 mL of D_2O. Ref = NME_4^+ resonance; asterisk = spinning side bands.

respectively. (3) The behavior upon acid treatment (downfield shift) and heating (decomposition with formation of H_2U).

None of the other two signals sets F′ and G′ corresponds to any of the N-1 complexes identified so far (1:1, 1:2 complex, bridged complexes). Since they are lost upon acid treatment and heating as well, they are tentatively assigned to complexes involving N-3 as a donor atom also. In the spectrum of an acidic (pD 0.4) heated sample, only resonances at 7.538 ppm (H_2U, partially deuterated at C-5), 7.694 ppm (B′), 7.743 ppm, and around 8.1 ppm are left (Figure 15b). An assignment of the 7.743-ppm signal as due to the $enPt(HU-N1)_2$ complex, although reasonable on the basis of its shift, is questionable considering the fact that its intensity is lower when the HU:Pt ratio is increased (cf. Figure 18). In the region of the C_2H_4 resonances of the en ligand, at least four signals can be differentiated in the low pD spectrum, all of which exhibit ¹⁹⁵Pt coupling bands ($J \simeq 40$ Hz). They are, in sequence of their intensities, 2.533 ($enPt(D_2O)_2^{2+}$), 2.668, 2.640 (B′), and 2.717 ppm.

From the relative intensities of the H_2U signals before and after acid treatment, it is evident that N-3 complexation is the preferred way of binding in slightly acidic medium. Raman spectroscopy fully confirms this: when following the changes in the ring-breathing region, one finds that besides the H_2U band at 782 cm⁻¹, which is present from the beginning, a band rapidly grows around 800–805 cm⁻¹, together with a weaker one around 820 cm⁻¹. There is no band observable at 790 cm⁻¹ that could be attributed to a (HU-N1)Pt species. The ring-stretching bands are consistent with this finding since there is no typical band of Pt(HU-N1) complexes around 1200 cm⁻¹. Thus the low-pH spectra are very much different from those at higher pH (vide infra).

Preparation at pH 7. ¹H NMR Spectra. The ¹H NMR spectrum of a "platinum uracil tan" prepared at pH 7 (for details on the preparation, cf. ref 13) and redissolved in D_2O consists of broad signals at 2.7 (C_2H_4), 5.4 (NH_2 and H-5), and 7.4 (H-6) ppm, as shown in Figure 16a. The half-width of the H-6 signal is about 0.75 ppm with no sign of resolution of individual signals. This probably is a consequence of both the oligomeric nature *and* the platinum mixed-valence oxidation state of the "tans" (cf. ref 49). If it were exclusively a consequence of the first property, at least a few sharp resonances of low molecular weight species might be detected. CF_3COOD treatment of a "uracil tan" results in an immediate downfield shift of the center of the H-6 resonance (Figure 16b) and the gradual appearance of several sharp signals on a very

Figure 17. H-6 resonances of "platinum uracil tan" sample shown in Figure 16d (24 h, 40 °C, pD 1.4): (a) after addition of CF_3COOD, pD $\simeq$ 0, 8 min, 80 °C; (b) after addition of CF_3COOD and NaCl, pD $\simeq$ 0, 8 min, 80 °C; (c) spectrum b after 24 h at 22 °C. No H-5 resonances are observed.

broad underground. No H-5 signals are observed. The distribution of products observed in the spectra of acidified "tans" strongly depends upon the pD, the reaction time, the temperature, and the anions present in solution. In particular, the temperature appears to have a considerable effect. This is demonstrated for the uracil H-6 resonances in Figure 16c,d: For example, in the sample (pD 1.4) kept at 40 °C, one observes intense signals of a Pt(HU-N3) species (7.399 ppm, D′) and H_2U (7.538 ppm) besides several others, whereas in the sample kept at 22 °C, these two bands are absent, and the relative intensities of the other bands at 7.477 (K′), 7.612 (C′), 7.681 (B′), 7.922 (E′), and 7.988 ppm (A′) are different. Further addition of acid (CF_3COOD; pD $\simeq$0) and heating (8 min, 80 °C) gives for both samples identical spectra with respect to the number and positions of signals (7.534 (H_2U), 7.596, 7.726, 7.767, and 7.93 ppm) but not with respect to relative intensities: in the sample originally kept at 40 °C, the H_2U signal is almost twice as intense as that in the sample kept at 22 °C. In Figure 17a, the H-6 resonances of a "uracil tan" of pD $\simeq$0 after heating is shown. One finds that the above mentioned sharp signals are superimposed with a broad signal. Addition of excess NaCl drastically simplifies the spectrum (Figure 17b). Besides the H_2U signal, only two resonances of uracil complexes are left, both of which exhibit ¹⁹⁵Pt satellites of J = 40 and 36 Hz, respectively. There is a further simplification of the spectrum with time (Figure 17c), leaving essentially a single type of platinum complex with N-1 coordination (7.771 ppm, $J_{195Pt-¹H}$ = 40 Hz) besides neutral uracil.

The disappearance of the broad underground signal after addition of well-coordinating chloride is a strong indication that a "cutting" of species of higher molecular weights occurs according to
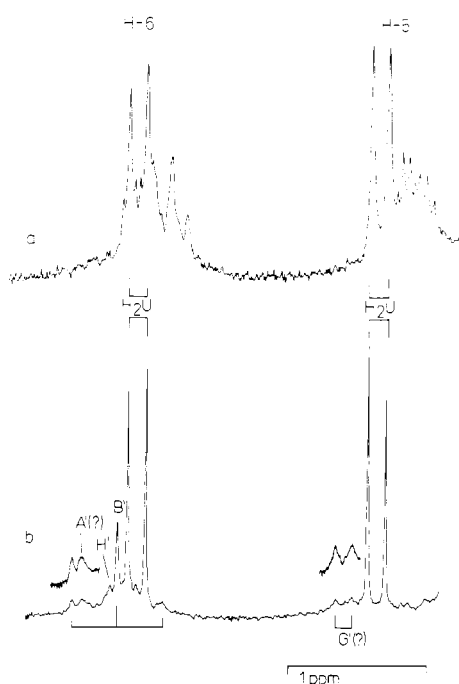
$$-Pt(en)HU-Pt(en)HU-Pt(en)HU- \rightarrow$$
$$n(enPt(HU-N1)Cl)$$
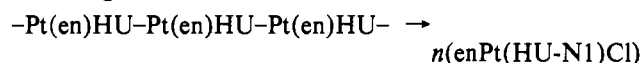
At the same time, any platinum species containing delocalized unpaired spins will be transferred into diamagnetic Pt(II) and Pt(IV) complexes containing ethylenediamine, chloride, and

HU-N1 ligands but no bridging uracilato ligands. The formation of a precipitate of enPtCl$_2$·enPtCl$_4$ (orange-red) in the samples shown in Figure 17b,c is consistent with this idea.[50]

Raman Spectra. As mentioned before, the Raman spectrum of a "platinum uracil tan" prepared at pH 7 is qualitatively different from that obtained in acidic medium. In the spectrum of a sample prepared at pH 7, intense Raman bands are observed at 790 and around 805 cm^{-1}, together with a weaker one at 820 cm^{-1}. In the ring-stretching region of the spectrum, a very intense band occurs around 1200 cm^{-1}, with much weaker ones around 1225 and 1245 cm^{-1}. In two parallel experiments, HCl and HNO$_3$ were added in order to study the different effects of a good (Cl$^-$) and a poorly coordinating anion (NO$_3^-$). Immediately after addition of either HCl or HNO$_3$, the spectra are essentially identical. The observed changes (805 → 800 cm^{-1}; new band at 1175 cm^{-1}) are due to protonation of uracil dianion bridges to give the corresponding monoanion bridges. In a slow secondary process, the 800-cm^{-1} band of the HCl-treated sample diminishes, whereas the 790-cm^{-1} band increases in intensity. This undoubtedly reflects the cleavage of uracil bridges Pt(HU-N1,X)Pt at the Pt-X bond. Upon brief heating of the HCl-treated sample, a spectrum is observed that consists of bands of HU-N1 complex(es) at 790 and 1203 cm^{-1} and free uracil at 783 and 1233 cm^{-1} only. Bands at 800, 1225, and 1245 cm^{-1}, which are characteristic of Pt(HU-N3) complexes, have disappeared. Thus Raman spectroscopy provides a rationale for the findings, made on a preparative scale before, that enPt(HU-N1)Cl and H$_2$U are formed as the two major compounds of "tans" prepared at pH 7 and decomposed with HCl.[13] In contrast to HCl, HNO$_3$ appears not to affect the stability of HU-N1,X bridges strongly, very similar to the effect of CF$_3$COOD in the ^{1}H NMR experiment. However, like HCl and CF$_3$COOD, HNO$_3$ also decomoses Pt(HU-N3) complexes if the sample is warmed, as indicated by the appearance of the H$_2$U bands.

Reaction in Alkaline Medium. With an excess of HU over enPt(H$_2$O)$_2$$^{2+}$, the pH of the reaction mixture does not drop during the reaction, and the solution remains alkaline. The Raman spectrum of such a sample is not markedly different from that of a sample prepared at pH 7 with Pt:(HU) = 1. N-1 binding is preferred.

In Figure 18, the ^{1}H NMR spectrum of a mixture of enPt(D$_2$O)$_2$$^{2+}$ and HU (1:1.2 ratio, pD ≃ 9) in the H-5, H-6 region is shown. The averaged HU/H$_2$U resonances of unreacted uracil are readily identified. The amount of unreacted ligand is surprising and suggests that the OH ligand bound to platinum is not easily replaced and/or that extensive bridging of the uracil ligand must occur. No attempts were made to assign the partially overlapping signals. No differentiation of signals in the region of the C$_2$H$_4$ signals of the en ligands is possible because of strongly overlapping resonances. Addition of CF$_3$COOD (pD 0.4) simplifies the spectrum considerably since most of the signals in the H-5 region are lost as a consequence of rapid isotopic exchange. With the exception of the H$_2$U doublet, which gradually diminishes over several days (the H-6 doublet decreases in intensity as well, and a H-6 singlet appears), and a weak doublet at 6.029 ppm, which is lost within 6 h at 40 °C, all the other H-5 signals are gone within 20 min. The remaining H-6 resonances are assigned to compounds A', B', and H' (Figure 18b). At least four individual C$_2$H$_4$ resonances, all of them with ^{195}Pt satellites of J ≃ 40 Hz, can be distinguished: 2.717, 2.668, 2.631, and 2.533 ppm (enPt(D$_2$O)$_2$$^{2+}$). From com-

Figure 18. ^{1}H NMR spectra in the H-5, H-6 region of uracil of a mixture of [enPt(D$_2$O)$_2$](NO$_3$)$_2$ (0.15 M) and KHU (0.18 M): (a) after 60 h at 40 °C, pD 9.3; (b) after addition of CF$_3$COOD to the spectrum a and 30 min at 40 °C, pD 0.4. (There was no further changes in spectrum a within 4 days at 40 °C.)

parison of the relative intensities of the H-6 resonances of H$_2$U before and after addition of acid and heating, it is evident that some of the originally complexed uracil must have been released during acid treatment. Again, it is suggested that the acid-labile ligands are N-3 bound.

cis-**Diammineplatinum(II) Complexes. N-1 Complexes of U, HU, and H$_2$U.** HCl treatment of a "platinum uracil blue" prepared at pH 7[1] leads to formation of *cis*-(NH$_3$)$_2$Pt(HU-N1)Cl and H$_2$U as the two major uracil components besides *cis*-(NH$_3$)$_2$PtCl$_2$ and *cis*-(NH$_3$)$_2$PtCl$_4$. Occasionally, in particular with uracil blues prepared at higher temperatures, the formation of NH$_4$[Pt(NH$_3$)Cl$_5$] and (NH$_4$)$_2$[PtCl$_6$] in HCl-treated samples has been observed. This may be a verification of suggestions made earlier that NH$_3$ might be released from "platinum pyrimidine blues".[51] However, any NH$_3$ release from "blues" almost certainly is not of a magnitude as that observed with chloro-*cis*-diammine(1-methylcytosine)platinum(II) chloride.[52]

The preparation of *cis*-(NH$_3$)$_2$Pt(HU-N1)Cl thus is analogous to that of the corresponding thymine complex.[4,12] It has now been synthesized in good yield in DMF as solvent (cf. Experimental Section). Because of its low solubility in water, no Raman solution spectra could be obtained of *cis*-(NH$_3$)$_2$Pt(HU-N1)Cl. Solid-state spectra, however, are consistent with N-1 coordination (792-, 1210-cm^{-1} bands), as is reaction with NH$_3$, which gives [(NH$_3$)$_3$Pt(HU-N1)]Cl.

An extremely water-insoluble 2:1 complex, *cis*-(NH$_3$)$_2$Pt(HU-N1)$_2$, has been isolated as well. Its characteristic Raman bands (solid state) are at 790 and 1205 cm^{-1}. Addition of excess NaOH gives Na$_2$[(NH$_3$)$_2$Pt(U-N1)$_2$]·6H$_2$O in crystalline form. This highly water-soluble compound exhibits its ^{1}H NMR resonances (pD 13) at 5.589 (H-5, doublet with J_{H-H} = 6.9 Hz) and 7.577 ppm (H-6, sextet with $J_{^{195}Pt-^1H}$ = 40.5 Hz), thus verifying N-1 coordination. Addition of acid causes a slight downfield shift of H-5 and a more pronounced one

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(50) As suggested by a reviewer, formation of Pt(III) dimers with bridging uracil might also account for the observed disappearance of the paramagnetism. The author agrees with this in principle. However, the preparative results (cf. ref 13) seem to exclude such a possibility in the preset case and rather support the idea of monomer formation.

(51) Barton, J. K.; Lippard, S. J. *Ann. N.Y. Acad. Sci.* **1978**, *313*, 686.
(52) Lippert, B.; Lock, C. J. L.; Speranzini, R. A. *Inorg. Chem.* **1981**, *20*, 808.

Table III. Chemical Shifts (ppm) of Uracil Resonances in *cis*-$(NH_3)_2Pt^{II}$ Complexes and Tentative Assignments

sym-bol[a]	pD	H-5	H-6	assignt[c]	stability[g]
A″	2.0	no[b]	7.914	HU-N1,O2	gradual dec to give B″ (?)
	1.8	no	7.972		
	0.4	no	7.984		
B″	2.0	5.696	7.733	$(NH_3)_2Pt(HU$-N1$)D_2O^+$	stable
	1.5	no	7.730		
	0.4	no	7.780		
C″	2.0	no	7.604	HU-N3,O4	
	1.8	no	7.559		
D″	4.2[d]	5.716	7.389	$(NH_3)_2Pt(HU$-N3$)D_2O^4$	dec to give H_2U
	3–2.4[d]	5.720	7.389		
	1.8[e]	no	7.408		
F″	3–2.4	5.912	7.361	HU-N3,X	dec
G″	2.4	6.020	7.301	?	
H″	13	5.589	7.577	$(NH_3)_2Pt(U$-N1$)_2^{2-}$	stable
	7–1	f			
	0.4	no	7.755		
	<0	no	7.890		
I″	3–2.4	no	7.2–8.3	?	
L″	2	no	7.661	HU-N1,X	dec to give B″

[a] The symbols used correspond to those used in the enPt^{II} system (Table II); e.g., A′ ≃ A″ but are different from those used in Table I.   *[b]* Not observed because of isotopic D/H exchange at C-5.   *[c]* Relevant acid–base equilibria omitted for clarity.   *[d]* Data taken from spectra of reaction *cis*-$(NH_3)_2Pt(D_2O)_2^{2+}$ + HU.   *[e]* Data taken from spectra of reaction *cis*-$(NH_3)_2Pt(HU$-N1$)Cl$ + AgNO$_3$.   *[f]* No spectra obtained due to insolubility in this pD range.   *[g]* Conditions: pD 0.4; 15 min; 90 °C.
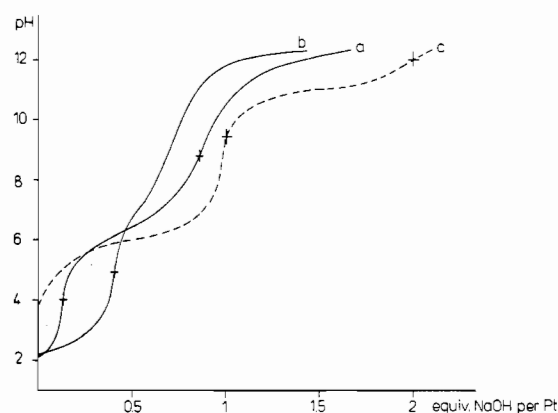
of H-6. Between 1.5 < pD < 7, no resonances are observed because of the very low solubility of *cis*-$(NH_3)_2Pt(HU$-N1$)_2$. In strongly acidic medium, the complex becomes protonated to give *cis*-$[(NH_3)_2Pt(HU$-N1$)(H_2U$-N1$)]^+$, and, because of the good solubility of the charged species, ^{1}H NMR spectra can be obtained again. However, isotopic ^{2}D/^{1}H exchange at the C-5 position has caused the H-5 resonance to disappear and has simplified the H-6 resonance into a triplet ($J_{^{195}Pt-^1H}$ = 40 Hz) (cf. Table III, signal H″).

With regard to the interpretation of some of the spectra discussed subsequently, the very low solubility of the neutral 2:1 complex and the resulting impossibility to obtain NMR spectra are noted.

The mentioned 2:1 complexes are good examples of the ability of N-1-platinized uracil to act as a dianionic (U), monoanionic (HU), and neutral (H_2U) ligand.

(Uracilato-*N1*)-*cis*-diammineaquoplatinum(II) Nitrate. Reaction of *cis*-$(NH_3)_2Pt(HU$-N1$)Cl$ with 1 equiv of AgNO$_3$ in water, as with the corresponding ethylenediamine compound, leads to condensation reactions. This is evident from the observed changes in the ^{1}H NMR spectrum and from potentiometric titration curves.

^{1}**H NMR Spectra.** The ^{1}H NMR spectrum of a freshly prepared solution (12 h after combining the Pt compound and AgNO$_3$ in D_2O, 22 °C, 0.1 M Pt, pD 2.0) consists of sextets for the H-6 (7.733 ppm, J_{H-H} = 7.6 Hz, $J_{^{195}Pt-^1H}$ = 36 Hz) and the H-5 (5.696 ppm, $J_{^{195}Pt-^1H}$ = 3.7 Hz) resonances (B″, Table III), very similar to the spectrum of compound B in the enPt^{II} system (cf. Figure 13). The NH$_3$ signal (Pt satellites with J ≃ 60 Hz) is observed around 4.2 ppm. The spectrum already shows signs of an isotopic exchange at the C-5 position as indicated by a weak singlet in the center of the H-6 resonance. Within several hours at 40 °C, the H-5 signal has disappeared completely and a series of H-6 singlets are formed

Figure 19. Titration curves of *cis*-$[(NH_3)_2Pt(HU$-N1$)H_2O]NO_3$ with NaOH: (a) 1 day after combining *cis*-$(NH_3)_2Pt(HU$-N1$)Cl$ and AgNO$_3$; (b) 4 days after combining *cis*-$(NH_3)_2Pt(HU$-N1$)Cl$ and AgNO$_3$, with the sample kept at 22 °C; (c) theoretical curve with no condensation, pK_1 = 6, and pK_2 = 11 assumed. The pH of starting point was calculated according to pH = 0.5 (pK_a − log C) and endpoint of first titration step according to pOH = 0.5 (pK_b − log C) with pK_a = 6 and pK_b = 8. The concentration of Pt was 0.05 M; that of NaOH was 0.2 M.
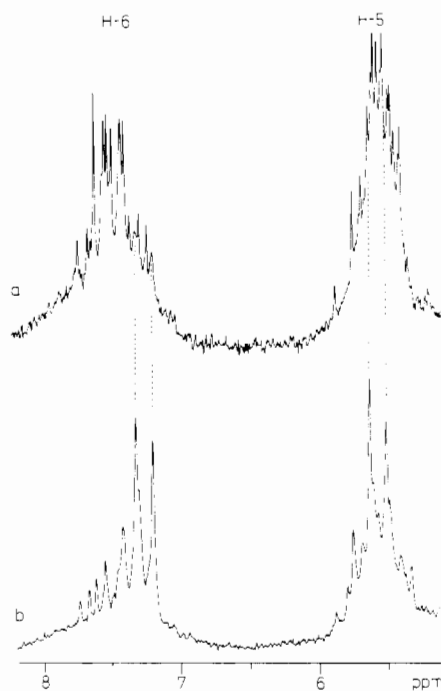
that are superimposed with a broad, unresolved signal of approximately 1-ppm width. After 6 days at 40 °C (pD 1.8), during which some precipitate has formed,[53] at least four sharp signals can be distinguished. In sequence of their relative intensities, these are 7.730 (B″, Pt(HU-N1)), 7.559 (C″, Pt(HU-N3,O4)), 7.408 (D″, Pt(HU-N3)), and 7.972 ppm (A″, Pt(HU-N1,O2)). This assignment is based on comparison with the corresponding enPt^{II} spectra and the changes observed on acid treatment and heating. The relative intensity of the 7.559-ppm signal is too high to assign it to the insoluble *cis*-$(NH_3)_2Pt(HU$-N1$)_2$ complex, even though the chemical shift at pD 1.8 might agree with such an interpretation. The signal:noise ratio of the spectrum rapidly diminishes with time, and this cannot be the sole consequence of the formation of a precipitate. Also, in a slow secondary process (2–3 weeks at 40 °C), most of the precipitate redissolves while the pD is slightly rising again (pD 2 after 3 weeks; olive green solution), but no resolution of individual NMR signals can be achieved after that time.

Potentiometric Titrations. The curves obtained for titration of (uracilato-*N1*)-*cis*-diammineaquoplatinum(II) nitrate with base give strong indication that condensation reactions have occurred. In Figure 19, two such titration curves are given, obtained 1 and 4 days after combining *cis*-$(NH_3)_2Pt(HU$-N1$)Cl$ and AgNO$_3$, and compared with the expected curve if no condensation had occurred. For this case, one should expect a pK_a ≃ 6 ± 0.5 for titration of the aquo group of $[(NH_3)_2Pt(HU)H_2O]^{+}$ [54] and a pK_a of 11 ± 0.05 for deprotonation of HU,[28] with complete titration of each group after addition of exactly 1 and 2 equiv of base.

The considerable acidity of the reaction mixture clearly tells that some deprotonation must have occurred. From comparison with the titration curve of A in Figure 12, it can be assumed that a similar bridge formation (N-1, O-2 (?)) is responsible for the high acidity of the uracil ligand in the *cis*-$(NH_3)_2Pt^{II}$ system. The fact that considerably less base is used up before a pH ≃ 9 is reached (expected endpoint for

(53) Elemental analysis indicates a Pt:uracil ratio of 1. The compound contains NO$_3^-$.

(54) (a) pK_1(enPt(H$_2$O)$_2^{2+}$) = 5.8, pK((dien)Pt(H$_2$O)$^{2+}$) = 6.53. Cf.: Lim, M. C.; Martin, R. B. *J. Inorg. Nucl. Chem.* **1976**, *38*, 1911. (b) pK_1-(*cis*-Pt(NH$_3$)$_2$(H$_2$O)$_2^{2+}$) = 5.6. Cf.: Jensen, K. A. *Z. Anorg. Chem.* **1939**, *242*, 87. (c) Perumareddi, J. R.; Anderson, A. W. *J. Phys. Chem.* **1968**, *72*, 414.

Figure 20. H-5 and H-6 resonance of water-soluble products obtained from reaction of *cis*-[(NH₃)₂Pt(H₂O)₂]²⁺ and HU at alkaline pH: (a) Pt:HU = 1:4, H₂O, 5 h, 90 °C, pH 9.8, brought to pH 7 with HNO₃, concentrated, cooled, filtered from precipitate, MeOH added; (b) Pt:H₂U = 1:1.6, H₂O, 10 h, 80 °C, pH readjusted by successive addition of 1.6 equiv of NaOH, concentrated, filtered from precipitate, Sephadex chromatography. (Other Sephadex fractions show minor spectral changes only.) Sample a redissolved in D₂O had a pD of 7.5; redissolved sample b (D₂O) had a pD of 7.6. Dotted lines refer to corresponding peaks and are inserted to demonstrate the differeing intensity distributions.

titration of [(NH₃)₂Pt(HU)H₂O]⁺ to give (NH₃)₂Pt(HU)OH is another strong indication for the occurrence of condensation reactions. Formation of hydroxo-bridged species according to

$$(NH_3)_2Pt(HU)OH + [(NH_3)_2Pt(HU)H_2O]^+ \rightarrow$$
$$[(NH_3)_2Pt(HU)(OH)Pt(HU)(NH_3)_2]^+ + H_2O$$
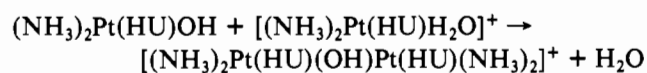
could also account for this finding. The existence of hydroxo-bridged platinum(II) dimers and trimers of composition [enPt(OH)]₂²⁺ and *cis*-[(NH₃)₂Pt(OH)]ₙⁿ⁺ (n = 2, 3) is well established,[55] and there are reports that these compounds may form "blues" under the influence of X-ray[55c] or UV radiation.[56] However, at present there is no hard evidence for such a possibility in the presence of uracil, and the good ligating properties of this ligand seem to make the formation of hydroxo bridges less likely.

Reaction of *cis*-(NH₃)₂Pt(H₂O)₂²⁺ with Excess HU. ¹H **NMR Spectra.** Reaction of the diaquo species of *cis*-(NH₃)₂PtCl₂ with an excess of HU (HU:Pt > 1; alkaline medium) gives NMR spectra similar to that shown in Figure 18 for enPtᴵᴵ. It has been found that the experimental conditions strongly affect the product distribution. This is demonstrated in Figure 20 for two products obtained under dif-

ferent conditions in H₂O (cf. figure legend). In both cases the reaction mixtures were concentrated to a small volume to precipitate products of low solubility (mainly unreacted H₂U, *cis*-(NH₃)₂Pt(HU-N1)₂, and *cis*-[(NH₃)₂Pt(HU-N1)(U-N1)]⁻). The highly soluble products were then obtained by precipitation with excess methanol and redissolved in D₂O.

If the reaction is carried out in DMF instead of water, the highly water-soluble products have yet another ¹H NMR spectrum (not shown). In all three cases, the resonances occur in the same spectral ranges (H-5, 5.3–5.9 ppm; H-6, 6.9–8.1 ppm) with many identical resonancs (if the pDs are identical). However, the intensity distribution of the individual resonances is markedly different in all three cases.

Attempts to separate individual components by means of column chromatography (Sephadex G 10) were unsuccessful. The various fractions, taken arbitrarily after identical volumes, showed minor differences in their ¹H NMR spectra only.[57] Between 10 and 20 individual peaks can be distinguished in both the H-5 and H-6 regions. This number could, theoretically, be accounted for by assuming 1:1 and 2:1 complexes only: for a₂Pt(HU-N1)OH, a₂Pt(HU-N3)OH, a₂Pt(HU-N1)₂, a₂Pt(HU-N3)₂, a₂Pt(HU-N1)(HU-N3) and their respective forms with U (averaged with the former), six sets of doublets, all of which having ¹⁹⁵Pt satellites either in the H-5 (N-3 coordination) or H-6 region (N-1 coordination), might be expected. The mentioned chromatography results could, at least in part, be interpreted in a similar way since any method separating compounds on the basis of size should be ineffective with the three 2:1 complexes, for example. The same applies, of course, for any other possible complexes of higher molecular weight containing an identical number of uracil ligands in different arrangements. It is noted that we have recently been successful in isolating different 2:1 products in the related cis-Ptᴵᴵ/thymine system with the use of high-pressure liquid chromatography.[58]

Raman Spectra. The study of the Raman-active ring-breathing and ring-stretching modes of the differently prepared high-pH products provides a rationale for the varying intensity distribution observed in the NMR spectra. One finds that the relative intensities of the bands attributed to different binding modes vary with the way of preparation. For example, the relative intensity of the Raman band around 1250 cm⁻¹, which is characteristic of N-3 binding, is more intense in the product with the NMR spectrum shown in Figure 20b compared with the one shown in Figure 20a, whereas this band is hardly detectable in the product prepared in DMF.

Acid Treatment of the High-pH Products. ¹H **NMR Spectra.** There exists a very important difference between the NMR spectra obtained from alkaline solutions and those obtained from acidic solutions of platinum–uracil complexes: the spectra obtained at high pH do not change with time as do the low-pH spectra. This is interpreted as being due to the difference between *cis*-(HN₃)₂Pt(HU)OH and *cis*-(NH₃)₂Pt(HU)H₂O⁺: while the former is coordinatively saturated with all four coordination sites of Pt blocked, the aquo complex behaves like a coordinatively unsaturated species that tends to become saturated by bridge formation with already coordinated uracil. With uracil being a multisite ligand, a multiplicity of reaction products can thus be formed at acidic pH. When acid is added to an alkaline solution of high-pH products, the spectrum undergoes considerable changes. The procedure of the addition of acid has an effect on the product distribution, as demonstrated in Figure 21 for a highly water-soluble product obtained from DMF solution with Pt:HU = 1:2.[59] If the pD is brought from 9 to 0.4 in one step

(55) (a) Cf. ref 54a. (b) Fagginani, R.; Lippert, B.; Lock, C. J. L.; Rosenberg, B. *J. Am. Chem. Soc.* **1977**, *99*, 777. (c) Stanko, J. A.; Hollis, L. S.; Schreifels, J. A.; Hoeschele, J. D. *J. Clin. Hematol. Oncol.* **1977**, *7*, 138. (d) Faggiani, R.; Lippert, B.; Lock, C. J. L.; Rosenberg, B. *Inorg. Chem.* **1977**, *16*, 1192. (e) *Ibid.* **1978**, *17*, 1941. (f) *Ibid.* **1978**, *17*, 2971.

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(57) Elemental analyses of the fractions differ with Pt:uracil ratios ranging from 0.6:1 to 0.7:1. As evident from IR, there is no NO₃⁻ present.
(58) Pfab, R.; Jandik, P.; Lippert, B., to be submitted for publication.
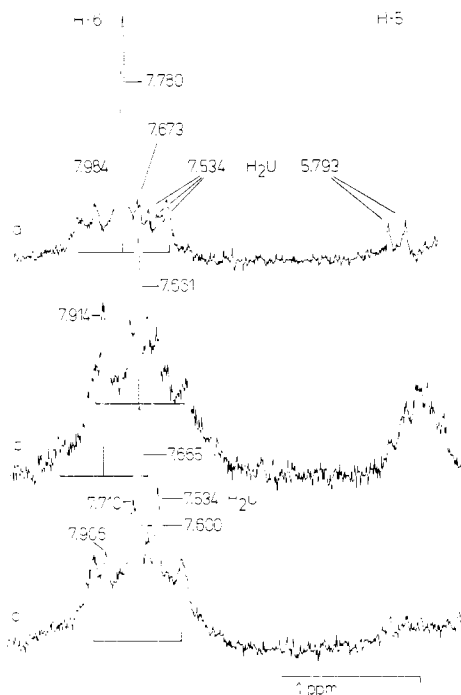
Figure 21. ^1H NMR spectra in the H-5, H-6 region of uracial (D_2O) of water-soluble product obtained from reaction of cis-[($NH_3)_2Pt$-$(DMF)_2]^{2+}$ and 2 mol of HU in DMF: (a) after addition of CF_3C-OOD (pD 0.4) and 8 min at 80 °C; (b) after addition of CF_3COOD (pD 2) and 20 h at 22 °C; (c) after addition of CF_3COOD (pD 2) and 20 h at 40 °C.

and the sample heated, one observes formation of a small amount of H_2U as a consequence of the decomposition of N-3-bound uracil (Figure 21a). With the samples of Figure 20 the same is observed, but the H_2U contents are clearly higher there, consistent with the conclusions drawn from the Raman spectra. If the pD is lowered to 2 only, the spectrum changes, depending on the experimental conditions. For example, after 20 h at 22 °C, the sample is yellow and exhibits H-6 resonances as shown in Figure 21b with some H-5 resonances still observable. Within 20 h at 40 °C, however, the color of the solution has changed to light green and to black-green, and there are no H-5 resonances left (Figure 21c). At least four sets of signals of platinum complexes besides the H_2U signal can be observed in the spectra at pD 2 with relative intensities that depend upon the reaction temperature. The assignment of three of these signals (C″, 7.600 ppm; B″, 7.710 ppm; A″, 7.91 ppm) appears to be rather safe. The fourth signal around 7.66 ppm, the most intense one (L″ in Table III), could be due to another uracilato-bridged species with N-1 being one donor atom (coupling of 40 Hz with ^{195}Pt). Addition of D^+ decreases the intensity of this resonance and increases the signal around 7.78 ppm, which is attributed to cis-$(NH_3)_2Pt(HU-N1)D_2O^+$ (B″).

If the pD 2 samples are brought to pD 0.4 and briefly heated, the spectra obtained are very similar to that shown in Figure 21a, but the content of H_2U increases in the order a < b < c. This finding clearly tells that there must be an interconversion of acid-stable into acid-labile species at pD 2 and that this interconversion is facilitated by an increase in temperature (cf. also Figure 16).

"Platinum Uracil Blues". Reaction of the cis-diaquodi-ammineplatinum(II) cation with uracil in the pH range below

ca. 7–8 leads to the formation of blue products. As with other "pyrimidine blues", the amorphous nature of the "uracil blue" has so far prevented a comprehensive understanding of this class of compounds. There is a reasonable understanding of the mixed-valence character of these compounds and their paramagnetism and general agreement on their oligomeric nature. As to the question concerning the coordination sites of platinum in these compounds, only the formation of N-1-coordinated complexes besides free ligand on HCl treatment has been established.[12] It had been suggested that "platinum urcil blue" might contain a mixture of N-1/O-2- and N-3/O-4-coordinated units or even N-1/O-2/O-4-bridged species.[14]

^1H **NMR Spectra.** The ^1H NMR spectrum of a "uracil blue" prepared according to a published procedure[1] consists of very broad, asymmetric peaks centered around 4 (unex-changed NH_3), 5.7 (H-5), and 7.5 (H-6) ppm. Addition of acid (CF_3COOD; pD 1) results in downfield shifts (ca. 0.2 ppm) of all three signals, to a gradual reduction of the H-5 signal intensity, and to a partial "resolving" of the H-6 signal. This "resolving" is not nearly as good as the one observed with a "uracil tan" (Figure 16) on addition of acid. After 2 days at 40 °C, four H-6 singlets are observed around 7.42, 7.55, 7.73, and 7.99 ppm which are assigned to $Pt(HU-N3)$ (D″), H_2U, $Pt(HU-N1)$ (B″), and $Pt(HU-N1, O2)$ (A″) respec-tively. These four signals are superimposed on a broad, un-resolved signal, ranging from approximately 7.1 to 8.3 ppm. If, during the reaction of cis-$(NH_3)_2Pt(D_2O)_2^{2+}$ and HU (1:1, 0.1 M each), the pH is not adjusted, one observes the growth of three sharp signal sets, D″, F″, and G″, besides the H_2U signal, as well as a broad, unresolved one, I″ (cf. Table III). The pD dropped rapidly to ca. 2.8 after 3 h at 40 °C, and a blue color developed. The positions of the new signals are almost identical with those observed in the corresponding $enPt^{II}$ spectra (cf. Figure 15a). Again, the most intense H-5 signal, D″, exhibits ^{195}Pt satellites ($J \simeq 14$ Hz), suggesting N-3 coordination. In contrast to the $enPt^{II}$ system, reaction with cis-$(NH_3)_2Pt^{II}$ can be followed for 1–2 days only (sample kept at 40 °C). Then individual H-5 signals can no longer be distinguished, and in the region of the H-6 resonances, only two singlets, H_2U and D″, can be observed. They are sitting on a broad resonance (7.1–8.3 ppm) which does not have any structural details. With application of higher concentrations of the starting compounds, the disappearance of sharp signals is even faster.[4] It had previously been demonstrated that the broadening (or disappearance) of H-5 and H-6 uracil reso-nances is accompanied by the appearance of an EPR signal.[4] The earlier interpretation (d_{z^2} hole state; delocalization on adjacent Pt centers) has essentially been confirmed and ex-tended.[9,15] Thus the broadness of the uracil resonances in "uracil blues" should be related to both the formation of different oligomers *and* the paramagnetism of the compounds formed.

Although of extremely low solubility in water, the colorless cis-$(NH_3)_2Pt(HU-N1)_2$ complex dissolves in aqueous cis-[($NH_3)_2Pt(H_2O)_2](NO_3)_2$ with formation of an intensely blue-black color (1:1 ratio, pH 2, 22 °C, 1–3 days). The ^1H NMR spectrum of the product obtained upon evaporation of the solution does not exhibit any signal whatsoever except that of the solvent, and even addition of CF_3COOD does not im-prove the spectrum greatly. Within several days at pD 1, only a very weak and approximately 1.5 ppm wide signal appears in the region of the uracil H-6 resonance, which does not show any resolved peaks. This finding does not prove the involve-ment of N-1 coordination in the formation of the blue color. As previously pointed out,[12] there is some evidence ruling against such a possibility. Formation of a "platinum blue" out of the bis(uracilato-*N1*) complex is believed to be rather a consequence of a change in coordination sites under the

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(59) Isolation of the product was achieved as follows. The DMF-insoluble components were treated with a very small amount of water and filtered from undissolved residue, and MeOH was added to the filtrate. The obtained product was then redissolved in D_2O. H-5 and H-6 muliplet structures similar to those shown in Figure 20 were obtained.

influence of the diaquo species, leading to an arrangement that actually stabilizes the blue component.

Summary

The versatility of unsubstituted uracil as a ligand of platinum has been demonstrated. $(NH_3)_3Pt^{II}$, $enPt^{II}$, and *cis*-$(NH_3)_2Pt^{II}$ form a variety of complexes which contain uracil in its neutral, monoanionic, and dianionic form bonded through N-1, N-3 in a monodentate bridging fashion or through different N,O atoms in a bidentate fashion. In aqueous solution at a pH <7, a series of different modes of coordination coexist. There is an interconversion of the various species under the influence of coordinatively "unsaturated" platinum species such as $(NH_3)_3Pt(H_2O)^{2+}$, $enPt(H_2O)_2^{2+}$, $(NH_3)_2Pt(H_2O)_2^{2+}$, $enPt(HU)H_2O^+$, or $(NH_3)_2Pt(HU)H_2O^+$, as demonstrated most clearly with the $(NH_3)_3Pt^{II}$ system. The interconversion in all cases seems to proceed via uracil-bridged species. The assignment of the donor atoms in these bridged species represents a problem. Only in one case, with compound A in the $enPt^{II}$ system, an assignment (N-1, O-2) was possible based on rather indirect evidence, whereas in all other cases no definitive conclusions have been possible. It is felt that only X-ray crystallography eventually can give an answer to the question concerning the different ways of bridging and go beyond a mere classification derived at by vibrational and NMR spectroscopy. The coexistence of different species in solution and the apparent easy interconversion seems to indicate very similar thermodynamic stabilities of the various species.

With respect to some of the characteristics of N-1 and N-3 tautomer complexes of uracil, the described results verify earlier findings[12,35] that N-3 complexes are more readily protonated and more easily decomposed by acid than the corresponding N-1 complexes. Interestingly, N-3 complexation of the uracil monoanion is favored over N-1 complexation in slightly acidic medium, whereas the situation is reversed in alkaline medium. N-1 and N-3 tautomer complexes (or bridged complexes involving these donor atoms) also exhibit different tendencies to undergo isotopic exchange at C-5 in D_2O: a rapid $^2D/^1H$ exchange takes place with complexes

containing N-1-bound platinum in acidic medium, with no exchange in N-3 complexes under comparable conditions.

As to the usefulness of the techniques applied in this study, ^1H NMR and Raman spectroscopy, the following conclusions can be drawn.

(1) The study of Raman-active vibrations of the heterocyclic ring in principle represents a useful tool for the differentiation of various types of metal binding. Raman spectroscopy is limited in its usefulness by the occasional strong overlap of corresponding modes in mixtures containing more than two or three different types of complexes and by the dark colors of some of the mixtures. A differentiation of 1:1 and 2:1 complexes with identical donor atoms cannot be achieved. On the other hand, Raman spectroscopy is able to distinguish complexes with their ligands being in a pH-dependent equilibrium.

(2) ^1H NMR spectroscopy appears to be a more stable technique for this type of studies on tautomer complexes. However, its applicability is restricted to kinetically inert species. With kinetically labile systems, information from NMR spectra is limited. The same applied to paramagnetic complexes (e.g., platinum uracil "blues" and "tans").

Contribution from The School of Chemical Sciences,
University of Illinois, Urbana, Illinois 61801

Effects of Steric Requirement and Ligand Basicity in Phosphine Substitution Reactions of Dicobalt Octacarbonyl

NANCY P. FORBUS and THEODORE L. BROWN*

The kinetics of the substitution of $Co_2(CO)_8$ by $P(i-Pr)_3$, $P(t-Bu)_3$, and $P(CH_2CH_2CN)_3$ in CH_2Cl_2 have been studied. The rate law for reaction with $P(t-Bu)_3$ and $P(CH_2CH_2CN)_3$ at 20 °C is first order in $Co_2(CO)_8$, with no dependence on base concentration. The first-order rate constants are 1.7×10^{-2} and 1.3×10^{-2} s^{-1}, respectively. Addition of CO results in a decrease in reaction rate. A mechanism involving a rate-determining CO dissociation is proposed. Reaction with $P(i-Pr)_3$ is complex; products formed are $Co(CO)_3[P(i-Pr)_3]_2^+Co(CO)_4^-$ and $Co_2(CO)_6[P(i-Pr)_3]_2$. Observed order in carbonyl is 1.5 at 0 °C and 1.3 at 25 °C. Nonintegral order in base is also observed. A radical chain mechanism analogous to that previously proposed for reaction with $P(n-Bu)_3$ accounts for the kinetic behavior. These results suggest that reaction with bases of low nucleophilicity or large steric requirement proceeds via a rate-determining CO dissociation. With more nucleophilic bases of small or intermediate steric requirement, a radical chain mechanism is observed. The manner in which the steric requirement of the base can affect the radical chain mechanism is discussed.

The reactions of dicobalt octacarbonyl with group 5 bases give rise to several different products. With phosphines, the usual initial product is $[Co(CO)_3L_2][Co(CO)_4]$.[1–7] This salt

can be converted to the dinuclear species, $Co_2(CO)_6L_2$, by heating in refluxing benzene.[8–11] The product obtained with

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