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Pt(II) Complexes of Thymine: Factors Influencing Binding Sites and Methods of Differentiation

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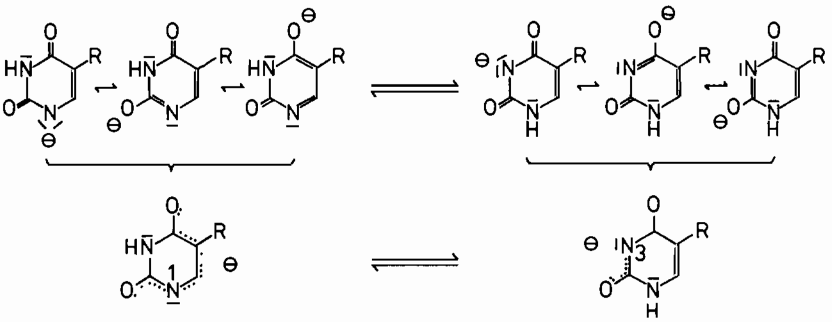
The complex forming properties of the thyminate anion with cis- *and* trans-*$Pt(NH_3)_2^{2+}$ in DMF and alkaline aqueous solution, and of $(NH_3)_3Pt^{2+}$ in water, have been studied using IR, Raman, UV, ^1H NMR spectroscopy and HPLC. Complexes containing thymine mono- and di-anions bound to Pt via N1, via N3 and bridging through N3 + N1 have been prepared, as well as two complexes containing thymine monoanions as counter ions. N1 and N3 binding of the thymine monoanion can be differentiated by ^1H NMR spectroscopy (HT-N^1: H5 $\cong$ 7.4–7.8 ppm, $J_{^{195}Pt-^1H(6)} \cong 40$ Hz; HT-N^3: H5 $\cong$ 7.0–7.3 ppm, no ^{195}Pt coupling; solvent D_2O), by Raman spectroscopy (HT-N^1: ring-breathing mode* ca. *769 cm^{-1}; HT-N^3:* ca. *797 cm^{-1}), by IR spectroscopy (HT-N^1: intense bands around 1640 and 1050 cm^{-1}; HT-N^3: 1550 and 1650 cm^{-1}) and by UV spectroscopy (HT-N^1: $\lambda_{max} \cong 290$ nm; HT-N^3: $\lambda_{max} \cong$ 265 nm). Using HPLC, three different bis(thyminato) complexes of* cis-*$Pt(NH_3)_2^{2+}$ containing the two tautomers of HT have been isolated and identified:* cis-*$Pt(NH_3)_2(HT\text{-}N^1)_2$,* cis-*$Pt(NH_3)_2(HT\text{-}N^1)(HT\text{-}N^3)$, and* cis-*$Pt(NH_3)_2(HT\text{-}N^3)_2$. Binding of the HT tautomers is affected by the solvent used, by pH (with water being the solvent), the solubilities of the complexes formed, by the reaction time, and by hydrogen bonding properties of adjacent ligands.*

Introduction**

With nucleobases representing multisite ligands, the questions concerning the selectivity of metal binding and factors influencing metal coordination sites have been of prime interest in recent years [1–6]. Apart from the well known property of metal ions to prefer one possible donor site over another due to their specific soft or hard character, the role of exocyclic groups of purine and pyrimidine bases for the stereochemistry and the stabilization of metal complexes has been recognized.

A particularly interesting situation occurs if different tautomers of a ligand are possible, and usually there is no way of predicting which complex is formed preferentially. This situation refers, for example, to the monoanions of unsubstituted uracil and thymine as well as related ligands, which are known to exist in solution in mixtures of N1 and N3 deprotonated forms [7–11]:



Metal coordination could conceivably take place at different sites of the two tautomers. Among the limited number of crystallographically-characterized metal complexes containing monoanions of unsubstituted thymine there is no example of N3 coordina-

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**Abbreviations used: H_2T = neutral thymine, HT = thymine monoanion, T = thymine dianion, TH-N^3 = monoanion coordinated to Pt via N3 *etc.* 1-MeC = 1-methylcytosine, en = ethylenediamine, *cis*-Pt(II) = *cis*-$Pt(NH_3)_2Cl_2$.

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tion, but only of N1 coordination [12–15]. With uracil monoanion complexes there is only one example of an X-ray structure on a N3 complex of Cd [16] and two examples of N1 coordination [14, 17]. There is a considerable controversy on metal binding sites of anionic thymine and uracil in studies not supported by crystal structure analyses, or no statements made on this subject [18–22]. Although the possibility of the coexistence of N1 and N3 tautomer complexes has been taken into consideration [23], only in the case of $(NH_3)_3Pt(II)$ has this been clearly demonstrated [24] until recently.

The metal coordination properties of neutral thymine and uracil are restricted to the exocyclic oxygens [25, 26] and possibly C5 (with uracil), unless protonation of the N1 or N3 coordinated thymine (uracil) anion occurs. Here the neutral ligand is present in a rare tautomeric form with one acidic proton located at an exocyclic oxygen [27].

The present study has been conducted to find out more about the factors that influence metal coordination sites on thymine monoanion tautomers, and on methods of differentiating between the complexes formed. It is a continuation of previous work on uracil complexes of *cis*-$Pt(NH_3)_2^{2+}$, $enPt^{2+}$ and $(NH_3)_3Pt^{2+}$ [27]. It originated in our interest in the nature of 'platinum pyrimidine blues' which represent interesting antitumor agents [28] of yet unknown structure [29].

Experimental

Spectroscopy

^1H NMR spectra were recorded on a Jeol JNM-FX 60 Fourier-transform spectrometer, infrared spectra on a Perkin Elmer 580 grating spectrometer, Raman spectra on a Coderg PH 1. Experimental conditions have previously been reported in detail [27]. UV spectra were recorded on a Cary 17 D spectrophotometer. Extinction coefficients are given in l mol^{-1} cm^{-1}. Reported pD values of D_2O samples were obtained by adding 0.4 to the pH-meter reading.

Potentiometric titrations

Reported pK_a values for the TH ligands in *5* and *4* were estimated from the obtained titration curves as previously mentioned [27]. Titration of *5* with NaOH gave the pK_a of the N3 complex, titration of *6* (dianion complex) with HCl gave the pK_a of the N1 complex *4*.

High Pressure Liquid Chromatography, HPLC

Analytical separations were carried out using a Philips Pye Unicam isocratic liquid chromatography system, consisting of LC-XPD pump, LC-UV variable wavelength detector, AR-55 linear recorder and Rheodyne 7120 sample injector with 20 μl sample loop. To extend the operating capabilities of the LC system to flow rates up to 30 ml/min, preparative versions of liquid head and pistons as well as of the detector flow cell, together with 2 ml sample loop, had to be used. Self-packed glass columns (Riedel-de-Haen 37990) were employed for chromatography on a analytical scale. For the packing of these columns with LiChrosorb RP 18 (10 m, Merck 9334) instructions given in the manual (R.d.H.) were followed. KNAUER 105.05, length 50 cm, shortened to 46 cm, ID 0.8 cm empty steel columns, self-packed with LiChrosorb RP 18, 10 μm were used on the preparative scale. A procedure for the filling of the above preparative column is described by the KNAUER instruction manual. Distilled water was used as the eluent. All separations were carried out at ambient temperature. Typically, about 0.5 ml of the sample (4.95 g solid reaction mixture in 9.5 ml water) were injected in a single run. A decrease of retention time of all peaks in the course of consecutive injections was observed. This was due to a gradual hydrolysis of the LiChrosorb filling material. The IR spectrum of a sample obtained on evaporation of 2 l of H_2O eluate following a separation of Pt complexes, indicated the presence of alkyl chains.

Materials and Preparation of Compounds

cis- and *trans*-$Pt(NH_3)_2Cl_2$ [30], *trans*-$Pt(N(CH_3)_2Cl_2$ [31], $[Pt(NH_3)_3Cl]Cl$ [32], K(HT) [33, 34] and *cis*-$Pt(NH_3)_2(HT\text{-}N^1)Cl$ [13] were prepared according to published procedures. K_2PtCl_4 was obtained from Degussa, thymine from Fluka. All other compounds were prepared as subsequently described. No attempts were made to optimize the yields. *trans*-$Pt(NH_3)_2(HT\text{-}N^1)Cl$, *2*, and *trans*-$Pt(NH_3)_2(HT\text{-}N^3)Cl$, *3*: 2 mmol *trans*-$Pt(NH_3)_2Cl_2$ were treated with 2 mmol $AgNO_3$ in 70 ml DMF and filtered from AgCl after 2 h at 25 °C. 2 mmol anhydrous K(HT) were added and the mixture stirred for 2 d. A white precipitate *3* was filtered off, washed with DMF, H_2O and EtOH and vacuum dried. Concentration of the filtrate to 25 ml gave a mixture of *2* and *3*. *2* dissolved in boiling water and could thus be separated from the less soluble *3*. Yields 23% (*2*), 64% (*3*). *Anal.* Calcd. for $C_5H_{11}N_4O_2PtCl$ C, 15.40; H, 2.80, N, 14.40. Found: C, 15.86(*2*), 15.46(*3*); H, 3.19(*2*), 2.99(*3*); N, 14.23(*2*), 14.37(*3*).

trans-*[Pt(NH₃)₂(1-MeC)(HT-N¹)] ClO₄·H₂O,* 2a, *and* trans-*[Pt(NH₃)₂(1-MeC)(HT-N³)] ClO₄·H₂O,* 3a

400 mg of *2* and *3*, respectively, were stirred with 130 mg 1-MeC in 500 ml H_2O for several days (N3: 2 d, N1:9 d). After filtration of unreacted Pt starting compound (N3 5%, N1 50%) and concentration

to 50 ml volume, 250 mg $NaClO_4 \cdot H_2O$ were added, and the reaction solutions allowed to evaporate at room temperature. In both cases colorless to slightly yellow crystals were obtained, which were recrystallized from H_2O. *Anal.* Calcd. for $C_{10}H_{20}N_7O_8Pt$ Cl: C, 20.12; H, 3.38; N, 16.43; O, 21.44; Pt, 32.68. Found: C, 20.16(*2a*), 19.89(*3a*); H, 3.68(*2a*), 3.42(*3a*); N, 16.28(*2a*), 16.42(*3a*); O, 21.33(*2a*); Pt, 33.2(*3a*).

$[Pt(NH_3)_3(HT\text{-}N^1)]NO_3 \cdot H_2O$, 4a, *and* $[Pt(NH_3)_3(HT\text{-}N^3)]J \cdot H_2O$, 5d

(1) 1.4 g $[Pt(NH_3)_3Cl]Cl$ was reacted with 1.5 g $AgNO_3$ in 30 ml H_2O and AgCl filtered off. 1.46 g K(HT) was added and the mixture kept at 25 °C for 1 d. Crude *4a* was filtered, washed with 6 ml 1 X NaOH to remove H_2T and recrystallized from water. Colorless needles. Yield 180 mg. Concentration of the filtrate to 7 ml volume, neutralization with HNO_3 and three passes over Sephadex G 10 (2.5 cm id, 38 cm length) gave 100 mg of $[Pt(NH_3)_3(HT\text{-}N^3)]NO_3$, *5b*.

(2) The respective $Pt(NH_3)_2(HT)Cl$ complexes (*1* or *2* for N1, *3* for N3 complexes) were stirred with aqueous NH_3 (25%) at 90 °C for 30 min with continous addition of fresh NH_3 solution. The almost-clear solution was then filtered and evaporated to dryness. Analytical data of the products agree with $[Pt(NH_3)_3(HT)]Cl$. Yield 90%. Replacement of Cl by X = NO_3, BF_4 *etc.* through AgX treatment gave the desired products. With the N3 complex, best results were obtained for the J salt, obtained from the NO_3 salt on addition of KJ and HJ (pH = 2) at 25 °C and recrystallization from water. Colorless needles, somewhat photosensitive. *Anal.* *4a*: Calcd. for $C_5H_{16}N_6O_6Pt$: C, 13.30; H, 3.58; N, 18.62. Found: C, 13.26; H, 3.41; N, 18.60. *Anal.* *5d*: Calcd. for $C_5H_{16}N_5O_3Pt$ J: C, 11.63; H, 3.13; N, 13.57; Pt, 37.79. Found: C, 11.88; H, 3.10; N, 13.45; Pt, 38.5.

$Pt(NH_3)_3(T\text{-}N^1) \cdot H_2O$, 6, *and* $Pt(NH_3)_3(T\text{-}N^3) \cdot H_2O$, 7

4a and *5b*, respectively, were dissolved in excess aqueous NaOH and concentrated to a small volume at 0 °C. The highly soluble white precipitate was filtered, treated with MeOH to remove NaOH and recrystallized from H_2O/MeOH. *Anal.* Calcd. for $C_5H_{15}N_5O_3Pt$: C, 15,46; H, 3.90; N, 18.04; Pt, 50.2. Found: C, 15.27(*6*), 15.58(*7*); H, 3.95(*6*), 4.43(*7*); N, 17.76(*6*); Pt, 50.4(*6*), 50.1(*7*).

$[(NH_3)_3Pt(T\text{-}N^1,N^3)Pt(NH_3)_3](ClO_4)_2 \cdot 2.5H_2O$, 8

600 mg of $[(NH_3)_3PtCl]Cl$ and 800 mg $AgBF_4$ were reacted in 20 ml H_2O and AgCl was filtered off, 950 mg of *4c* (BF_4 salt, monohydrate) was added, and the pH of the solution kept at 7 by repeated addition of NaOH. After 4 d at 40 °C the solution was concentrated to 5 ml, filtered from unreacted *4c*, passed over a Sephadex G 10 column (H_2O elution), and brought to dryness (550 mg). Recrystallization from H_2O/MeOH (1:1), to which 400 mg $NaClO_4 \cdot H_2O$ had been added, gave 360 mg of yellow crystals. *Anal.* Calcd. for $C_5H_{27}N_8O_{12.5}Pt_2Cl_2$: C, 6.98; H, 3.17; N, 13.03. Found: C, 7.37; H, 3.55; N, 12.96.

$[Pt(NH_3)_3(HT\text{-}N^1)](HT) \cdot 1.5H_2O$, 9

To 600mg *4a*, dissolved in 11 ml H_2O at 90 °C, 1.35 ml 1 *N* NaOH and 170 mg H_2T were added. Upon cooling colorless needles (330 mg) were obtained and recrystallized from water. *Anal.* Calcd. for $C_{10}H_{22}N_7O_{5.5}Pt$: C, 22.94; H, 4.24, N, 18.37; Pt, 37.3. Found. C, 22.84; H, 4.37; N, 18.47; Pt, 37.2.

$[Pt(NH_3)_4](HT)_2 \cdot 1.5H_2O$, 10

To 700 mg $[Pt(NH_3)_4]Cl_2$, dissolved in 3 ml H_2O at 70 °C, 2 ml 1 *N* NaOH and 250 mg H_2T were added. Concentration to 1.5 ml volume gave 700 mg colorless needles, which were recrystallized from acetone/H_2O. *Anal.* Calcd. for $C_{10}H_{25}N_8O_{5.5}Pt$: C, 22.22; H, 4.67; N, 20.74. Found· C, 21.97; H, 4.36; N, 20.84.

$[Pt(NH_3)_2(HT)_2$, 11–14

10 mmol *cis*-Pt(II) and *trans*-Pt(II) were reacted with 20 mmol $AgNO_3$ in 70 ml H_2O at 60 °C to give the respective diaquo species. 40 mmol K(HT) were added and the mixture heated to 90 °C for 1 h. The precipitate (*I*) filtered off consisted of H_2T, *11* and *14*, respectively. The filtrate *I'* (pH = 10.5) was brought to pH = 7 by addition of HNO_3 and more H_2T was filtered. The filtrate *I"* was then used for analytical HPLC. Prior to preparative HPLC the filtrate was concentrated to 5 ml volume and filtered from more H_2T and some KNO_3. *cis*-$Pt(NH_3)_2(HT\text{-}N^1)_2 \cdot 2H_2O$, *11*, was obtained from precipitate *I* (2.56 g) after NaOH treatment (5 min with 20 ml 1 *N* NaOH at 25 °C) to remove H_2T, and recrystallization from boiling water. Colorless, extremely insoluble microneedles. Yield 2.05 g (40%). *Anal.* Calcd. for $C_{10}H_{20}N_6O_6Pt$: C, 23.30; H, 3.92; N, 16.31. Found. C, 23.36; H, 3.95; N, 16.17.

cis-$Pt(NH_3)_2(HT\text{-}N^1)(HT\text{-}N^3) \cdot 4H_2O$, 12

was obtained after HPLC of filtrate *I"* as fraction 6 (*cf.* Results and Discussion), and subsequently recrystallized from hot water. Colorless microneedles. Yield 1.09 g (20%). *Anal.* Calcd. for $C_{10}H_{24}N_6O_8Pt$· C, 21.78; H, 4.40; N, 15.24. Found: C, 21.87, H, 4.25; N, 15.37. *cis*-$Pt(NH_3)_2(HT\text{-}N^3)_2 \cdot 3H_2O$, *13*, was obtained after HPLC of filtrate *I"* as fraction 2 on freeze drying. Colorless powder. Yield 200 mg (4%). *Anal.* Calcd. for $C_{10}H_{22}N_6O_7Pt$: C, 22.51; H, 4.16; H, 15.78. Found: C, 22.63; H, 3.88; N, 15.86.

trans-*Pt(NH$_3$)$_2$(HT-N^1)(HT-N^3)·2H$_2$O*, 14

Precipitate *1* (5.05 g) was stirred with 20 ml 1 *N* NaOH for 5 min to remove H_2T. The undissolved material was washed with water and dried with acetone. Very insoluble white powder. Yield 4.15 g (83%). HPLC gave a single peak for this compound, thus proving that it was a single species and not a mixture. *Anal.* Calcd. for $C_{10}H_{20}N_6O_6Pt$: C, 23.30; H, 3.92, N, 16.31. Found: C, 23.34, H, 3.95; N, 16.14.

trans-*Pt(N(CH$_3$)$_3$)$_2$(HT-N^1)Cl·H$_2$O*, 15

620 mg *trans*-$Pt(N(CH_3)_3)_2Cl_2$ and 275 mg $AgNO_3$ were reacted in 60 ml DMF and filtered from AgCl. 265 mg anhydrous K(HT) were added, and the mixture stirred for 20 h at 25 °C. After filtration of some residue, the sample was evaporated to dryness, treated with 10 ml H_2O, filtered and recrystallized from MeOH. Yellow needles. Yield 180 mg (25%). *Anal.* Calcd. for $C_{11}H_{23}N_{14}O_2PtCl$: C, 26.85; H, 5.13; N, 11.39. Found: C, 26.85; H, 4.78; N, 11.24. Raman spectroscopy showed the major species present in the H_2O filtrate to be N1 coordinated (769 cm^{-1}) with very little N3 coordinated product (799 cm^{-1}) only. Based on relative scattering coefficients of these two signals, the ratio of N1 N3 coordination was estimated to be 5:1 in the filtrate.

Results and Discussion

Mono(thyminato) Complexes of cis- *and* trans-*Pt(II)*

cis-*Pt(NH$_3$)$_2$(HT-N^1)Cl*, 1

The preparation of this compound has been described [13]. N1 coordination of thymine has unambiguously been confirmed by the crystal structures of two forms of 1-methylcytosine derivatives, *cis*-[$Pt(NH_3)_2$(HT-N^1)(1-MeC)]ClO_4 (anhydrate [15] and trihydrate *1a* [13]).

trans-*Pt(NH$_3$)$_2$(HT-N^1)Cl*, 2, *and* trans-*Pt(NH$_3$)$_2$-(HT-N^3)Cl*, 3

Two compounds *2* and *3* of identical composition but differing solubilities and IR spectra were obtained on reaction of *trans*-[$Pt(NH_3)_2Cl(DMF)$]NO_3 and anhydrous K(HT) in DMF. Replacement of the chloro ligands in *2* and *3* by 1-methylcytosine gave crystalline, water soluble complexes of composition *trans*-[$Pt(NH_3)_2$(HT-N^1)(1-MeC)]ClO_4, *2a*, and *trans*-[$Pt(NH_3)_2$(HT-N^3)(1-MeC)]ClO_4, *3a*, respectively. The assignment of Pt binding sites in *2*, *2a*, *3* and *3a* was achieved in all cases by IR spectroscopy and, because of sufficient solubilities, with *2a* and *3a* also by ^{1}H NMR spectroscopy.

IR Spectra. In Fig. 1 sections of the IR spectra of *1*, *2*, *3* are given, which exhibit tautomer-specific features, and compared with *14* (*trans*-$Pt(NH_3)_2$-(HT-N^1)(HT-N^3)) which contains both tautomers bound simultaneously. As expected, only minor differences are observed when going from the *cis*- to the *trans*-isomer of $Pt(NH_3)_2$(HT-N^1)Cl (*1*, *2*), for example a splitting of the 1385 cm^{-1} band of *2* into 1380, 1390 cm^{-1} in *1*. In contrast, the spectrum of *3* differs markedly from those of *1* and *2*, in particular in the double-bond stretching region: there are two intense bands at 1550 and 1650 cm^{-1} as compared to a single one at 1640 cm^{-1} in *1* and *2*. The 1550 cm^{-1} band in *3* is assigned to a $(4)O \cdots C \cdots N(3) \cdots C \cdots O(2)$ stretching motion in analogy to the N3 deprotonated thymine anion [34] or the monoanion of 1-methylthymine [35, 36] which have strong IR bands at 1500 and 1525 cm^{-1}. The shift of the 1500 cm^{-1} band of free N3 deprotonated thymine to higher energy in complex *3* (1550 cm^{-1}) is in agreement with expectations on binding of a metal electrophile to the N3 position:

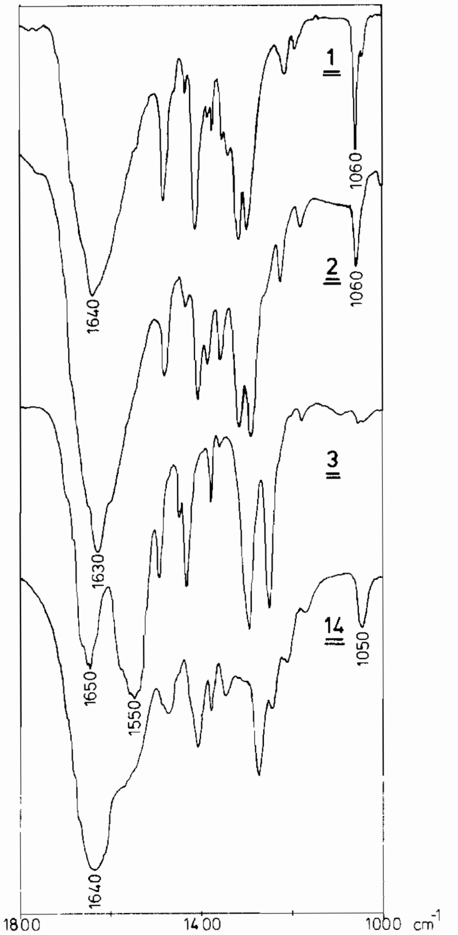


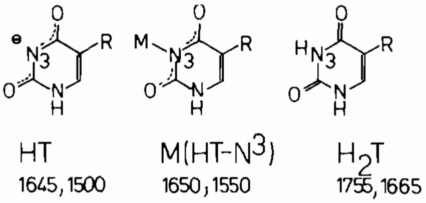
Fig. 1. IR spectra (KBr) between 1800 and 1000 cm^{-1} of *cis*-$Pt(NH_3)_2$(HT-N^1)Cl, *1*, *trans*-$Pt(NH_3)_2$(HT-N^1)Cl, *2*, *trans*-$Pt(NH_3)_2$(HT-N^3)Cl, *3*, and *trans*-$Pt(NH_3)_2$(HT-N^1)(HT-N^3), *14*.

TABLE I. ^{1}H NMR Spectra (D_2O, *ca.* 0.1 *M* Pt) of Mixed HT/1-MeC Complexes (in ppm relative to TMS, Coupling Constants J in Hz).

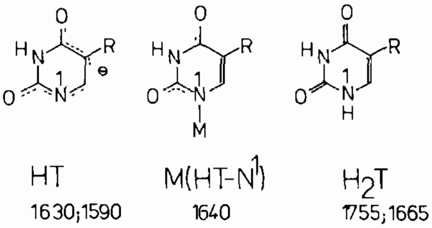
	1-MeC					HT			
	CH_3	H5	H6	J_{H5-H6}	$J_{^{195}Pt-^1H5}$	CH_3	H6	J_{CH_3-H6}	$J_{^{195}Pt-^1H6}$
2a	3.444	6.041	7.622	7.6	15	1.871	7.753	0.9	40
3a	3.444	6.061	7.635	7.6	15	1.853	1.287	0.7	–
1a	3.420	5.972	7.564	7.6	15	1.785	7.514	n.o.[a]	36

[a] n.o. = not observed.

it should lead to a charge distribution in the heterocyclic ring intermediate between the free ligand HT and the protonated ligand H_2T. Similar changes have been observed for complexes of *cis*-Pt(II) with 1-methylthymine [35, 37] and are also believed to be responsible for the formation of mixed CH_3Hg/Na complexes with the same ligand [38].



In contrast to the N3 tautomer, metal binding to the N1 position of the thymine anion causes a smaller shift in this spectral region, but there also bands of the Pt complex in the double-bond stretching region are in between those of the free ligand and neutral thymine.



We have previously reported IR and Raman bands characteristic of N1 platinum coordination of thymine [34]. They are in agreement with the compounds described here. With regard to an IR spectroscopic differentiation of N1 and N3 coordination, apart from the above mentioned differences in the 1700–1500 cm^{-1} range, the only other intense band that proved to be of reliable diagnostic value was the 1050 cm^{-1} band, present both in HT-N^1 and T-N^1 complexes, but missing in the corresponding N3 compounds. It is removed upon deuteration. A band of comparable intensity also occurs in the N1 deprotonated thymine monoanion (1025 cm^{-1}), but not in the N3 deprotonated one [34], and is also observed in neutral thymine (1026 cm^{-1} in the monohydrate, 1030 cm^{-1} in the anhydrate) [34, 39].

^{1}H NMR spectra. The ^{1}H NMR spectra of *2a* and *3a* in D_2O show minor differences in the positions of the 1-methylcytosine resonances, but considerable differences in thymine resonances (Table I).

The differences in (HT-N^1) resonances between corresponding *cis-* (*1a*) and *trans-* (*2a*) complexes, with the thymine resonances of the *cis-* complex absorbing at higher field, probably are a consequence of a diamagnetic anisotropy due to ring current effects. It is also observable for the 1-methylcytosine resonances, although less pronounced.

The additional upfield shift of the thymine resonances in *3a* appears to be a direct consequence of an electronic change within the ligand, and is attributed to the change in coordination site as compared to *1a* and *2a*. As will be shown below for a variety of other thymine monoanion complexes, H6 resonances generally are observed around 7.0–7.3 ppm in N3 complexes and between 7.4 and 7.8 ppm in N1 complexes in D_2O as solvent.

This interpretation is further supported when ^{195}Pt–^{1}H coupling is considered: such coupling is well observable for H6 of thymine both in *1a* (36 Hz) and *2a* (40 Hz), hence indicating N1 platinum binding, but it is missing in *3a*. Coordination of the 1-methylcytosine ligand to Pt in all three compounds is through N3, as evident from ^{195}Pt–^{1}H5 coupling (^{4}J = 15 Hz), and in agreement with earlier results [40, 41]*.

Thymine Complexes of $Pt(NH_3)_3^{2+}$

Triammineplatinum(II) complexes of thymine were prepared via two routes:

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*We reported incorrectly on two occasions (refs. 15 and 42) the ^{195}Pt–^{1}H5 coupling constant in 1-MeC complexes to be around 20 Hz. It is actually 15 Hz in both cases.

TABLE II. Ammine Vibrations of $[(NH_3)_3Pt(HT\text{-}N^1)]BF_4$, *4c*, in Its ^1H and ^2D Form, respectively (in cm^{-1}).[a]

ν NH_3	3360–3140 (IR)	ν ND_3	2460–2280
δ_d NH_3	n o.[b]	δ_d ND_3	1150
δ_s NH_3	1340 (IR)	δ_s ND_3	1030
ρ NH_3	830 (IR)	ρ ND_3	610[c]
ν Pt–NH_3	537 (Ra)[d]	ν Pt–ND_3	493

[a] ν = stretching, δ = deformation, ρ = rocking [b] Not observed, hidden under intense HT modes. [c] Superimposed with thymine mode [d] Only one Pt-NH_3 mode observed.

– *reaction of* $[(NH_3)_3Pt(H_2O)]^{2+}$ with HT in analogy to the preparation of the corresponding uracil complexes [24] and separation of the tautomer complexes by chromatography.

– reaction of chloro(thyminato)diammineplatinum(II) with aqueous NH_3 according to

$$Pt(NH_3)_2(HT)Cl + NH_3 \rightarrow [Pt(NH_3)_3(HT)]Cl$$

and subsequent replacement of Cl by another anion at will. The second method proved to be easier than the first one. As concluded from IR, the mode of thymine binding is not altered during this reaction and, expectedly, the νPt–Cl band around 335 cm^{-1} in the starting compounds has disappeared in the spectra of the triammineplatinum(II) complexes.

$[Pt(NH_3)_3(HT\text{-}N^1)]X\cdot nH_2O$ ($X = NO_3$, 4a, ClO_4, 4b, BF_4, 4c) and $[Pt(NH_3)_3(HT\text{-}N^3)]X\cdot nH_2O$ ($X = Cl$, 5a, NO_3, 5b, BF_4, 5c, J, 5d)

A differentiation of the two types of tautomer complexes has been achieved by IR, Raman, ^1H NMR and UV spectroscopy, as well as by their differing behaviour upon acid treatment.

IR spectra (solid state). The above mentioned differences in IR absorptions of the two different tautomer ligands are confirmed with the triammine complexes. Changes in anions usually result in minor differences only, except with bands of NH_3 and NH character and, of course, anion vibrations This is probably a consequence of differing hydrogen bonding and/or crystal packing in the solid state. NH_3 and NH* vibrations were identified by deuteration experiments. Typically, NH_3 absorptions were observed as indicated in Table II for *4c*.

In the IR spectra of both HT tautomer complexes bands around 1410 cm^{-1} are observed that are removed on deuteration, and which are also missing in the T complexes. They are consequently assigned to $NH_{i.p.}$ modes as with neutral thymine [39]. The corresponding o.o.p. modes** in both cases occur around 890 cm^{-1} and are shifted to *ca.* 610 cm^{-1} in the deuterated compounds, superimposed with ND_3. Differences in respective NH band positions in the HT tautomer complexes are not sufficiently large to be of any particular value with respect to a differentiation of N1 and N3 coordination.

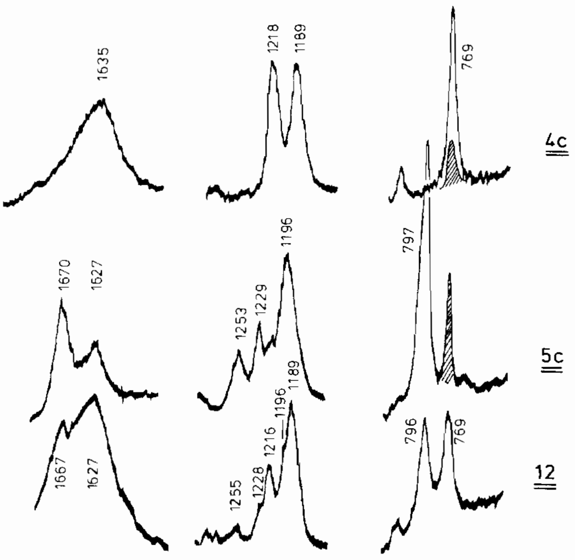

Fig 2. Sections of the Raman spectra (H_2O) of $[(NH_3)_3Pt(HT\text{-}N^1)]BF_4$, *4c* (pH = 3.5), $[(NH_3)_3Pt(HT\text{-}N^3)]BF_4$, *5c* (pH = 4.4), and *cis*-$Pt(NH_3)_2(HT\text{-}N^1)(HT\text{-}N^3)$, *12* (pH = 6). Slit widths 6 cm^{-1} (*5c*), 8 cm^{-1} (*4c*, *12*). Shaded band is due to $\nu_1 BF_4$ In the case of *4c* it is superimposed with the HT-N^1 mode.

Raman spectra (solution). Because of their relatively strong intensities in the Raman effect, heterocyclic ring vibrations are particularly useful for a differentiation of tautomers [11] or tautomer complexes [27]. The strongest Raman band of $[(NH_3)_3Pt(HT\text{-}N^3)]^+$ complexes, the ring-breathing mode of the HT ligand, is observed at 797 cm^{-1} (10)*** compared to 769 cm^{-1} (10) in the N1 complex (H_2O solution) Other differences refer to bands around 1200 cm^{-1} with 1229(5.4) and 1253 cm^{-1} (3.3) absorptions in the spectra of the N3 complexes, yet a single 1218 cm^{-1} (7.2) absorption in the N1 complexes (Fig 2).

^1H NMR spectra. The positions of the H6 resonances of the (thyminato)triammineplatinum(II) complexes vary in a similar way as those of the

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*It is emphasized that in heterocyclic compounds there are usually no pure NH modes because of substantial intramolecular coupling.

**i.p = in plane; o.o.p. = out of plane.

***Relative intensities are given in brackets and refer to signal heights.

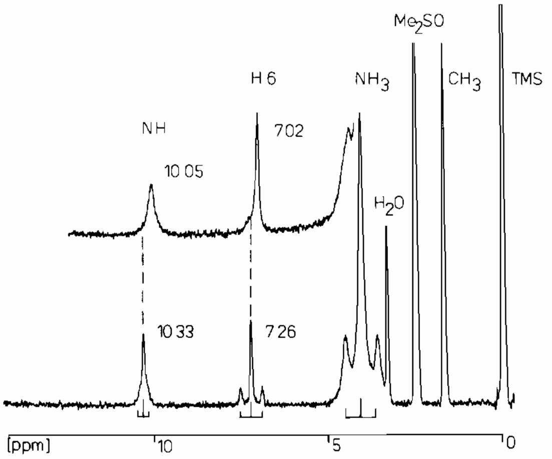


Fig. 3. ^{1}H NMR spectra (Me_2SO-d_6, 0.14 *M* Pt) of $[(NH_3)_3$-$Pt(HT$-$N^1)]BF_4$, *4c* (bottom) and $[(NH_3)_3Pt(HT$-$N^3)]BF_4$, *5c* (top).

diammineplatinum(II) complexes: with D_2O as solvent, the N1 complexes exhibit this resonance around 7.6 ppm, N3 complexes around 7.2 ppm. ^{195}Pt coupling with H6 is observed for the N1 complexes (37 Hz), but not for N3 complexes. With Me_2SO-d_6 as solvent, H6 resonances are shifted upfield, but the relative positions of HT-N^1 and HT-N^3 are maintained. NH resonances are observed around 10 ppm with N3 complexes and around 10.3 ppm with N1 complexes. ^{195}Pt coupling with NH is observed with the N1 complex and around 12 Hz (*cf.* Fig. 3).

UV spectra. The UV spectra of the two tautomer complexes differ in a way expected from a comparison of the monoanions of 3-methylthymine and 1-methylthymine [43]. For example, *4c* (λ_{max} = 291 nm, = ϵ 10160) shows the same bathochromic shift as does the 3-methylthyminate anion (λ_{max} = 290 nm) and compares with λ_{max} = 264 nm of H_2T. *5c,* on the other hand, has λ_{max} at 266 nm (ϵ = 8630) similar to the 1-methylthyminate ion (λ_{max} = 270 nm).

Acid treatment. As has previously been demonstrated by us [27, 37], the Pt-N3 bond in complexes of pyrimidine-2,4-dione ligands is easily cleaved in the presence of acid at elevated temperatures (≥70 °C). In contrast, the Pt–N1 bond is extremely stable under these conditions and is broken only after several hours boiling of the complex in concentrated acids. The same holds for the triammine complexes described here. For example, *5c* readily gives neutral thymine when kept at 80 °C at pD = 0 (D_2O, CF_3COOD), as evident from ^{1}H NMR and IR spectroscopy, whereas *4a* is quite stable under identical conditions.

There is an interesting difference between corresponding thymine and uracil complexes on acid treatment, however: unlike H5 and H6 resonances of the (HU-N^3) complex, the H6 resonances of the (HT-N^3) complexes *5* are considerably less sensitive in their shifts in the pD range studied. While H5 and H6 uracil resonances in (HU-N^3) complexes are shifted by almost 0.3 ppm downfield when the pD is lowered from 4 to 0, the H6 signal of the (HT-N^3) complexes are shifted 0.04 ppm only in the same pD range.

Acidity of NH protons in 4 *and* 5. The acidity of the remaining NH proton in the N1 and N3 tautomer complexes of the thymine monoanion ligands has been determined by potentiometric titration and found to be around 11.5 for both *4* and *5*. This means that platinum binding has increased the acidity of the thymine monoanion by 1.5 log units (pK_2 H_2T = 13 [44]). Similar values have been reported for the corresponding uracil complexes [24]. Crystalline triammineplatinum(II) complexes containing the thymine dianion T have been isolated and will be dealt with subsequently.

Thymine dianion complexes: $Pt(NH_3)_3(T$-$N^1)$, 6, *and $Pt(NH_3)_3(T$-$N^3)$,* 7

UV, ^{1}H NMR and IR spectra of *6* and *7* show minor differences only, but Raman spectra do permit a differentiation.

UV spectra. Both complexes have λ_{max} at 286 nm with rather similar extinction coefficients (8300(*6*) and 8100(*7*)).

^{1}H NMR spectra. The H6 resonances of *6* and *7* exhibit a much smaller separation than the HT complexes, and occur at 7.51 and 7.39 ppm, respectively. CH_3 resonances are virtually identical (1.82 ppm).

IR spectra

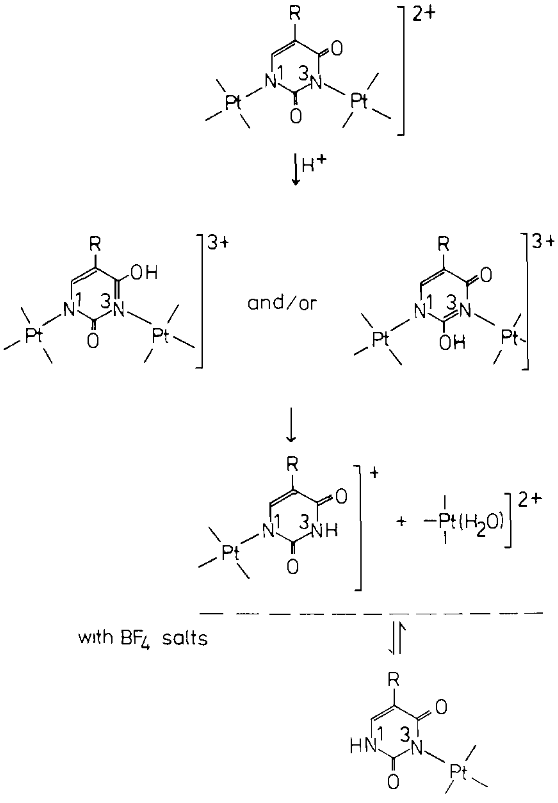
There are shifts to lower energy for the intense bands in the double-bond stretching region of *6* and *7* as compared to the corresponding HT complexes. The most intense bands at 1630, 1510, 1480 and 1450 cm^{-1} of *7* are close to those of *6* at 1615, 1525, 1480 and 1450 cm^{-1}.

Raman spectra (H_2O). The most intense Raman bands, due to ring-breathing modes, are shifted to higher energy on deprotonation: *6* has this mode at 807 cm^{-1}, *7* at 780 cm^{-1}.

A dinuclear complex with a T bridge: $[(NH_3)_3Pt$-$(T$-$N^3, N^1)Pt(NH_3)_3](ClO_4)_2\cdot 2.5H_2O$, 8

$[(NH_3)_3Pt(HT$-$N^1)]^+$, *4c,* reacts with $[(NH_3)_3$-$Pt(H_2O)]^{2+}$ in neutral or weakly acidic solution with release of protons, as indicated by a drop in pH. In the Raman spectrum a new band of high intensity appears at 803 cm^{-1}, while the ring-breathing mode of *4c* at 769 cm^{-1} diminishes. After gel chromatography of the reaction solution and recrystallization from an aqueous NaClO$_4$ solution a compound of composition $Pt_2(NH_3)_6(C_5H_4N_2O_2)(ClO_4)_2 \cdot 2.5H_2O$ has been isolated with a strong Raman band at 803 cm^{-1}. The identical compound was isolated when $[(NH_3)_3Pt(HT\text{-}N^3)]^+$, *5c*, and $[Pt(NH_3)_3Pt(H_2O)]^{2+}$ were reacted. A similar reaction had been observed by us in the uracil system using ^1H NMR and Raman spectroscopy [27], but no product had been isolated. The way of preparation of *8* via two different routes, starting both with an N1 and an N3 complex, is a strong argument in favour of an N3, N1 bridge in this compound.

^1H NMR spectra. N1 binding of T in *8* is evident from ^{195}Pt coupling with the H6 resonance (^3J = 37 Hz). Chemical shifts are not very different from those of *6* and *7*. Specifically, H6 of *8* absorbs at 7.42 ppm and CH$_3$ at 1.82 ppm in D$_2$O, pD = 7.5. Addition of acid (CF$_3$COOD) causes protonation of *8* as concluded from the downfield shifts of H6 and CH$_3$ (7.89 and 1.99 ppm, respectively, at pD = 0.75), and supported by UV spectroscopy (new band at 312 nm besides the original 288 nm band). The protonated complex is decomposed with formation of the N1 bound HT complex which precipitates from solution.



At 0.2 *M* Pt, pD = 1.2, 25 °C, 50% of the dinuclear complex is decomposed within 40 h. Due to the relatively low solubility of $[(NH_3)_3Pt(HT\text{-}N^1)]ClO_4$ no formation of the N3 complex is observed. On the other hand, reaction of the soluble BF$_4$ salt *4c* with $[(NH_3)_3Pt(D_2O)]BF_4$ yields the (HT-N^3) complex in equilibrium, and so does the reverse reaction between *5c* and $[(NH_3)_3Pt(D_2O)]BF_4$. Thus the thymine complex behaves much like the corresponding uracil complex [27].

Complexes Containing the Thymine Anion as Counterion

$[Pt(NH_3)_4](HT)_2 \cdot 1.5H_2O$, 9

In the presence of excess sodium thyminate, $[Pt(NH_3)_4]Cl_2 \cdot H_2O$ crystallizes as the thyminate salt *9*. The IR spectrum with its two strong bands at 1638, 1575 and 1022 cm^{-1} is indicative of N1 deprotonated HT [34], as in the Raman solid state spectrum with its intense bands at 757, 814 and 1183 cm^{-1}.

$[Pt(NH_3)_3(HT\text{-}N^1)](HT) \cdot 1.5H_2O$, 10

Reaction of *4a* with HT in hot water yields the thyminate salt *10*. Two sets of thymine resonances are observed in the ^1H NMR spectrum in D$_2$O, corresponding to N1 coordianted (H6, 7.59 ppm, J = 37 Hz) and free HT (H6, 7.41 ppm). In the IR spectrum, bands of the two kinds of HT strongly overlap, in particular in the 1700–1500 cm^{-1} range, and therefore do not provide reliable information concerning the tautomeric form of the counterion in the solid state. The solid state Raman spectrum exhibits grossly overlapping bands as well, and no straightforward assignment of the tautomeric structure of the HT ion is possible. Only a single band is observed in the region of the intense ring-breathing mode, at 763 cm^{-1}. This position compares with 756 and 755 cm^{-1} of K(HT)tri- and monohydrate, respectively, which are both N1 deprotonated, and 763 cm^{-1} of the N3 deprotonated tautomer [34], and 758–771 cm^{-1} of Pt(II) complexes with N1 coordinated HT [15, 34]. Even though the 763 cm^{-1} position in the spectrum of *10* could indicate N3 deprotonation of the HT anion in *10*, a detailed comparison of all other Raman bands with those of the two HT tautomers [34] seems to suggest that the HT counterion is actually N1 deprotonated. This assumption is based on the existence of three minor bands at 1598, 1284 and 1193 cm^{-1}, and of a strong one at 1341 cm^{-1} in the spectrum of *10* at positions closer to those of the N1 deprotonated HT tautomer than those of the N3 deprotonated one.

With evidence derived from solid state Raman spectra being as conflicting as outlined above, the limitations of this technique for the determination of tautomeric structures in the solid state are reached. Only X-ray crystallography can eventually give an answer.

Bis(Thyminato) Complexes of cis- *and* trans-*Pt(II)*

Reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with thymine in 1:1 ratio at pH values below 7–8 leads to formation of 'platinum thymine blue' [28]. When strongly alkaline conditions are applied, or with a large excess of HT over Pt, no blue products are formed. Reaction of *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with 4 HT at 90 °C yields several Pt complexes, three of which were unambiguously identified and isolated.

cis-*Pt(NH₃)₂(HT-N¹)₂·2H₂O,* 11

This extremely water-insoluble compound precipitates from the reaction mixture. In its IR spectrum, strong and sharp bands typical of N1 coordination of HT are observed at 1640 and 1050 cm^{-1}, with no band around 1550 cm^{-1} that would be indicative of N3 binding.

cis-*Pt(NH₃)₂(HT-N¹)(HT-N³)·4H₂O,* 12

It is obtained by preparative HPLC of the filtrate after separation of *11* and unreacted thymine (*cf.* Experimental), and identified using Raman, ^1H NMR and UV spectrometry. In H_2O, the most intense Raman bands are observed at 769 and 796 cm^{-1}, which are characteristic of N1 and N3 bound HT, respectively. Both bands are of the same intensities, thus indicating identical scattering coefficients of the two ring vibrations. The ^1H NMR spectrum of *12* in D_2O shows the expected two sets of thymine resonances at 1.80 (CH_3, N1), 1.74 (CH_3, N3), 7.44 (H6, N1) and 7.19 ppm (H6, N3). With Me_2SO-d_6 instead of D_2O, these resonances each appear slightly upfield and in addition, the NH resonances are observable: 9.99 ppm (HT-N^3) and 10.27 ppm (HT-N^1). The UV spectrum shows two absorptions with maxima at 293 nm (HT-N^1, ϵ = 12020) and 268 nm (HT-N^3, ϵ = 8560). Interestingly, *12* has recently been shown to be one of the two main species in the white component of 'platinum thymine blue' [45].

cis-*Pt(NH₃)₂(HT-N³)₂·3H₂O,* 13

It is separated by HPLC (fraction 2) from the reaction mixture. From IR (1640vs, 1570vs, 1540vs; 1050 cm^{-1} band missing) and ^1H NMR spectra (H6, 7.05 ppm, no ^{195}Pt coupling, pD = 7.3) it is concluded that *13* is the bis(HT-N_3) complex.

HPLC, other products

Both Raman (solution) and ^1H NMR spectra of freeze-dried samples of the reaction mixture (brought to pH = 6 and filtered from the bulk amount of *11* and H_2T) indicate the presence of a series of species, and so does HPLC. For example, in a typical ^1H NMR spectrum as shown in Fig. 4, in the H6 region at least five signals can be distinguished: 7.55 ppm (HT-N^1), 7.46 ppm (T-N^1, N^3), 7.34 ppm (H_2T), 7.13 ppm (HT-N^3) and 7.05 ppm (HT-N^3).

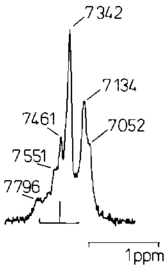


Fig. 4. H6 resonances of thymine species present in a mixture obtained from reaction of *cis*-$Pt(NH_3)_2^{2+}$ with 4 equiv. of HT (1 h 90 °C, then brought to pH = 6 and filtered from precipitate). Solvent D_2O.

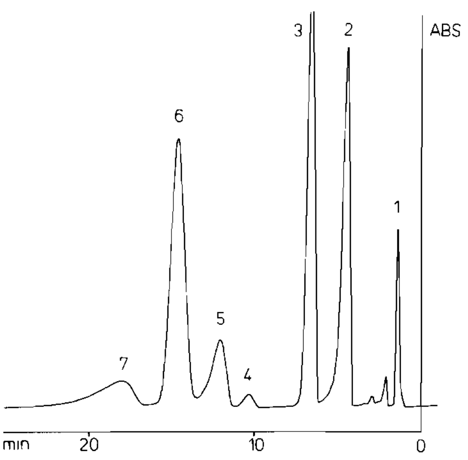


Fig. 5. HPLC chromatogram of reaction mixture *cis*-$Pt(NH_3)_2^{2+}$/4 HT (*cf.* Experimental section) Sample: 4 g freeze-dried compound in 10 ml water, column· analytical LiChrosorb RP 18, detector· 254 nm, 1.28 AUFS; mobile phase: distilled water; flow rate: 1 ml/min.

Analytical HPLC gives seven major peaks (Fig. 5), three of which are identified by comparison of retention times of the isolated components: KNO_3(1), H_2T(3) and *11*(7). There is definitely no *trans*-complex present as evident from the HPLC diagrams obtained from reaction mixtures of *trans*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ with HT.

Preparative HPLC and characterization of the fractions using IR, Raman, NMR and UV spectroscopy, as well as elemental analysis, confirmed the assignments of fractions 1, 3, 7. In addition, fraction 6 was identified as *12* and fraction 2 as *13*.

The composition of fractions 4 and 5 is not fully understood. Even though their preparative separation is difficult as expected for values of K′ > 5*, re-chromatography results seem not be unexplainable on the basis of poor separation: rechromatograms of collected individual fractions 4 and 5 (kept in solution for a day or longer) are almost identical with the original chromatogram of combined 4 + 5. This suggests that the components of these two fractions are in slow equilibrium. ^{1}H NMR spectra of isolated fractions 4 and 5 exhibit a series of signals ranging from 7.7–7.0 ppm, with relative intensities that do not permit a straightforward interpretation. Raman solution spectra show bands characteristic of HT-N^1, HT-N^3 and T-N^1, N^3. Elemental analyses of freeze-dried samples of 4 and 5 give Pt:C:N values that indicate the Pt:thymine ratio to be n.(n + 1) with $5 \geqslant n \geqslant 2$. Therefore it is feasible that fractions 4 and 5 contain complexes of the kind

$$HT(NH_3)_2Pt[-T-Pt(NH_3)_2]_x-T-Pt(NH_3)_2HT \qquad 0 \leqslant x \leqslant 3$$

with bridging T and terminal HT ligands. In support of this interpretation it has to be noted that the Raman band typical of T-N^1, N^3 bridging is not detected in any of the other fractions. Moreover, in the solid state IR spectra of fractions 4 and 5, intense bands are observed at 1505 cm^{-1} at a position where complex *8* exhibits its most intense absorption and where for the two other dianion complexes *6* and *7* are strong bands found.

No charged complexes are isolated from the reaction mixture using HPLC. As seen for the charged complexes *4*, *5* and *8*, their retention times are close to that of KNO_3. However, fraction 1 definitely does not contain any Pt species, in agreement with quantitative measurements proving all Pt species to be in fractions 2–7.

The influence of the reaction time on the product distribution under otherwise fixed experimental conditions was studied using analytical HPLC. After 1 h reaction time at 90 °C, the distribution of fractions 7, 6, 2 (4 + 5) was 10:5:3:1. With prolonged reaction times, the yields of (4 + 5) increase at the expense of 2 and 6. Because of precipitation of 11 (fraction 7), no accurate data are available for this compound. With reaction times shorter than 1 h, formation of ‘thymine blue’ is observed, when the pH of the reaction mixture is lowered to 6. This probably is a consequence of reaction of thyminato complexes with still available *cis*-$[Pt(NH_3)_2OH]_2^{2+}$ [46]. With *trans*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ instead of the corresponding *cis*-complex, reaction with HT under identical experimental conditions gave complex *14* in more than 80% yield with no signs of any other neutral complex (HPLC).

trans-*Pt(NH$_3$)$_2$(HT-N^1)(HT-N^3)·2H$_2$O*, 14

The Raman solid state spectrum of *14* exhibits bands typical of both N1 and N3 coordination of HT, *e.g.* at 769 and 791 cm^{-1}. As expected, the IR spectrum of 14 does not differ markedly from that of the *cis*- isomer *12*. The same is true for the UV spectrum: HT-N^1, 294 nm, ϵ = 10700; HT-N^3; 273 nm, ϵ = 7400.

Reaction of HT with cis-*Pt(N(CH$_3$)$_3$)$_2^{2+}$*

With the exceptions of the *cis*- compounds *12* and *13*, we observed N3 coordination of HT only with Pt species carrying two NH_3 groups in *trans* positions each, *e.g.* in *2*, *5* and *14*. This suggested some influence of hydrogen bonding between the HT ligand and the NH_3 neighbours on the coordination behaviour of thymine. Similar hydrogen bonding interactions have been previously suggested to be of importance for metal binding to N1 substituted thymine [47], and hydrogen bonding between the exocyclic oxygens of uridine and NH_3 and H_2O ligands of *cis*-$Pt(NH_3)_2H_2O^{2+}$ [48]. In order to test this hypothesis in the case of HT complexation, reaction with *trans*-$Pt(N(CH_3)_3)^{2+}$ was studied. By substituting the protons of NH_3 for CH_3 groups, hydrogen bonding interactions with the heterocyclic ligand should be minimal

trans-*Pt(N(CH$_3$)$_3$)$_2$(HT-N^1)Cl*, 15

Reaction of *trans*-$Pt(N(CH_3)_3)_2Cl(DMF)^+$ with HT in DMF gives predominantly the N1 coordinated complex *15*, whereas *trans*-$Pt(NH_3)_2Cl(DMF)^+$, under identical conditions, gives the N3 product *3* in considerably higher yield than the N1 product (64% *versus* 23%). N1 binding of HT in *15* is evident from IR, Raman and UV spectroscopy. For example, the IR spectrum shows bands at 1635 vs and 1050 cm^{-1}, s, with no intense band around 1550 cm^{-1}. The νPt–Cl occurs at 335 cm^{-1}. The UV maximum at 293 nm (ϵ = 8800) is close to those of other N1 complexes mentioned above.

Factors Influencing Coordination Sites

Solvent

With the two thymine monoanions being present roughly in a 1.1 ratio in aqueous solution at room temperature, metal complex formation might be expected to lead to both N1 and N3 coordination products at the same ratio. This is indeed observed with the reaction of uracil and $[(NH_3)_3Pt(H_2O)]^{2+}$ at 90–100 °C [24]. It is, however, not the case with the thymine complexes. For example, reaction of *cis*-$Pt(NH_3)_2(H_2O)^{2+}$ with excess HT does not give a 1:2:1 distribution of (HT-N^1)$_2$, (HT-N^1)(HT-N^3),

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*K′ = $(t_R - t_o)/t_o$ with t_R = retention time, t_o = dead time.

(HT-N^3)$_2$ products but one of at least 2:1:0.2. Also, reaction of *trans*-Pt(NH$_3$)$_2$(H$_2$O)$^{2+}$ with HT essentially gives a single species with one HT bound through N^1, the second one bound through N^3. With reactions carried out in DMF, HT-N^1 complex formation should be favoured since the N1 deprotonated ligand greatly exceeds the N3 deprotonated one. This indeed holds for formation of *cis*-Pt(NH$_3$)$_2$-(HT-N^1)Cl, *1*, but it does not for the corresponding *trans* complex. There the ratio of N3:N1 product is 2.7:1.

pH

With the uracil ligands, it had been previously noticed that the pH of aqueous solutions has a strong effect on the product distribution. For example, high pH favours N1 platinum coordination, whereas low pH favours N3 binding [27]. This is also true for the thymine ligands. As deduced from ^{1}H NMR spectra, reaction of [(NH$_3$)$_3$Pt(D$_2$O)]$^{2+}$ and HT (1:1, 60 °C, pD dropping from originally 5.6 to 3.4 after 3 h), almost exclusively gives the N3 product. Reaction at 90 °C yields two more products, (HT-N^1), 18%, and (T-N^1, N^3), 12%, but (HT-N^3) remains the preferred species (70%). Alkaline conditions (pD = 10.5), as obtained by application of a threefold excess of HT over Pt, increase the amount of the (HT-N^1) product to 50%.

Solubility

Greatly differing solubilities of the tautomer complexes certainly strongly affect the product distribution by shifting the equilibrium towards the most insoluble compound. It is suspected that at least in two instances – reaction of *cis*-Pt(NH$_3$)$_2$-(H$_2$O)$_2^{2+}$ with 4 HT, leading to the (HT-N^1)$_2$ product in high yield, and reaction of *trans*-Pt(NH$_3$)$_2$(H$_2$O)$_2^{2+}$ with 4 HT which yields mainly the mixed (HT-N^1)-(HT-N^3) product – the very low solubilities of these compounds is *the* reason why they are formed preferentially.

Reaction Time and Bridge Formation

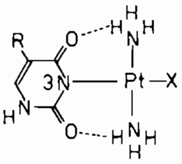
There appears to be a dependence of the product distribution from the reaction time, as suggested by the following findings:

– Reaction of [(NH$_3$)$_3$Pt(D$_2$O)]$^{2+}$ with HT (pD dropping, 90 °C) gives the (HT-N^3) product first, and (HT-N^1) and (T-N^1, N^3) products at a later stage only. This suggests a kinetic preference for the N3 product in this system.

– Variation of the reaction time in the *cis*-Pt-(NH$_3$)$_2$(H$_2$O)$_2^{2+}$/HT (1:4) leads to changes in the product distribution (*cf.* HPLC results). Again, increasing reaction times favour dianion bridge formation. This also has been verified using Raman spectroscopy. When following the intensity of the 797 cm^{-1} band (HT-N^3) and taking the ν_1NO$_3$ band at 1049 cm^{-1} as internal standard, one finds that under the experimental conditions (50 °C, 4 HT per Pt) a maximum of N3 coordination is reached after 30 h. After a phase of relatively constant intensity (150 h), N3 coordination diminishes with $\tau_{0.5} \cong 23 \pm 7$ d. At the same time a new band grows at 803 cm^{-1}, indicative of (T-N^1, N^3).

Other Ligands, Intracomplex Hydrogen Bonding

As mentioned above, favourable hydrogen bonding interactions between the exocyclic oxygens of the thymine anion and two NH$_3$ ligands *trans* to each other (and both *cis* relative to HT, respectively) at the Pt appear to contribute considerably to a preferential coordination of the N3 tautomer.



Our earlier results on the preferred binding of deprotonated uracil via its N3 atom at low pH to give *cis*-Pt(NH$_3$)$_2$(HU-N^3)(H$_2$O)$^+$ might be rationalized in a similar way by assuming hydrogen bonding with adjacent NH$_3$ and H$_2$O ligands. The decrease in N3 coordination products at higher pH might then be attributed to differences in hydrogen bonding properties of H$_2$O and OH ligands, with H$_2$O acting as H donor and OH acting essentially as H acceptor. Although this concept may contribute to the observed pH-dependent changes in coordination behaviour, it almost certainly does not govern it. Otherwise no N1 product should be expected with (NH$_3$)$_3$Pt^{2+}, for example, and this is in clear contrast to experimental findings both with uracil and thymine ligands.

Acknowledgements

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