Carboplatin decomposition in aqueous solution with chloride ions monitored by X-ray absorption spectroscopy

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Carboplatin aqueous solutions, with chloride ions added at different concentrations, were studied by X-ray absorption spectroscopy (XAS). The comparison of solid and solution spectra shows that carboplatin and cisplatin spectra are strongly different, and that the carboplatin ligands induce a specific structure of the spectrum, conserved in solution. Hence, it is possible to study by XAS the evolution of carboplatin in solution. This study shows that carboplatin is the major compound present in solution, even after 15 days, in neutral solutions with chloride concentration less than 9%, exposed to light or not. On the contrary, with high chloride concentrations (18%) or in acidic solutions (0.1 M HCl), the carboplatin is chlorolysed, the evolution of the solution composition can be followed by XAS and cisplatin formation is evidenced.

Cisplatin (Fig. 1) figures among the first antitumoral drugs used. It offers a wide field of therapeutic applications and is quite useful, but it presents a great nephrotoxicity. Because of this, some new molecules have been synthesised. A particularly used one is carboplatin (Fig. 1), which presents the same field of effects but is much less toxic. However, the stability of this compound in solutions and bags for injections is questioned. In particular, if the solution contains some chloride anions, as may be the case during drug administration, chlorolysis of the carboplatin into cisplatin could occur.

The question of the stability of the carboplatin has already been approached, using techniques like HPLC or electrophoresis.[1–6] These different studies showed that carboplatin slowly decomposes into a family of different species; thus, the injectable solutions must be prepared without chloride anions. The nature of the different degradation products is not well defined, and seems to depend on the light exposure of the solution.[5] The detection methods used in these studies presented the drawback of being indirect methods of studying the platinum environment, and in particular the HPLC column itself may lead to some of the observed degradation products. NMR spectroscopy gives direct information about the platinum co-ordination; it has been used to investigate similar platinum complexes either in the solid state (for instance, by ^{13}C experiments where the authors followed the flexibility of a carboplatin derivative)[7] or in solution by ^{195}Pt experiments where cisplatin and transplatin hydrolysis was analysed before its interaction with DNA.[8] This last NMR technique presents the disadvantage of needing a special enrichment of the sample in ^{195}Pt and so prevents any work on the drug itself.

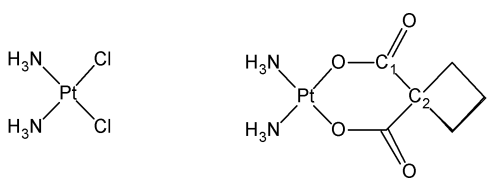

Fig. 1 Formulas of cisplatin (left) and carboplatin (right).

For the title study, we have applied X-ray absorption spectroscopy (XAS), which is a technique that probes specifically the local environment of the platinum ion and that may be applied directly on the carboplatin drug solutions as used in pharmaceutical applications. During the experiments here presented, and taking into account the sensitivity of this technique, the information obtained will concern platinum complexes present in the acid solutions as major components.

We first studied the solid forms of carboplatin and cisplatin, to quantify the differences between their EXAFS features and compare them with their solutions. This preliminary work showed that EXAFS spectra present, as expected, strong differences between the two compounds. We then prepared several aqueous solutions of carboplatin, under diverse pH conditions and chloride concentrations, and we followed the evolution of these solutions by XAS. Among these, the spectra of the hydrochloric acid solutions showed a quick evolution from the carboplatin spectrum towards the cisplatin one.

The aim of this work is to determine under which physical and chemical conditions carboplatin can lead to cisplatin, and

to check the sensitivity of the XAS method for this kind of system. During further studies, we will study these solutions under the well-defined conditions of therapeutic drug conservation and administration.

Experimental

Sample preparation

The solid samples were prepared as pellets. The pellets were prepared so that the platinum concentration leads to an edge jump of about unity at the platinum L_{III} edge, and completed to 60 mg with cellulose. Cisplatin was purchased from Sigma Chemicals; the carboplatin used was obtained from a pharmaceutical preparation from Bristol–Myers Squibb ("paraplatine", ref. 331 720.0).

We also prepared a saturated aqueous solution of cisplatin, by adding solid cisplatin to water until no more dissolution occurred, and filtering.

The details of the different carboplatin solutions used is presented in Tables 1 (neutral solutions) and 2 (acidic solutions). Each solution was prepared from pharmaceutical ready-to-inject paraplatine (10 mg mL^{-1} of carboplatin solution, which gives nearly 2.7×10^{-2} mol L^{-1} of platinum). For the XAS measurements, 0.1 mL of each solution was placed in a Teflon cell, closed with Kapton. For samples stored in the dark, the cell was also protected from light with an aluminium foil, nearly transparent to X-rays around the platinum L_{III} edge.

Solutions S_1 to S_5 (aged solutions) were prepared 15 days in advance, so that eventual degradation products would be in sufficient concentration to be detected by XAS. The other solutions were prepared just before the measurements.

After 15 days, the two 18% NaCl solutions (S_{5d} and S_{5l}) gave an important yellow precipitate. This precipitate was isolated by centrifugation, dried for three days in a drying oven and pressed into a pellet.

The acidic solutions quickly lead to a similar yellow precipitate, within the experimental time.

Table 1 Composition of the different neutral carboplatin solutions studied. All were made by adding 4 mL of paraplatine to the indicated mass of solid NaCl

Solution	NaCl/mg	Storage condition
S_{1l}	0 (0%)	Light
S_{1d}	0 (0%)	Dark
S_{2l}	13.1 (0.45%)	Light
S_{2d}	13.1 (0.45%)	Dark
S_{3l}	36.3 (0.9%)	Light
S_{3d}	36.3 (0.9%)	Dark
S_{4l}	73.3 (1.8%)	Light
S_{4d}	73.3 (1.8%)	Dark
S_{5l}	880 (18%)	Light
S_{5d}	880 (18%)	Dark
S_6	0 (0%)	Direct usage
S_7	36.3 (0.9%)	Direct usage
S_8	234 (5.8%; 1 M)	Direct usage

Table 2 Composition of the different acidic carboplatin solutions studied. All were made by adding the indicated volume of HCl to 1 mL of paraplatine

Solution	HCl/mL	Initial [HCl]/mol L^{-1}	Final [Cl^-]/mol L^{-1}
S_9	0.0254	1.97	0.05
S_{10}	0.0508	1.97	0.1
S_{11}	0.254	1.97	0.4
S_{12}	0.1	11.5	1

XAS measurements

All the spectra, except the cisplatin solution, were recorded at LURE (Orsay, France), on the EXAFS 13 experimental station (beamline D41, DCI storage ring, with a current of about 250 mA), at the L_{III} platinum edge (11 564 eV). A Si(1 1 1) double-crystal monochromator was used; the energy was calibrated using the L_{III} edge of a gold foil. At this energy, and on this storage ring, there is no need to eliminate harmonics. The cisplatin solution was studied on the EXAFS 2 experimental station of LURE. On this station, it was not possible to use the Si(1 1 1) monochromator, and we used a Si(3 1 1) crystal; the calibration was done with a gold foil, and no harmonic rejection was needed.

The cisplatin solution was studied by fluorescence mode, because of the dilution of the sample. The detector was a 7-elements Ge detector from Eurisys Mesures, placed at about 5 cm from the sample to avoid detector saturation (we observed less than 5% of dead time). The L_{III} fluorescence line was selected by electronic filters (SCA). This cisplatin solution was also studied in transmission mode, under the same conditions as the carboplatin solutions (see below), to check that the contribution of this low solubility cisplatin solution can be neglected during a transmission mode spectrum.

All the other samples were exclusively studied in the transmission mode, the X-ray intensities being detected by two ionisation chambers filled with air. Measurements where made from 11 400 to 12 600 eV with a step of 3 eV and a counting time of 1 s per point. The resulting recording time was about 20 min for each spectrum.

For the reference samples (solids) and the aged solutions (S_1 to S_5), for which no evolution was expected, two spectra were acquired.

For the fresh solutions (S_6 to S_{12}) expected to evolve, the spectra were recorded repeatedly during either at least half a day or until we got a stable absorption spectrum.

XAS analysis

The XAS analysis has been performed using a classical model with LASE (Logiciel d'Analyse des Spectres EXAFS), developed by one of us[9] and offering new tools for error estimation. When possible (solid samples, solutions showing no evolution within the experiment time), averages where made at the very beginning of the data treatment, on the experimental absorption coefficient. Error bars were computed simultaneously and propagated all along the data analysis, including Fourier filtering, according to the model developed by some of us.[10]

All the data treatment used a k^2 weighting of the EXAFS oscillations (k is the wave vector), to compensate for the decrease of the oscillations as k increases. The conversion to R-space (R is the inter-atomic distance) was achieved by using a Fourier transformation (FT) with a Kaiser–Bessel function as the windowing function, between 1 and 14 $Å^{-1}$. All the FT figures presented in this paper are uncorrected for phase shifts and so the R distances are just apparent path lengths, smaller than the true values (even <2 Å).

As expected, strong differences are observed between the carboplatin and the cisplatin spectra. To explain these differences, we used the known structures of cisplatin[11] and carboplatin[12] to create a structural model. That model was computed using the FEFF 7.02 software.[13] We detail the new experimental spectra fitting procedure we have developed in LASE. Using the classical least-squares algorithm we minimised the sum S defined by

$$S = \frac{1}{N}\sum_{i=1}^{N}\left\{\chi_{exp}(k_i) - \sum_{j=1}^{M}\frac{N_j f_j(k_i')}{k_i' R_j^2} \times \exp\left[-2\sigma_j^2 k_i'^2 - 2\frac{R_j}{\lambda(k_i')}\right]\sin[2k_i' R_j + \phi_j(k_i')]\right\}^2$$

where N is the number of experimental points in the filtered spectrum and M is the number of shells used in the model. The electronic terms $f_j(k_i')$, $\phi_j(k_i')$ and $\lambda(k_i')$ were computed by FEFF, whereas the structural parameters were fixed (N_j) or were allowed to vary while fitting (σ_j^2 and R_j). Because of the uncertainties in the edge energy E_0 determination, one also introduces $\Delta E_0 = E_{0,\,\mathrm{exp}} - E_{0,\,\mathrm{FEFF}}$ as a fit parameter—which leads to the use of k_i' instead of k_i. The errors on the fitted values were determined with the help of a Monte–Carlo simulation included in the LASE software. These errors only account for the statistical uncertainties induced by the statistical fluctuations of the different recordings. Hence, one can obtain very small errors bars; the real uncertainties are probably somehow higher, because of systematic error effects, not taken into account in this method. On this delicate question of error estimation in EXAFS analysis our work is still in progress.

Results and discussion

We first present the results comparing the EXAFS spectra of the platinum complexes in the solid state and aqueous neutral solutions excluding chloride ions.

Carboplatin complex

Carboplatin solid. The FT of the EXAFS spectrum of solid carboplatin is reported in Fig. 2(a). We observe a narrow main peak, due to the first coordination shell, and minor peaks at greater distances. The theoretical model confirms that carboplatin's first peak FT comes from a single scattering shell, containing four light atoms like oxygen or nitrogen [as the electronic terms $f(k)$ and $\phi(k)$ are very similar for these two kinds of atom, XAS cannot distinguish them] at an average distance of 2.0279 ± 0.0002 Å. This result is coherent with the known structure of carboplatin, in which platinum is linked to two nitrogen and two oxygen atoms located at 2.021 ± 0.008 and 2.025 ± 0.006 Å, respectively.[12] The complete results are given in Table 3. The very small value of the error bar results from the small statistical uncertainty and probably underestimates the real error because of systematic errors; the same effect arises for the other results presented in this article.

To explain the other features of the EXAFS spectrum, we started with a simple model of multiple scattering in the first co-ordination shell of the platinum atom: a planar square with two oxygen and two nitrogen atoms. The FEFF computations show that, among the diverse multiple scattering paths, the most important is the $Pt \rightarrow N_1 \rightarrow Pt \rightarrow O_2 \rightarrow Pt$ path, the nitrogen and oxygen atoms being diagonally opposed. The second most important path is the $Pt \rightarrow N_1 \rightarrow O_2 \rightarrow Pt$ path. All other paths are much less important and can be neglected. This result is coherent with the well-known effect of atom alignment being related to the increased contribution of multiple scattering paths.

With the help of the crystallographic co-ordinates of carboplatin,[12] we built a quite complete model to reproduce the main features of the full spectrum of the carboplatin in its solid form. This model's results are shown in Table 4; because of the previous result, we only include the most significant multiple scattering paths. The results show that the scattering by the cyclobutanedicarboxylate atoms plays an important role. The comparison of the theoretical spectrum and the experimental spectrum is shown on Fig. 2(a).

One can note the high value for ΔE_0, close to −12 eV. This is not surprising, since the edge white line is due to a $2p \rightarrow 5d$ transition, the 5d level being around 8 eV below the ionisation energy.[14] Taking the edge energy E_0 in the white line rising necessarily leads to an incorrect E_0 value. But, since this work

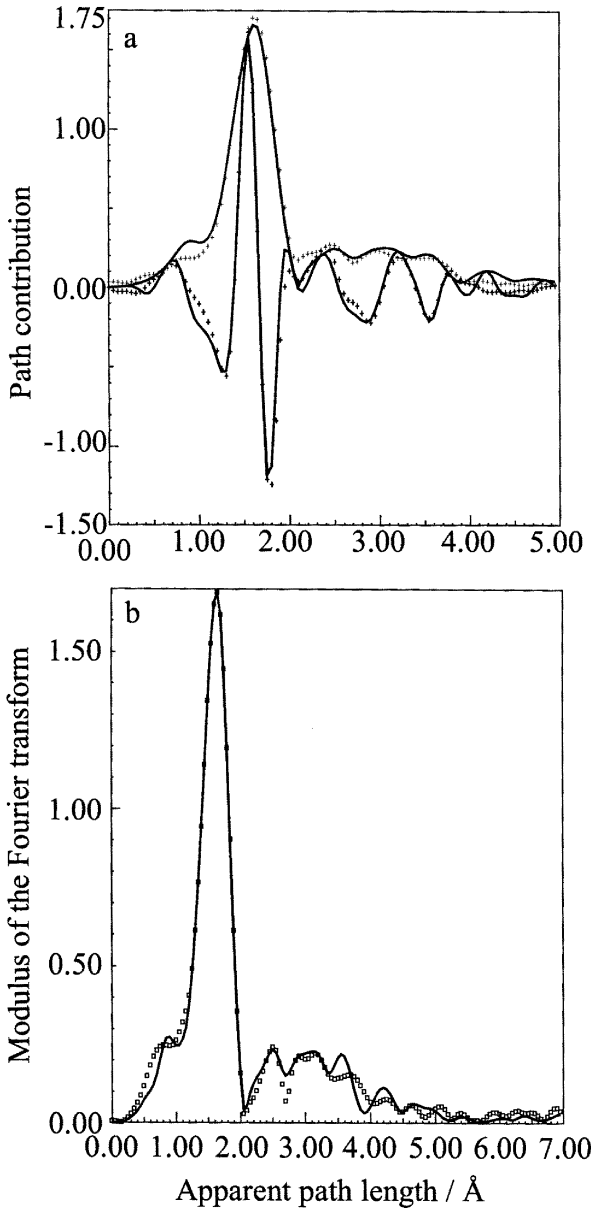

Fig. 2 (a) Comparison of the experimental (solid line) and theoretical (+++) FT (modulus and imaginary part) of the EXAFS spectrum of solid carboplatin. The main features of the FT are reproduced by the model. Some long distance contributions—probably involving the platinum atoms of neighbouring molecules—are not model. (b) Comparison of the FT (modulus) of the EXAFS spectra of carboplatin in the solid form (solid line) and in aqueous solution (squares). The spectra are nearly identical.

Table 3 Results of the fitting of the first peak of carboplatin. A single shell including two oxygen atoms and two nitrogen atoms is sufficient to model the spectrum. The final error is $S = 1.03 \times 10^{-3}$ and $\Delta E_0 = -7.98 \pm 0.04$ eV

Path	N (fixed)	R/Å	$\sigma^2 \times 10^3$/Å^2
Pt → N/O → Pt	4	2.0279 ± 0.0002	1.91 ± 0.02

Table 4 Results of the fitting of the complete spectrum of carboplatin. The final error is $S = 0.012$; $\Delta E_0 = -12.3 \pm 0.2$ eV

Path	N (fixed)	R/Å	$\sigma^2 \times 10^3$/Å^2
Pt → N/O → Pt	4	2.028 ± 0.002	2.00 ± 0.14
$Pt \rightarrow C_1 \rightarrow Pt$	2	2.94 ± 0.06	20 ± 60
$Pt \rightarrow C_2 \rightarrow Pt$	1	3.16 ± 0.14	80 ± 18
$Pt \rightarrow N_1 \rightarrow Pt \rightarrow O_2 \rightarrow Pt$	1	4.067 ± 0.006	2.5 ± 1.4

compares the XAS spectra of two compounds and since one can expect the same effect in the cisplatin spectrum, it is important to have a precise definition of the edge energy, and the common definition used in this work is more convenient.

Carboplatin aqueous neutral solution. The spectrum of the fresh aqueous solution of carboplatin (solution S_6) did not show any significant change from the first spectrum to the last one (with 9 h delay between them). Hence, we averaged all the spectra and compared the average EXAFS oscillations and Fourier transform to the solid carboplatin spectrum [Fig. 2(b)]. This comparison shows that, under these conditions and the stated time interval, carboplatin is stable in aqueous solution, at the detection level of XAS.

One can note that not only the first peak, but also the weaker second peak, is conserved in solution. That means that the complex is also well-defined in solution. This result is confirmed by the comparison of the model obtained for the solid and the spectrum obtained from the solution [Fig. 3(a) and (b) respectively in k and R spaces]. This shows that X-ray absorption spectroscopy is a powerful tool to study the environment of a specified atom in solution, and is not limited to the first-shell analysis.

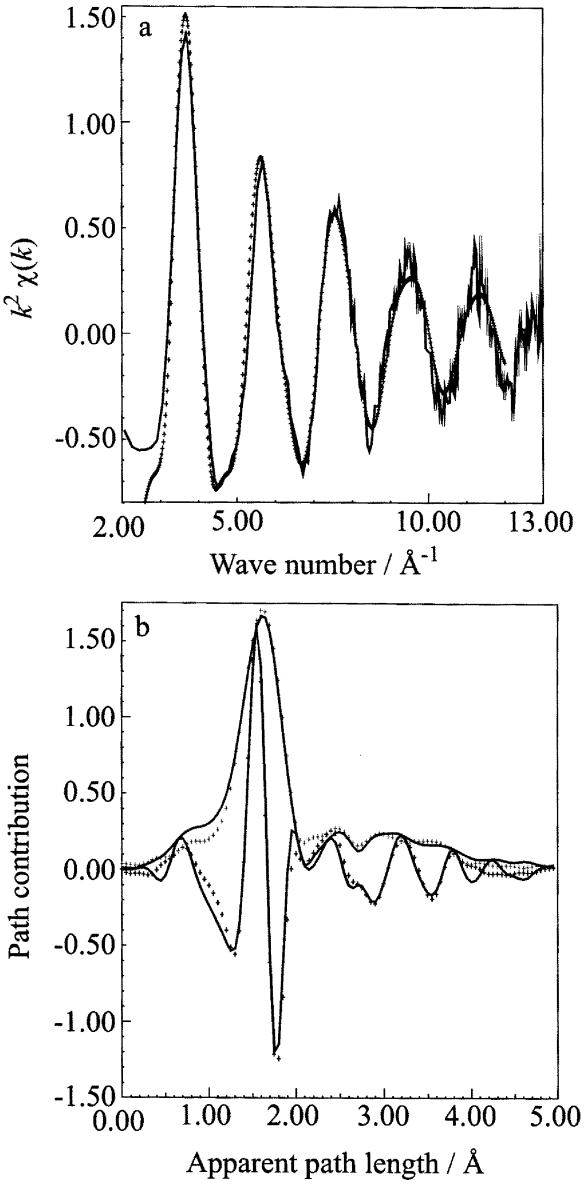

Fig. 3 Carboplatin in aqueous solution (solid line) compared with the theoretical model obtained for the solid (+++). (a) $k^2\chi(k)$, EXAFS normalised. (b) FT (modulus and imaginary part). The model is still correct.

Cisplatin complex

Cisplatin solid. The FT of the EXAFS spectrum of solid cisplatin is reported in Fig. 4(a). On this FT we notice a much broader main peak than in the case of carboplatin. This strong difference was expected as this peak results from two interfering contributions due to the nitrogen and chloride co-ordination atoms. Two smaller peaks are present at greater distances.

We thus considered a two-shell model to reproduce this nearest cisplatin co-ordination—see Table 5 for the complete results. The first shell contains two nitrogen atoms at 2.032 ± 0.007 Å and the second shell contains two chloride atoms at 2.314 ± 0.004 Å. This is coherent with the known structure of cisplatin,[11] in which 2.00 ± 0.04 Å for the Pt–N distance and 2.33 ± 0.01 Å for the Pt–Cl distance were found.

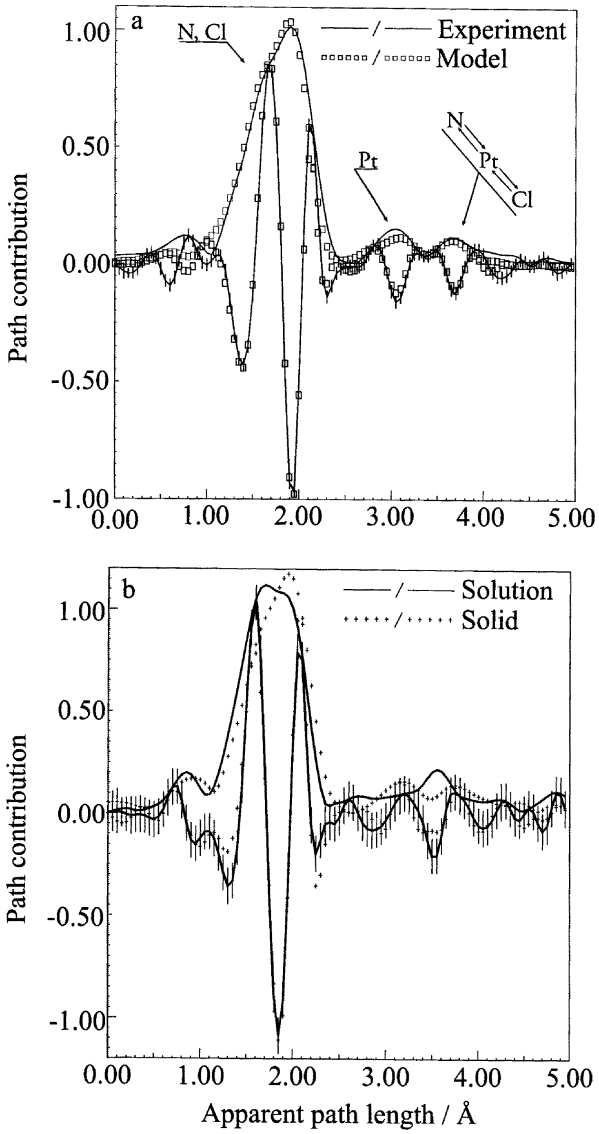

Fig. 4 (a) Comparison of the FT (modulus and imaginary part) of the EXAFS spectrum of solid cisplatin (solid line) and the model (squares). We assigned all the peaks by studying the multiple scattering paths and molecular packing. (b) Comparison of the cisplatin EXAFS FT in the solid state (+++, in transmission mode) and neutral aqueous solution (solid line, in fluorescence mode). One can note, for the solution, in the first main peak, a decrease of the longer distance contribution, which might reveal the onset of cisplatin hydrolysis.

Table 5 Results of the fitting of the first peak of solid cisplatin. Two shells are needed, one with the two nitrogen atoms and one with the two chlorine atoms, to model the spectrum. ΔE_0 was constrained to be identical for the two shells and was -12.9 ± 0.1 eV. The final error is $S = 2.03 \times 10^{-3}$

Path	N (fixed)	R/Å	$\sigma^2 \times 10^3$/Å^2
Pt → N → Pt	2	2.032 ± 0.007	3.3 ± 1.0
Pt → Cl → Pt	2	2.314 ± 0.004	3.4 ± 0.4

Using this crystallographic structure, we have demonstrated that the peak observed on the FT [Fig. 4(a)] at a 3.6 Å apparent path length is mainly due to multiple scattering through the platinum atom: Pt → N → Pt → Cl → Pt. The peak at nearly 3 Å apparent path length is assigned to a Pt–Pt signal related to the packing in the solid and we have checked that this contribution disappears when considering a single complex model.

Cisplatin neutral aqueous solution

The recording of the solution spectrum has been tested in transmission mode but the Pt L_{III} edge jump is then too small, in relation with its low solubility: even for this saturated solution the height is near 0.04 (the recommended value to allow a good extraction of the EXAFS spectra is between 0.4 and 1). During our further study on carboplatin solution stability we worked in transmission mode, and so an eventual contribution of cisplatin in solution, even in its hydrolysed form, will not produce a significant contribution to the detected signal. We have thus studied cisplatin solution in fluorescence mode [Fig. 4(b)]. As usual the quality of the measurements is then reduced [error bars increase in Fig. 4(b) relative to Fig. 4(a)] and we just give a qualitative analysis.

When we compare solid and solution spectra, we note differences in the FT spectra. The peak at 3 Å has disappeared. This is not surprising as it is related to Pt–Pt intermolecular interactions. The main peak still contains two contributions but their relative ratio has changed: the chloride contributions is less apparent than in the solid form. This might reveal the onset of cisplatin hydrolysis but we have not analysed this phenomenon more deeply: the investigation of this delicate question is not the aim of this paper and has been extensively studied.[8,15–17] The purpose of this paper is to follow the carboplatin decomposition into cisplatin in chloride-containing media, which is the subject of the remainder of this paper, after these preliminary results.

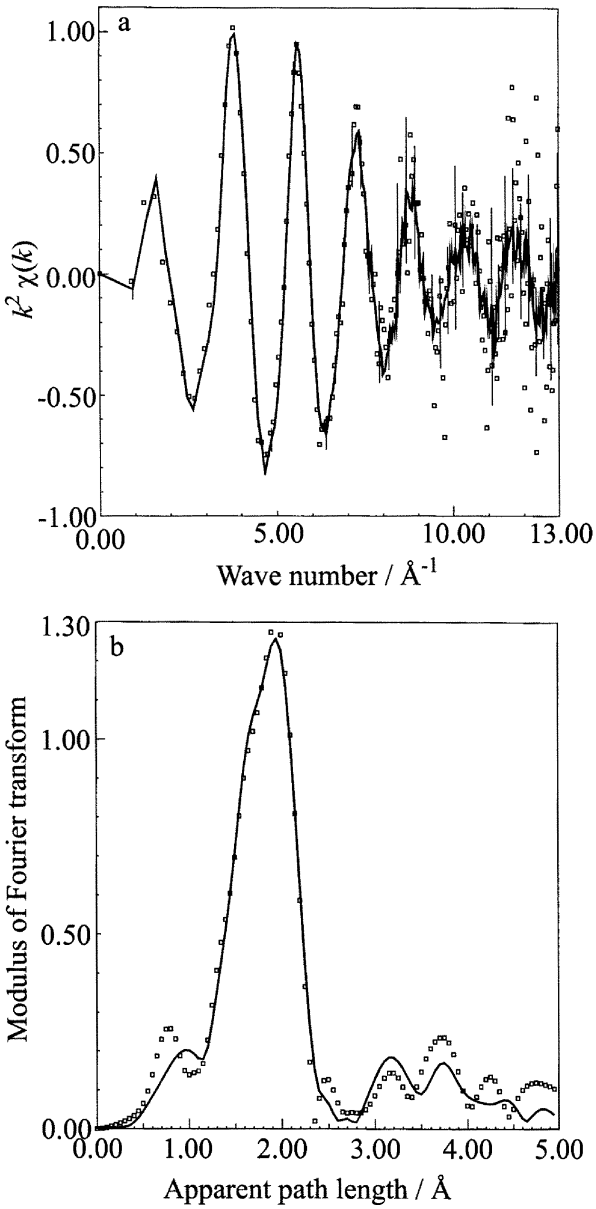

Fig. 6 Comparison of the spectra of solid cisplatin (solid line, with error bars) and solution 12 (supernatent) (squares). (a) $k^2\chi(k)$, normalised. (b) FT modulus. The spectra are identical; the degradation product of carboplatin is cisplatin.

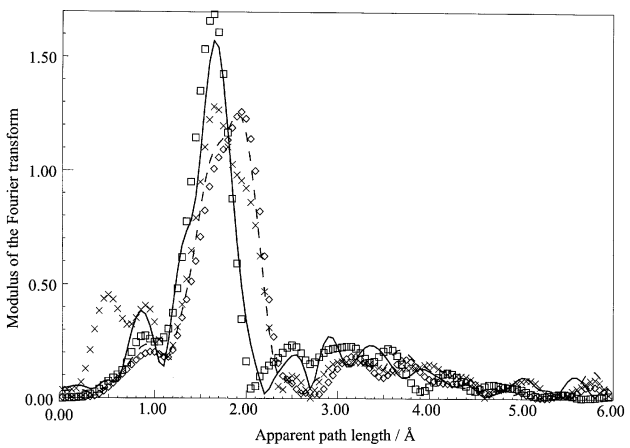

Fig. 5 Evolution of the FT modulus of the EXAFS spectrum of a carboplatin solution in 1 M HCl. Squares: solid carboplatin, diamonds: solid cisplatin. Solid line: $t = 2$ min; crosses: $t = 40$ min; dashed line: $t = 120$ min.

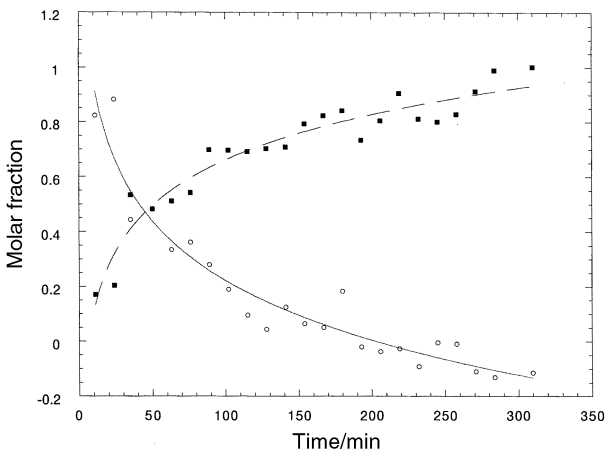

Fig. 7 Evolution of the cisplatin (squares) and carboplatin (circles) molar fraction in 0.4 M HCl solution, obtained by linear decomposition of the EXAFS spectra (see text). The conversion of carboplatin into cisplatin is evident.

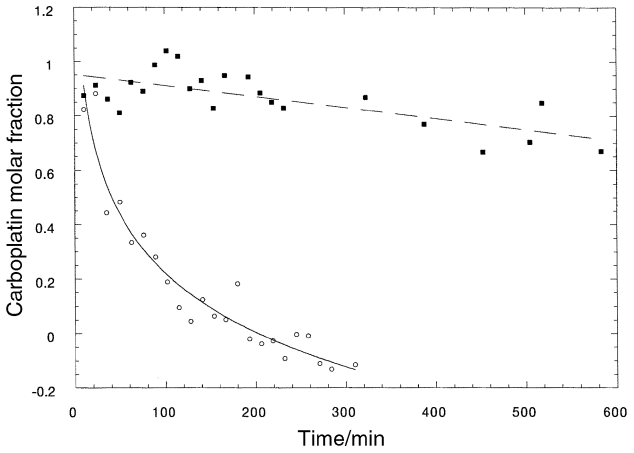

Fig. 8 Evolution of the carboplatin molar fraction in 0.4 M (circles) and 0.05 M (squares) HCl solutions, obtained by linear decomposition of the EXAFS spectra (see text). The decrease of pH accelerates the carboplatin decomposition.

NaCl carboplatin solutions

The fresh solutions (S_7 and S_8) show no visible evolution of the spectrum between the first one and the last one; all spectra are comparable to the carboplatin spectrum, either solid or in solution, during the experimental time (7 h for S_7 and 1.5 h for S_8).

After two weeks, only the 18% NaCl solutions (S_{5d} and S_{5l}) show an alteration: a yellow compound precipitates. The spectrum of this compound is identical to the cisplatin spectrum. The remaining solution itself presents a very small absorption edge (about 3% of the original absorption edge), indicating that almost all the platinum is in the precipitate.

All other solutions (S_1 to S_4) showed no precipitate. Their EXAFS spectra are comparable to the carboplatin solution spectrum. These results show that the carboplatin is not decomposed under these conditions, at the detection level of XAS.

HCl carboplatin solutions

The spectra of the 0.1, 0.4 and 1 M HCl solutions showed a rapid evolution during the recording time; this evolution is accompanied by the formation of a yellow precipitate in the solution. This evolution is evident in the FT, as Fig. 5 (with 1 M HCl) shows. The single peak characteristic of the carboplatin decreases, whereas a shoulder appears on the long path length side of the peak. A comparison between these FTs and the cisplatin FT shows that this shoulder appears at the same distance as the part of the first peak of the cisplatin FT due to the chloride atom contribution. For the 0.05 M solution, the reaction is slower and just the beginning of the degradation is observed.

For solution S_{12}, we waited for a few hours until the reaction was complete, giving a yellow precipitate and a supernatent solution the spectra of both the precipitate and the supernatent solution can be superimposed onto the cisplatin spectrum (Fig. 6). This floating solution is evidently not homogeneous and may contain solid fine particles of cisplatin. Despite this lack of homogeneity, the precipitation of cisplatin from a hydrochloric acid carboplatin solution is not questionable.

Qualitatively, it is possible to confirm the relatively quick conversion of carboplatin into cisplatin with these HCl solutions: since EXAFS oscillations $\chi(k)$ are linearly additive, if α is the molar fraction of cisplatin in solution and β that of carboplatin, we must have for each spectrum $\chi_{exp}(k) = \alpha\chi_{CisPt}(k) + \beta\chi_{CbPt}(k)$, where $\chi_{CisPt}(k)$ is the signal of cisplatin and $\chi_{CbPt}(k)$ is the signal of carboplatin. We used different methods to determine α and β from the experimental spectra; for instance, a least-square minimisation of

$$S' = \sum_{i=1}^{N} [\chi_{exp}(k_i) - \alpha\chi_{CisPt}(k_i) - \beta\chi_{CbPt}(k_i)]^2$$

allowing α and β to vary, using the solid state or the aqueous solution spectra of carboplatin and cisplatin as references, and we effectively observed that α increases with time. Fig. 7 shows the result of such an analysis for the 0.4 M solution, when working with a k^2 weighting: the conversion of carboplatin into cisplatin is evident. The fact that $\alpha + \beta$ is around unity, without constraints, confirms the validity of the decomposition hypothesis. However, the obtained values cannot be used as quantitative results, because of the heterogeneity we have mentioned previously, but they give a main tendency of the carboplatin into cisplatin conversion and can be used to compare qualitatively the evolution of different solutions.

Fig. 8 compares the values obtained for the 0.4 M and the 0.05 M HCl solutions, applying the same calculation for both solutions. These results clearly show that the higher the hydrochloric acid concentration, the faster the carboplatin conversion.

Conclusion

This XAS study shows that this method is suitable for studying the evolution of platinum-based antitumoral drugs in solution, under various conditions, at least qualitatively. In particular, we were able to determine the conditions under which carboplatin is stable: room temperature, light exposure or dark, aqueous medium solution, neutral pH, chloride concentration smaller than 0.9%, and use within a fifteen-days delay.

When carboplatin conversion occurs, specifically by addition of hydrochloric acid or under high chloride anion concentration, our XAS study demonstrates that cisplatin is always the major degradation product. Although the evolution of the spectra is clear, the lack of homogeneity of the solutions prevents us from determining the kinetics parameters of this carboplatin conversion.

We plan to apply XAS spectroscopy to study other platinum drugs that are today under pharmaceutical evaluation and which are expected to form homogeneous systems.

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