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Structural study of amorphous platinum 5-fluorouridine green sulfate

Veli Eteläniemi,*[a] Ritva Serimaa,[a] Tarja Laitalainen[b] and Timo Paakkari[b]

[a] *Department of Physics, PO Box 9, FIN-00014, University of Helsinki, Finland*
[b] *Department of Chemistry, PO Box 55, FIN-00014, University of Helsinki, Finland*

Amorphous platinum 5-fluorouridine green sulfate was studied by means of anomalous wide angle X-ray scattering. Experiments were made with synchrotron radiation in the vicinity of the platinum L_{III} absorption edge. The Pt · · · Pt distances of 3 and 5.4 Å were determined. The refinements suggest that the sample is a mixture of di- and mono-nuclear platinum units.

1 Introduction

Amorphous platinum pyrimidine blues discovered by Rosenberg[1] and co-workers and afterwards modified to give selectively platinum pyrimidine greens[2,3] are of interest due to their antitumor activity[4–12] and rich phenomenology,[13–16] the detailed reference coverage of the field appearing in reviews.[17–20] The present knowledge about the correlation between the structure and the chemical nature of the amorphous platinum blues is largely based on the studies of crystalline platinum pyrimidine complexes,[17,21–23] the breakthrough being the crystal structure determination of tetranuclear platinum *α*-pyridone blue.[24] Studies on amorphous platinum nucleoside (modified nucleosides) complexes in the solid state have been carried out by extended X-ray absorption fine structure (EXAFS),[25,26] wide angle X-ray scattering (WAXS),[27–31] anomalous wide angle X-ray scattering (AWAXS),[32,33] small angle X-ray scattering (SAXS)[34] and in solution by SAXS,[3,30,31,35] UV/VIS spectroscopy[36–38] and ^{195}Pt, ^{15}N and ^{13}C NMR spectroscopy.[37,39,40]

Recently the structure of platinum uridine green sulfate was studied in the solid state by AWAXS and EXAFS methods. The studies showed that it is a mixture of di- and mono-nuclear platinum complexes.[33] In this AWAXS study the research is continued by studying the effects of substitution of the ligand on the average platinum nuclearity in the solid state. 5-Fluorouridine[41] and its derivatives[42] are cytotoxic. The synthesis and SAXS study of several aqueous solutions of platinum greens, including 5-fluorouridine green sulfate, have been previously published.[3] Although the latter is green, its elemental composition resembles more closely that of platinum uridine blue sulfate than platinum uridine green sulfate. The results of this AWAXS study are compared with those obtained for platinum uridine green.[33]

2 Experimental

Platinum 5-fluorouridine green sulfate

A 0.1 M solution of *cis*-diamminediaquaplatinum(II) sulfate, $[Pt(NH_3)_2(H_2O)_2]SO_4$, was made by the method of Dhara[43] from K_2PtCl_4 obtained from Aldrich. 5-Fluorouridine was obtained from Sigma, acetone from LAB-SCAN and Fractogel TSK HW-50(S) from Merck. Microanalysis was performed by H. Kolbe, Mikroanalytisches Laboratorium, Germany. The VIS spectra were recorded on a Schimadzu UV-200 double beam spectrometer and IR spectra on a Bio-Rad FTS-7 FTIR spectrometer.

A reaction mixture of $[Pt(NH_3)_2(H_2O)_2]SO_4$ (31.4 cm^3, 3.14 mmol), 5-fluorouridine (0.8242 g, 3.14 mmol) and hydrogen peroxide (57.8 cm^3, 31.3%) was heated in an oil-bath at 54 °C for 7 h under an argon atmosphere to give a pale green solution and further at room temperature for 3 h. The product was purified by gel filtration and the eluate allowed to drop directly into acetone (300 cm^3). The precipitation was completed at 8 °C during 12 h to give a fine and sticky product. The solution was decanted off and fresh acetone added to loosen the sticky product. Then the product was filtered off with a sintered glass funnel (G4), washed with acetone and dried under vacuum (2 mmHg, *ca.* 266 Pa) for 10 h to give a green coarse powder, 1.0701 g (62% when based on Pt) (Found: C, 18.47; H, 3.55; F, 2.41; N, 9.45; S, 3.79; Pt, 35.54). VIS(H_2O): λ_{max} 777 nm. IR(KBr): 1652 cm^{-1}

AWAXS measurements

The AWAXS measurements were carried out at the Stanford Synchrotron Radiation Laboratory on the wiggler beamline 4–3 utilizing a Si(111) double-crystal incident beam monochromator and a two-circle diffractometer in symmetrical transmission mode. The parasitic scattering was reduced using helium paths but the sample itself was at normal atmosphere pressure. The scattered intensity was measured with a high purity germanium solid state detector and the primary beam intensity was monitored by a scintillation counter. The intensity curves were measured with equidistant steps 0.05 Å^{-1} in k scale [$k = (4\pi/\lambda)\sin\theta$ is the magnitude of the scattering vector, 2θ the scattering angle, and λ the wavelength] in three parts increasing the accumulation time to collect at each point 100 000 counts at least. The count rate was always less than 10 000 counts s^{-1}. Each scan took about 7 h. The employed photon energies, 10.6 and 11.5 keV (eV ≈ 1.6×10^{-19} J), were below the platinum L_{III} absorption edge (11.564 keV). One measurement was performed without a sample to take parasitic scattering into account. The thickness of the flat sample was 0.024 cm, the density 1.9 g cm^{-3} and the atomic density 0.09 atom Å^{-3}.

The experimental intensity curves were corrected for absorption and normalized to absolute scale with the large angle method. Normalization involved determined and subtraction of fluorescence and subtraction of the calculated Compton intensity.[44–46] The energy-independent atomic form factors and incoherent scattering functions were taken from ref. 47. Anomalous scattering factors used in the data analysis were evaluated from experimental X-ray absorption coefficients using the Kramers–Kronig dispersion relation: $f' = -12.76$ (-7.52) and $f'' = 3.82$ (4.42) at 11.5 (10.6) keV.

3 Theoretical background

The structure of an amorphous material is described in terms of partial radial distribution functions $4\pi r^2\rho_{\alpha\beta}(r)$, which represent the density of β-type of atoms at the distance r from an average α-type of atom. These functions yield structural parameters, atomic distances and co-ordination numbers, which can be found out experimentally by WAXS, AWAXS and EXAFS methods.

In WAXS studies the scattered intensity $I(E,k)$ is measured at fixed energy E as a function of the magnitude of the scattering vector k. It is a weighted sum of partial structure factors $S_{\alpha\beta}(k)$, related by Fourier transform to the partial radial distribution functions. In AWAXS studies the intensity is measured using two or more photon energies E in the vicinity of the absorption edge of the chosen element. Near the absorption edge the anomalous scattering factor f' of the element varies more than those of the other elements. Therefore the difference of two intensity curves is approximately a weighted sum of only partial structure factors that involve the chosen element.[44]

The treatment of WAXS data resembles XAFS data analysis. The coherently scattered intensity I is extracted from the measured intensity curve and the function $\langle f^2\rangle$ is subtracted from the intensity curve I to obtain the total structure factor TSF(k), eqn. (1). In AWAXS data analysis the differential

$$\mathrm{TSF}(k) = [I(E,k) - \langle f^2(E,k)\rangle]/\langle f(E,k)\rangle^2 \qquad (1)$$

structure factor $\mathrm{DSF}_{ij}(k)$ is calculated from two intensity curves as in eqn. (2) where $f(E_i,k)$ are the scattering factors at the energies E_i, $i = 1,2,\ldots$.

$$\mathrm{DSF}_{ij}(k) = \frac{I(E_i,k) - I(E_j,k) - (\langle f(E_i,k)^2\rangle - \langle f(E_j,k)^2\rangle)}{\langle f(E_i,k)\rangle^2 - \langle f(E_j,k)\rangle^2} \qquad (2)$$

From the structure factors TSF and DSF one can evaluate the total and differential radial distribution functions (RDF, DDF) as in eqns. (3) and (4) where ρ_0 is the average atomic

$$\mathrm{RDF}(r) = 4\pi r^2\rho_0 + \frac{2r}{\pi}\int_0^\infty \mathrm{TSF}(k)k\sin kr\,dk \qquad (3)$$

$$\mathrm{DDF}(r) = 4\pi r^2\rho_{0\beta} + \frac{2r}{\pi}\int_0^\infty \mathrm{DSF}(k)k\sin kr\,dk \qquad (4)$$

density and $\rho_{0\beta}$ the average density of the β component in the sample. Here we shall discuss also the functions (5) and (6).

$$\Delta\mathrm{RDF}(r) = \mathrm{RDF}(r) - 4\pi r^2\rho_0 \qquad (5)$$

$$\Delta\mathrm{DDF}(r) = \mathrm{DDF}(r) - 4\pi r^2\rho_{0\beta} \qquad (5)$$

4 Results

The experimental coherent intensity I and the function $\langle f^2\rangle$ are shown in Fig. 1 and the functions ΔRDF and ΔDDF are shown in Fig. 2(a) and 2(b) by solid lines. The positions of the most pronounced maxima of ΔRDF and ΔDDF are given in Table 1 along with the selected results for platinum uridine green sulfate.[33] The precision of the positions of the maxima is about ±0.03 Å. It is noted that the true atomic distances may differ from these positions due to overlapping of the peaks and termination ripples in the Fourier transformation. The accuracies of the Pt $\cdots$ Pt distances to be discussed is therefore estimated to be 0.1 Å. The average co-ordination numbers at 2.1 and 3 Å were determined as the areas of the maxima of the RDF and the DDF. The atomic density ρ was 0.09 atom Å^{-3}. The precision of the co-ordination numbers remains around 15% because the maxima are not well resolved, which is partly due to small k range available.

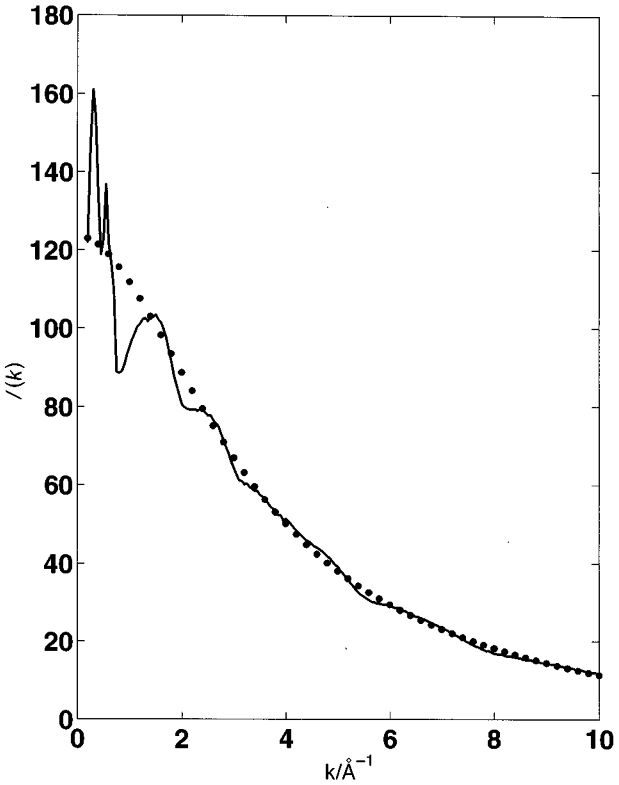


Fig. 1 The experimental coherent WAXS intensity (solid line) and the function $\langle f^2(E,k)\rangle$ (dotted line) of platinum 5-fluorouridine green sulfate as a function of k (Å^{-1}) at 11.5 keV

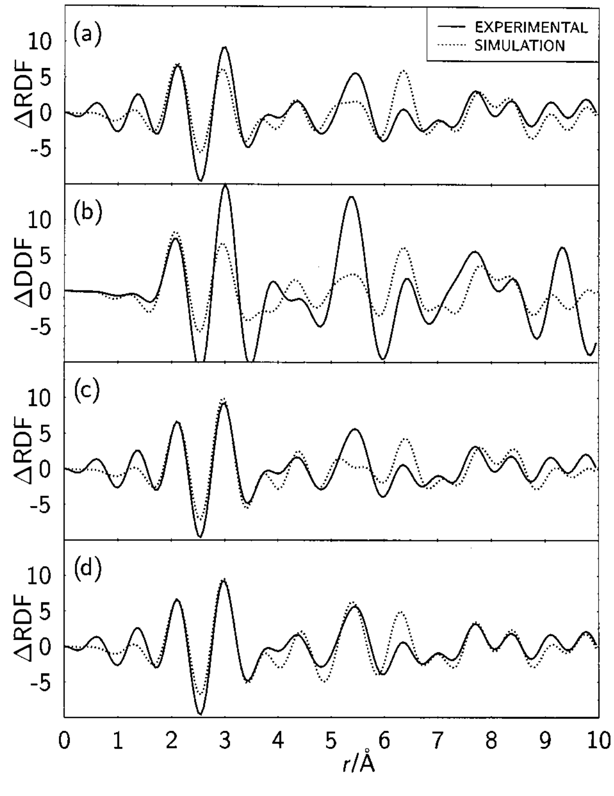


Fig. 2 Calculated ΔRDF for a scattering unit consisting of (a) a mononuclear platinum unit, (c) mono- and di-nuclear platinum units and (d) mono- and di-nuclear platinum units where the distance of mononuclear Pt units is 5.4 Å. (b) Calculated ΔDDF for the case (a). The experimental curves are shown by solid lines. See text for details

The radial distribution function RDF is not species specific, since it is calculated from the TSF, which is a weighted sum of all partial structure factors. The DDF is calculated from the DSF, which is a weighted sum of only those partial structure factors which involve the chosen element,[44] here Pt, and only the distances between Pt atoms and the light elements (H, C, N, O, F, S) contribute to it. The fact that the partial radial distribution functions involving Pt have different weights in the RDF

Table 1 The positions of the most prominent maxima (in Å) of the ΔRDF and ΔDDF and the average co-ordination numbers (CN) at 2 and 3 Å. The CNs were determined as areas of the maxima of the RDF and the DDF

Platinum 5-fluorouridine green				Platinum uridine green[33]			
ΔRDF		ΔDDF		ΔRDF		ΔDDF	
Distance	CN	Distance	CN	Distance	CN	Distance	CN
1.35							
2.09	4.6	2.05	6	2.0	4.8	2.0	6
2.99	9.5	3.00	15	3.03	10	3.0	14
4.28		3.89		4.2		4.0	
5.44		5.38		5.1		4.9	
6.3		6.4		5.6		5.6	
7.6		7.6		7.6		7.3	

and DDF can be utilized in interpretation of the AWAXS results. The first maximum at 1.4 Å arises from C–C, C–N, C–O and S–O distances and it diminished in ΔDDF whereas the maximum at 2.1 Å, which is not diminished in ΔDDF, arises mainly from Pt–N and Pt–O distances. Moreover, the pronounced maxima at 3 and 5.4 Å are higher in the ΔDDF than in the ΔRDF and we propose that they arise from Pt···Pt distances. Since the maxima at 4 Å are larger in the ΔRDF than in the ΔDDF, they cannot arise from Pt···Pt distances.

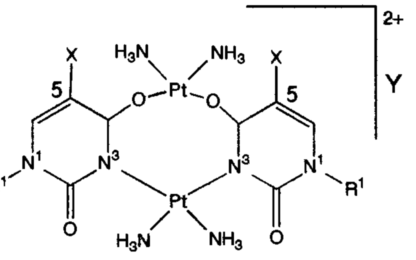
5 Discussion

To interpret the experimental results for platinum 5-fluorouridine green sulfate, model diplatinum(II) units, **2**,**4** and platinum(II) units **5**,**6** were constructed. The models **2**,**4** are both based on crystalline dinuclear *cis*-$[Pt(NH_3)_2(mura)]_2[NO_3]_2$ (mura = 1-methyluracil) complexes: head-to-head **1**[48] and head-to-tail **3**,[49] where the ligand represents the closest analog available to 5-fluorouridine. The structure of an analog of **5**,**6** with 1-methyluracil has not been determined and the *cis*-$[Pt(NH_3)_2(mura)_2]^{2+}$ [50] was not considered, since the elemental analysis for platinum 5-fluorouridine green sulfate excludes a ligand : Pt ratio larger than 1 : 1. The closest analogs available to build **5**,**6** are *cis*-$[Pt(NH_3)_2(mcyt)(H_2O)][NO_3]_2{\cdot}H_2O$[51] (mcyt = 1-methylcytosine) and aqua[1,1-bis(aminomethyl)cyclohexane]-sulfatoplatinum(II) monohydrate.[52]

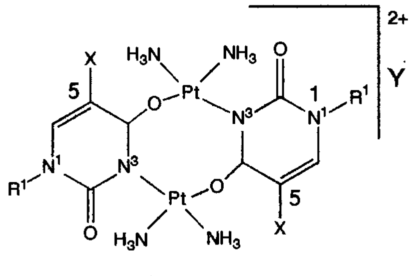
Since the crystal structure of 5-fluorouridine (fura) has not been determined, the conformation and the structure parameters of the ligand for the models **2**, **4**, **5** and **6** were taken from the crystal structure of 5-chlorouridine[53] by changing the C–Cl bond length for the C–F bond length. Then the positions of *cis*-$(NH_3)_2Pt^{II}$ units were varied with respect to the ligands to fit ΔRDFs in accord with the experimental one.

The average co-ordination number at 3 Å depends on the platinum nuclearity and gives us a rough estimate of the Pt···Pt co-ordination number at this distance. The Pt···Pt co-ordination number has been determined using three different methods. The estimated areas under the maxima of the DDF and RDF at 3 Å are presented in Table 1. The ratio of the areas is 1.5 ± 0.3 : 1. The same ratio is also estimated using the models **1**–**6**. The number of Pt···N, Pt···O, and Pt···C distances around 3 Å is about five per platinum. Thus, for the mononuclear platinum complexes **5**,**6** the ratio is 1.0 : 1 and for the dinuclear complexes **1**–**4** it is 1.7 : 1. The experimental ratio of 1.5 : 1 suggests that the Pt···Pt co-ordination number is in the range 0.5–0.8.

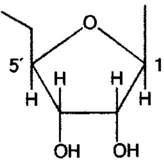
The co-ordination number estimated from the areas of the maxima of the RDF and DDF depends on the applied atomic density. The density is not needed when the co-ordination number is estimated by fitting a model TSF to the experimental one. The model TSF is calculated using the well known Debye formula which involves the calculation of the sum $\Sigma_i\Sigma_j f_i f_j^* \sin(kr_{ij})/kr_{ij}$ where r_{ij} is the distance between atoms *i* and *j*. The first refinement was carried out by fitting three atomic distances, namely the Pt–N,O distances about 2 Å and Pt···Pt distances of 3 and 5.4 Å to the experimental TSF. When no disorder parameter was included the refinements predicted Pt···Pt co-ordination numbers of 0.6–0.7 and 0.4–0.5 at the distances of 3 and 5.4 Å, respectively. Similar refinements of AWAXS data predicted Pt···Pt co-ordination numbers of 0.5 and 0.4 at these distances. The differences in the WAXS and AWAXS results may arise from the distances that do not give any contribution to AWAXS data and from the lower precision of AWAXS data. When a disorder parameter (Debye–Waller factor) is included in the refinement of WAXS data the co-ordination number at 3 Å increases to 1.



1: X = H, R¹ = CH_3, Y = $[NO_3^-]_2$
2: X = F, R¹ = β-D-ribofuranosyl
Y = $[SO_4]^{2-}$



3: X = H, R¹ = CH_3, Y = $[NO_3^-]_2$
4: X = F, R¹ = β-D-ribofuranosyl
Y = $[SO_4]^{2-}$



β-D-ribofuranosyl-

5: $[Pt^{II}(NH_3)_2(fura)(H_2O)]\ SO_4^{2-}$
6: $[Pt^{II}(NH_3)_2(fura)(SO_4)]$

The contribution of all types of distances to the radial distribution function is estimated by fitting the calculated TSF of the models **1**–**6** to the experimental one. No disorder parameter was included in these fits. Therefore the following percentages should be understood as the minimum shares of dinuclear platinum units. Fig. 2 shows the model radial distribution functions ΔRDF (a) and ΔDDF (b) calculated by including only the intramolecular distances of the platinum 5-fluorouridine complex **5** (*i.e.* no intermolecular distances are introduced). The calculated ΔRDF disagrees with the experimental one at 3 Å and the disagreement of the calculated and experimental ΔDDF is even more pronounced. Thus we can rule out that platinum 5-fluorouridine green is a mononuclear complex. Similarly it is possible to show that the sample is not a dinuclear platinum complex though the disorder parameter is included. The agreement is improved, see Fig. 2(c) by including both mono- and di-nuclear platinum units in the model. Refinement of a mixture model which consisted of dinuclear platinum 5-fluorouridine complex **2** and a mononuclear *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ complex predicted that 60% of platinum atoms are in dinuclear and 40% in mononuclear units. When the *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ complex was replaced by the mononuclear platinum 5-fluorouridine complex **5** the fraction of Pt atoms in dinuclear complexes decreased to 0.5 because in the mononuclear complex **5** there are more Pt···O and Pt···C distances at around 3 Å than in *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$.

Now comparing the Pt···Pt co-ordination numbers determined using the three different methods we can conclude that the minimum co-ordination number is about 0.5. We do not rule out that for a disordered structure the co-ordination number could be up to one. The low X-ray energy applied here due to AWAXS studies hinders us from giving a good estimate for the disorder parameter.

5.1 Long range order

The ΔRDF has an additional maximum at 5.4 Å which is not well reproduced by the Pt···F distances in 5-fluorouridine complexes **2**, **4**, **5** and **6**. The other features in the range 1–8 Å show a reasonable agreement though the maximum at 6.3 Å of the simulated ΔRDF is too large. It arises from distances between Pt and the ribose part of 5-fluorouridine. Variation of this bond angle did not move the maximum to 5.4 Å.

The 5.4 Å maximum may arise from a Pt···Pt distance between two mononuclear or dinuclear units. For instance, Fig. 2(d) shows the ΔRDF of a mixture of platinum units **2** and **5** when the separation between part of the mononuclear units **5** was 5.4 Å. Similarly, it is possible to show that the maximum can arise from a Pt···Pt distance between two dinuclear units by varying the mutual orientation of the dinuclear units **2** to fit the Pt1···Pt1′ and Pt2···Pt2′ distances to the positions of the maxima of the experimental ΔRDF in the range 7.5–8.0 Å. Thus the peak at 5.4 Å can be assigned to intermolecular distances but that at 7.6 Å can arise from the intra- or the intermolecular distances. The fit between 4 and 6 Å is not so good as at the other distances. We have not used any extra fitting parameters, such as disorder, to improve the goodness of the fit because the origin of the peak cannot be unambiguously determined. The fact that all the features of the experimental ΔRDF cannot be reproduced by the intramolecular distances shows that there is a favoured short range order. However, this order is not so well defined as in crystalline materials. The small differences hinder us from giving any detailed information about the short range order of the platinum complexes except that the average Pt···Pt distance is 5.4 Å.

5.2 Comparison of platinum 5-fluorouridine green sulfate with platinum uridine green sulfate

We have previously proposed that platinum uridine green sulfate is a mixture of di- and mono-nuclear platinum uridine complexes and *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$.[33] In view of the WAXS studies the effects of substitution of the ligand on the average platinum nuclearity is low though it could be that the average nuclearity in platinum 5-fluorouridine green sulfate is higher. More differences were observed at intermolecular distances, namely the ΔRDF of platinum uridine green sulfate contains two maxima at 5 and at 5.6 Å whereas in platinum 5-fluorouridine green sulfate there is only one maximum at 5.4 Å, see Table 1. We propose that the dinuclear platinum units are similar in both samples and that the differences arise from the different mononuclear units and not from the different intermolecular order of dinuclear units caused by fluorine. Platinum uridine green sulfate contains *cis*-$[Pt(NH_3)_2(H_2O)_2]^{2+}$ species whereas in platinum 5-fluorouridine green sulfate the major mononuclear complexes are 5-fluorouridine complexes **5** or *cis*-diammine(5-fluorouridine) complexes **6**. This would agree with the elemental analysis results which predict a lower ligand : Pt ratio for platinum uridine (0.7 : 1) than for platinum 5-fluorouridine (0.9 : 1) green sulfate. Their S : Pt ratios were about the same (0.70 : 1 in platinum uridine green sulfate).

6 Conclusion

Two Pt···Pt distances of 3.0(1) and 5.4(1) Å were determined from AWAXS data of platinum 5-fluorouridine green sulfate. The Pt···Pt co-ordination number at 3 Å was estimated from the area under the maxima in RDF and DDF, and from refinements that include only the Pt···Pt distance or by using plausible molecular models. Each analysis predicted a similar co-ordination number and thus we rule out that platinum 5-fluorouridine green sulfate contains only mononuclear units. The fraction of Pt atoms in dinuclear units was estimated as 0.5–1.0. We propose that platinum 5-fluorouridine green sulfate is a mixture of major dinuclear complexes similar to **2** and **4** and of mononuclear complexes similar to **5** and **6**. The Pt···Pt distance of 5.4 Å is assigned to intermolecular distances.

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