New reactions of anticancer-platinum complexes and their intriguing behaviour under various experimental conditions

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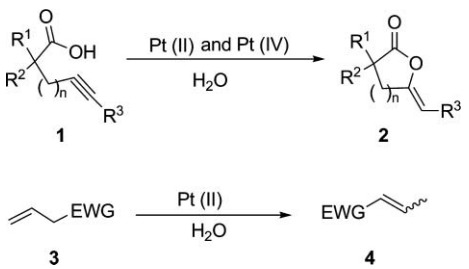
The anticancer platinum complexes here described react with organic substrates (such as acids, alkenes, alkynes) and catalyze transformations that can occur in biomolecules which contain unsaturated functions. We have analyzed the role of the platinum complexes in the observed reactions and studied the progress of the detected transformations upon variation of the reaction conditions.

Introduction

Cisplatin is still the most important metallodrug in the clinic, in spite of its severe side effects and the tumor resistance observed after prolonged treatment. Thus, thousands of platinum complexes have been tested during the last half-century, but further improvements slowed for many years.[1] However there has been an important impulse regarding metallodrug design in recent years, not only affording novel compounds but also, and more importantly, moving further towards the understanding of their mechanism of action. *Trans*-platinum complexes provide one of the most remarkable examples, especially because in the beginning the *trans* geometry was dismissed as lacking potential. Specifically, Barnett Rosenberg observed and reported a lack of activity for such complexes.[2] However, since the earliest examples of active *trans*-platinum complexes by Farrell and co-workers,[3] several additional classes of biologically active *trans*-platinum(II) complexes were developed as "rule-breaker" platinum antitumoral complexes.[4,5] Nowadays the anticancer relevance of *trans*-platinum complexes has been demonstrated by a number of publications and reviews published in the last twenty years.[6,7] In particular, the studies of the interaction of these complexes with other representative biomolecules besides DNA has become a relevant field of research.[8,9]

In this context, and considering the wide variety of platinum complexes, we were intrigued by the ability of these species to modify other biomolecules in the human body. We have recently studied the catalytic activity of these platinum compounds[10] in the alkyne-acid cyclization reaction and also in the double bond isomerization reaction (Scheme 1). In general, these transformations are known to proceed with different catalysts. However, as far as we know, the catalytic activity of Pt(II) anticancer complexes was never studied. We found that these reactions proceeded with a low catalyst loading (up to 0.1 mol%) and a high conversion in water relative to organic solvents (Scheme 1).[10] In this previous work, we selected a group of fifteen platinum complexes with different features regarding geometry, ligands and oxidation states, all of which have showed cytotoxicity against tumor cells. From this group of tested complexes, only some of them were catalytically active. The alkyne-acid cyclization of substrates such as (*Z*)-icos-5-enoic acid (present on the cell membrane), was catalyzed by these active platinum species. Additionally, it was also observed that Pt(II) complexes with *cis* geometry were more active than the corresponding *trans*-Pt(II), whereas Pt(IV) with *cis* geometry were less active than the corresponding *trans* complexes (Fig. 1).



Scheme 1 Recent alkyne-acid cyclization and alkene-isomerization studied by our group (EWG: electron withdrawing group).

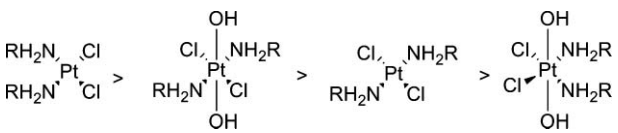


Fig. 1 Necessary features for the catalytic transformation.

In view of these results, some questions immediately arose concerning a possible connection between this catalytic activity and the intracellular activation of the platinum complexes by aquation reactions,[11] as well as the influence of different factors such as the presence of biological ions in the media which could potentially modify the activity of this kind of biologically active complexes.[8] In this work, we will present our attempts to clarify these questions as well as some aspects of the reaction mechanism.

Results and discussion

The variation of several mechanistic aspects that may have an important influence on intra- and/or extracellular reactions was studied in the model reaction. First we looked at the influence of the following variations: the concentration of platinum catalyst, the effect of stirring, the reaction time and the importance of the

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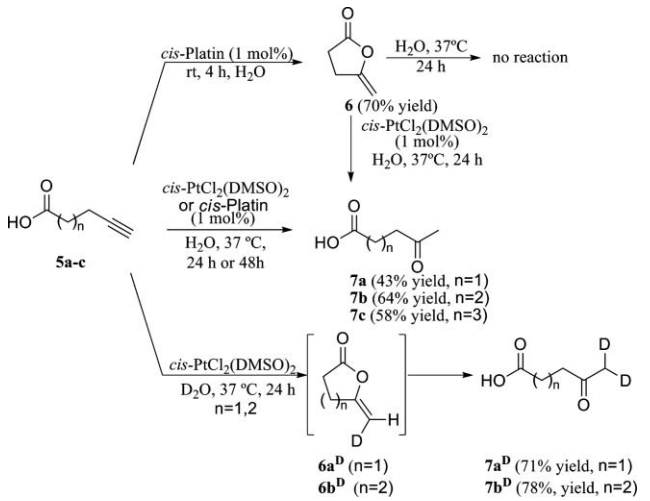
solvent (water) in the reaction. After analyzing these results and finding that the presence of water was essential, we looked at the mechanism of the platinum complex as a catalyst using 2D [^{1}H ^{15}N] HSQC NMR. Finally we tried to connect the results obtained from the study of these mechanistic aspects of the catalytic platinum complexes with their activity as antitumor drugs.[11] We also studied the reaction of these complexes with organic substrates that are significant model compounds in human metabolism.

Influence of Reaction Time on the Reactivity of Pt Complexes

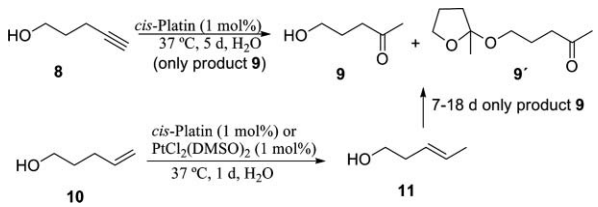
We initially observed that cisplatin was able to transform all the starting material from **5a** to **6**[10](equation 1, Scheme 2), after 4 h at room temperature. However, when the reaction was maintained for 24 h, we observed traces of a new product. Thus, we decided to force the conditions with *cis*-$PtCl_2(DMSO)_2$, one of the most active platinum(II) complexes used as a catalyst in this work, at 37 °C, identifying the new product as 4-oxopentenoic acid **7a** (equation 2). In order to discover if the catalyst was intervening in the process, compound **6** was isolated and placed under the same conditions without the platinum complex, and no reaction was detected after 24 h (equation 1, top right, Scheme 2). However, when compound **6** was placed in the presence of the catalyst, full conversion to product **7a** was observed (right-down-equation 1, Scheme 2). We also checked the influence of the alkyl chain length of compounds **5b–c** (n = 2, 3), observing full conversion to oxo-acids **7b–c** (equation 2).



Scheme 2 Influence of reaction time and conditions on the obtained products.

Cisplatin was able to catalyze the reaction, and *cis*-$PtCl_2(DMSO)_2$ required double the reaction time (48 *versus* 24 h). The reaction was also performed with D_2O (equation 3, Scheme 2), obtaining the open-chain compound **7a^{D}–b^{D}** with double incorporation of deuterium at the terminal methyl group. This process was conducted through the intermediate **6a^{D}** which was demonstrated by the study and isolation of this intermediate under smoother reaction conditions [rt, D_2O and *cis*-$PtCl_2(NHMe_2)_2$], the second deuterium being incorporated when the ring of **6a^{D}** was opened, leading to compound **7a^{D}**.

Following up on these results with acid substrates, we turned our attention to the study of the triple and the double bond reactivity with alcohol substrates (Scheme 3). Thus, the reaction of pent-4-yn-1-ol and cisplatin after 5 days at 37 °C led to the oxo-alcohol ketone **9** (equation 1, Scheme 3). Also we could observe the acetal **9′** as a byproduct (22%), which is in accordance with other similar procedures described in the literature.[12,13] This byproduct **9′** can finally be transformed into **9** by longer reaction times (7 days). However, it should be highlighted that such reactivity, compared to the alkyne-cyclization, was much slower. In fact **9** was only isolated with full conversion after five days. Regarding the alkene-transformation, the alcohol **10** was transformed to the more thermodynamically stable compound **11** after one day with *cis*-$PtCl_2(DMSO)_2$, with 50% conversion (equation 2, Scheme 3). Slightly lower conversion was found with cisplatin, with which products **9**, **9′** and **11** were detected in the crude mixture. Longer reaction times (seven days with *cis*-$PtCl_2(DMSO)_2$ or eighteen days with cisplatin) provoked the transformation of the double bond **11**, finally affording **9** in full conversion.



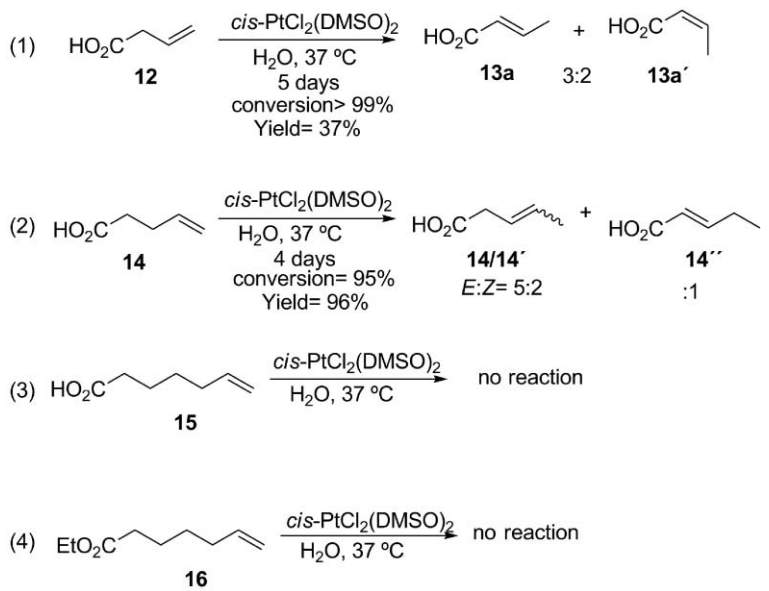
Scheme 3 Influence of reaction time on the obtained products (d: days).

The isomerisation of compound **12** to **14** was also observed with alkenes bearing an acid moiety.[10] Thus alkenes **12** and **14** were transformed into the corresponding isomers **13a/13a′**and **14/14′/14″**, obtaining full conversion for both reactions (equations 1, 2, Scheme 4). Using a different catalyst such as cisplatin, the same reactivity was observed with longer reaction times. However this transformation required a key feature in the structure of the organic substrate: the presence of an acid moiety linked to the double bond by an alkyl chain of no more than five carbons. For instance, no reaction was observed with the longer acid **15**, (equation 3) or with the ester **16** (equation 4 Scheme 4).

In summary, three main reactivity pathways were detected and they are described as follows; the alkyne-cyclization was the preferred transformation and also occurred in shorter times (4–12 h), however longer reaction times produced open-chain products (transforming the alkyne moiety into a ketone) (Scheme 2). The alkynols and alkenols were also transformed into the corresponding ketones after longer time periods (days, Scheme 3). Finally, we also found isomerization of double bonds to form conjugated or more stable double bonds (days, Scheme 4).

Effect of Concentration and Stirring

During some specific NMR experiments (see mechanistic aspects and NMR studies sections) we observed some important variations in the conversion time of the reactions comparing the catalyst studies with the *in vitro* studies. In our previous work, we observed that the standard reaction (with **5a**, top equation, Scheme 2) with *cis*-$PtCl_2(NHMe_2)_2$ led to the final cyclized product in four hours. However, when we tried to reproduce the same reaction in an NMR tube we found longer reaction times (up to 14 h) were necessary.



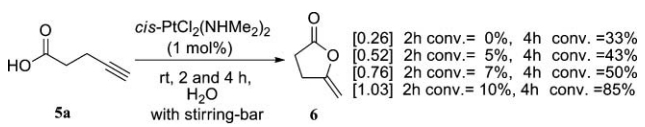
Scheme 4 Reactions of some alkene-acids and esters.

In order to clarify these differences, we started studying the effects of stirring and concentration on the sample.

After several experiments performed in standard flasks and directly in NMR tubes, we detected that the conversion time of the model reaction was not equal in both systems. The conversion in a standard flask took place in shorter reaction times (1 to 4 h) than the conversion in the NMR tube (from 8 to 12 h). As the only difference in both systems was that the NMR tube experiment was performed without stirring, we studied the model reaction in a standard flask without stirring and on this occasion after four hours no conversion was observed.

It is clear, then, that variations of the reaction conditions (*e.g.* the stirring) can have an important influence on the final value of the conversion. The stirring effect may have special relevance in biological systems, where more dynamic conditions are found in the circulatory system than for example in the inner cell.

Concentration is also an important factor for the reaction times. In order to evaluate this effect the model reaction (Scheme 5) was studied using four different concentrations of the substrate **5a** ([M] = 0.26, 0.52, 0.76, 1.03) and *cis*-$PtCl_2(NHMe_2)_2$ ([M] = 0.0026, 0.0052, 0.0076, 0.0103) and the check-times in these assays were two and four hours for each run. When a higher concentration was used, the rate of conversion at two hours was higher (*e.g.* conversion = 10% at [M] = 1.03 and conversion = 0% at [M] = 0.26). The rate of conversion was also substantially increased at 4 h, obtaining 85% conversion at [M] = 1.03, and 33% at [M] = 0.26. This later fact may indicate that the platinum complex is acting as a pre-catalyst that requires some time for activation (see below, influence of water).



Scheme 5 Influence of the concentration on the conversion.

Table 1 Influence of different electrolytes on the conversion reaction

	No buffer	NaF	NaCl	NaBr	CsF	CsCl	$KClO_4$
Conversion (%)	49	48	18	51	62	30	47

Presence of Electrolytes and Biological Ions

One of the most abundant anions in physiological solutions is chloride,[14] the extracellular and intracellular concentrations of which are typically 110 mM and 5–15 mM, respectively. The alteration of this anion concentration across biological membranes can induce physiological effects and modulate the action of certain metallodrugs like cisplatin which is supposed to cross membranes by passive diffusion and/or with certain metalloproteins as CTR1.[15] To determine the effectiveness of the conversion in the presence of chloride anions, a test was run with *cis*-$PtCl_2(NHMe_2)_2$ and NaCl, which produced a lower final conversion rate than that in the presence of water (Table 1). The presence of fluoride or bromide did not produce any effect in the conversion values.

The electrostatic stabilization of the carboxylic acid against the conversion could have been caused by a possible interaction with the cation. So, the substitution of Na^+ by a Cs^+ was studied and turned out to have a slight impact on the nature of the reaction when comparing NaF with CsF; and NaCl with CsCl (see values Table 1). Better results were obtained using the caesium ion salts than the sodium ions, which might indicate that the negative charge of the carboxylic acid is stabilized more by the sodium ion (smaller size) than by the caesium ion. The electrolyte used (ClO_4^-) did not produce changes in the reactivity values, being the best electrolyte to perform these experiments.

Influence of Water

The very striking feature of these platinum catalysts was the good conversion values in aqueous solution. This same conversion has been reported to take place with some other metals but using organic solvents (dichloromethane and acetone) and also longer reaction times.[16–18] Very recently we reported how these *trans*-platinum anticancer-complexes were activated by aquation reactions.[11,19] The role of water in the mechanism of this conversion is important and we decided to study the mechanism of the model reaction in detail using the 2D [^{1}H ^{15}N] HSQC NMR technique. This tool allows simultaneous detection of all the species without isolation of the reaction intermediates. But in order to carry this out, a previous knowledge of the intermediates was needed as the range of this technique is very broad and appreciable changes on NMR values were observed depending on the ligands around the platinum atom.[20]

The reaction was performed in dry chloroform and chloroform with 10% and 1% water. The results showed 100% conversion only in the experiment with water and no conversion at all in the reaction performed with the dry solvent. This result is in agreement with the activation *via* aquation reaction, indicating that water is essential for the activation of these platinum complexes.

Mechanistic Aspects and NMR Studies

Knowing that the presence of water is essential, the mechanism of the platinum pre-catalyst was studied using 2D [^{1}H ^{15}N] HSQC NMR. This technique has been proven to be an excellent tool for studying aquation reactions, with high sensitivity at the low physiological concentrations used for antitumor platinum complexes (containing amine donor ligands).[11] The mechanism of action for the majority of this kind of antitumor platinum complexes, including cisplatin,[21] has been accepted to be based on the aquation reaction of the chlorido ligands, with the aqua species being responsible for the DNA damage. The 2D NMR tool will be of special interest in the study of the catalytic mechanism as it allows simultaneous detection of all the species (*via infra*), dichlorido, mono, bisaqua and/or some other potential species.[22] Moreover the aquation of *trans*-[$PtCl_2$(^{15}N-amine)(^{15}N-amine')] complexes, here used as pre-catalysts, was already described[11] using 2D [^{1}H ^{15}N] HSQC NMR. The obtained kinetic data and species characterization have been essential information used to perform the catalytic studies presented here. These results were obtained with the *cis*[19] and *trans*[11] platinum complexes in 100 mM $NaClO_4$, and at pH 4.2–4.8, which is a very important variable in the chosen model of catalytic conversion because deprotonation of the formed aqua species will afford non-active hydroxo complexes.

Using the conditions previously reported for the model catalytic reaction, the reaction of 4-pentynoic acid with complex *cis*-$PtCl_2(NHMe_2)_2$ has been monitored by ^{1}H NMR at pH: 2.8–3 (Fig. 2). This pH condition is caused by the alkene-acid substrate used in the catalytic reaction.

As shown in Fig. 2, monitoring the reaction using ^{1}H NMR, the conversion of the acid substrate started to become clear at five hours but was only fully detected after 20 h of reaction time. This fact was not surprising considering the results included in the stirring conditions studies regarding the optimization of our model reaction (see section below). Thus, the detected reactivity delay in the NMR tube allows a wider time range for finding the possible intermediates in the next two dimensional experiment.

The evolution of the 2D [^{1}H ^{15}N] HSQC NMR (ii and iii in Fig. 3) spec6strum was studied under the same conditions. Only the dichlorido starting material (i in Fig. 3) was observed in the freshly prepared sample. Afterwards the monoaqua species arose after one hour (data not shown); this speciation being in agreement with the data published before[19] (Fig. 3: data showed from after five hours when the conversion was first detected). The monoaqua species remained throughout the reaction and more importantly, no bisaqua species was found in the spectra. In order to corroborate the precise assignment of the monoaqua crosspeaks, the titration of the sample was performed and the monoaqua complex afforded the expected hydroxo species, while no hydroxo-dinuclear or any other species were observed. These data seemed to indicate that the presence of the monoaqua species was essential in the alkene-cyclation.

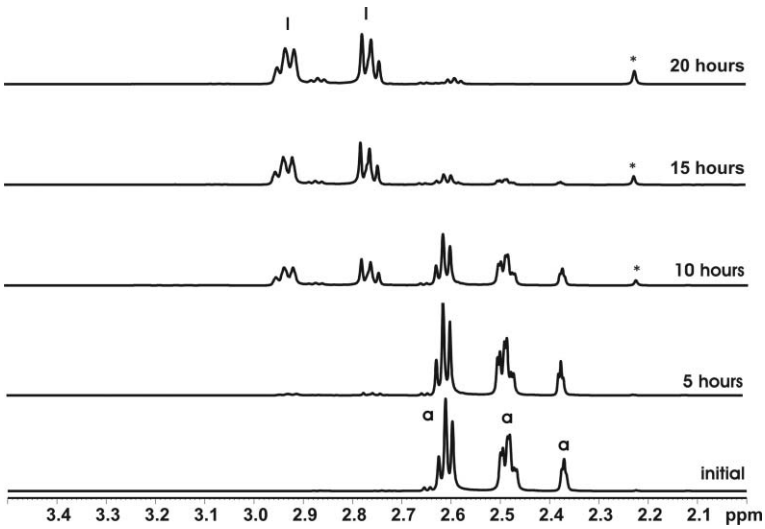


Fig. 2 Progress of the reaction of complex *cis*-$PtCl_2(NHMe_2)_2$ with 4-pentynoic acid, monitored by ^{1}H NMR (a: acid, l: lactone).

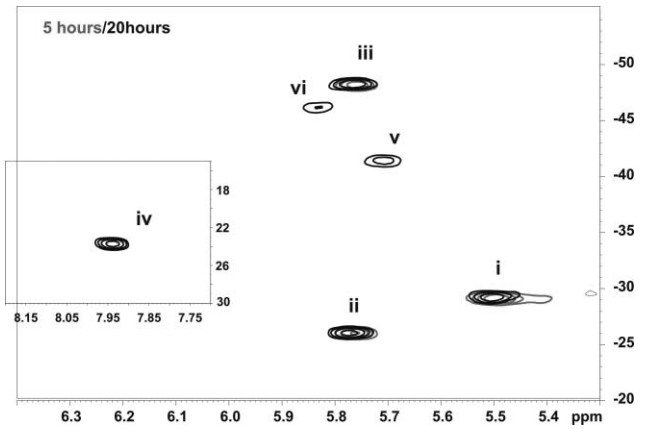


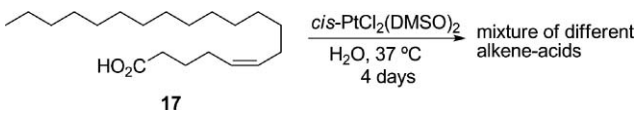
Fig. 3 2D [^{1}H ^{15}N] HSQC NMR spectra after 5 h reaction and 20 h reaction of complex *cis*-$PtCl_2(NHMe_2)_2$ and 4-pentynoic acid. Detail from the positive $\delta(^{15}N)$ area is also included.

But after 20 h, two new species were detected at $\delta(^{15}N/^{1}H)$: –42/5.75 ppm for the species number **v** and at $\delta(^{15}N/^{1}H)$: –46/5.85 ppm for species number **vi**, though these new species were 5% and 4% of the total respectively, compared to 45% for the monoaqua species.[22] The area of these crosspeaks (**v** and **vi**) decreased with time, being 2% and 3% respectively at 72 h. Simultaneously to these novel species and outside the area typically described for aqua/hydroxo platinum complexes, another crosspeak was detected at 24/7.9 ppm (species **iv** in the extra area displayed in Fig. 3) as one of the major products (30% *versus* 45% of the aqua species) which corresponds to free dimethylamine.[23]

With all the optimization matters resolved, the next step was to look at the possible action of these platinum complexes with important substrates in biological media.

Modifications of Biomolecules

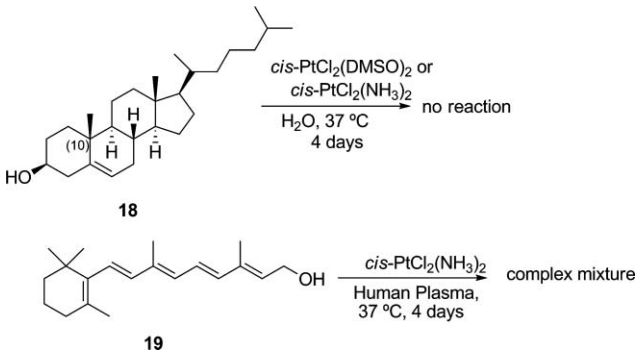
One of the most important features of these platinum complexes, besides the antitumor activity, is the ability to modify different molecules, including bioactive ones. We started our investigation studying the isomerization of the double bonds present in some fatty acids, such as oleic acid (Scheme 6). When the acid **17** was placed in aqueous conditions at human body temperature, unidentified modified alkenes were formed. The transformation of compound **17** might indicate that platinum complexes could modify some other fatty acids which are present in tissues of plants and animals and are also key structural components of biological membranes.



17

Scheme 6 Transformation of alkene-acid **17**.

Considering that the key structural feature for catalytic activity shown by the platinum complexes is the presence of a chelating group (oxygen, acid) and unsaturation next to the chelating group (less than 6–7 carbons), we started to look other potential molecules with relevant biomolecular properties and these key features. Cholesterol and retinol (vitamin A) (Scheme 7) were identified as meeting the requirements for the possibility of being modified with platinum complexes due to their double bonds.



Scheme 7 Transformation of some selected biomolecules.

The cell membrane component cholesterol was tested in the presence of complexes with *cis* geometry such as cisplatin and the DMSO derivative. No changes were observed after four days in the starting material (**18**) at 37 °C. This is probably because of the inadequate orientation of the oxygen moiety and the methyl group (position 10) that might be blocking the coordination of the platinum complex to the double bond.

Finally, retinol (**19**) was tested at pH = 6.8 for four days at 37 °C in water with cisplatin (1 mol%) and monitored by ^{1}H NMR. The transformation of retinol was detected in the first 24 h and no retinol was observed after 4 days, obtaining full decomposition. This fact indicates a high incompatibility of retinol with these platinum complexes. The results with retinol, which is usually found in plasma and enters the cell by diffusion, have important implications, and could indicate that animals or patients under treatment with platinum complexes could suffer modifications of biomolecules by different mechanisms. *In vivo* studies regarding modifications of these biomolecules are in progress and will be reported at a later date.

Conclusions

We have demonstrated that platinum complexes catalyzed transformation of some unsaturated organic compounds *via* their aqua species. We have studied the progress of the reaction varying the reaction conditions. In addition, we have shown that anticancer platinum complexes react with organic substrates (such as acids, alkenes, alkynes) and with some selected important biomolecules which contain unsaturated functions.

Experimental

Materials and methods

NMR spectra were acquired on a Bruker 300 spectrometer, running at 300 and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^{1}H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). ^{13}C NMR spectra were acquired in a broadband decoupled mode. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or $KMnO_4$ dip. Purification of reaction products was carried out by

flash chromatography (FC) using silica 60 A C_C 35–75 μm (SDS VOTRE PARTENAIRE CHIMIE). The following compounds were synthesized according to published procedures: *cis* Pt(II) complexes *cis*-$Pt(DMSO)_2Cl_2$,[24,25] cisplatin (Sigma-Aldrich) and *cis*-dichloridodimethylamine platinum(II).[19] Blood samples were obtained from patients that agreed to have their blood used for scientific purposes through signed consent. Blood was drawn from an arm vein into Vacutainer tubes containing EDTA (final concentration, 1.5 mg ml^{-1}). Samples were centrifuged immediately (15 min, 3000 rpm, 4 °C). Plasma was collected by aspiration, and samples were immediately immersed in crushed ice. Plasma samples (1.5 mL aliquots) were frozen.

General Procedure for the alkyne-acid cyclization in aqueous media

In an ordinary vial the corresponding platinum complex (1 mol%, 0.002 mmol) was added to a stirred solution of the corresponding alkyne acid (0.2 mmol) in 0.2 mL of water. After complete consumption of the alkyne acid (usually 6–10 h, monitored by ^{1}H NMR spectroscopy), the reaction mixture was diluted with 5 mL of 10% HCl and extracted with CH_2Cl_2 (2 × 5 mL). The organic phase was dried with anhydrous Na_2SO_4 and finally the product was purified following the procedure indicated in each case.

Dihydro-5-methylenefuran-2(3H)-one (6). The product was directly obtained following the standard procedure using the catalyst indicated in Scheme 2 as yellow oil (14 mg, 70% yield) after FC (5 : 1 hexane–EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68 (d, J = 2.2 Hz, 1H), 4.26 (d, J = 2.2 Hz, 1H), 2.85–2.79 (m, 2H), 2.63–2.57 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 155.6, 88.4, 27.8, 24.9 MS (TOF ES$^+$): $[M]^+$ calcd for $C_5H_6O_2$ 98.0368; found 98.0373.

General Procedure for the oxoacid compounds in aqueous media

In an ordinary vial the corresponding platinum complex (1 mol%, 0.002 mmol) was added to a stirred solution of the corresponding alkyne acid (0.2 mmol) in 0.2 mL of water. After complete consumption of the alkyne acid (monitored by ^{1}H NMR spectroscopy), the reaction mixture was diluted with 5 mL of 10% HCl and extracted with AcOEt (2 × 5 mL). The organic phase was dried with anhydrous Na_2SO_4.

4-Oxopentanoic acid (7a). The product was directly obtained with full conversion following the standard procedure after 12h using the catalyst indicated in Scheme 2 as yellow oil (10 mg, 43% yield) without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.37 (bs, 1H), 2.68 (t, J = 6.3 Hz, 2H), 2.55 (t, J = 6.3 Hz, 2H), 2.12 (s, 3H), 2.63–2.57 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.7 (C), 177.2 (C), 36.8 (CH_2), 28.7 (CH_3), 27.0 (CH_2). MS-ESI$^+$: $[M+Na]^+$ calcd for $C_5H_8NaO_3$ 139.0365; found 139.0368.

5-Oxohexanoic acid (7b). The product was directly obtained with full conversion following the standard procedure after 30 h using the catalyst indicated in Scheme 2 as yellow oil (17 mg, 64% yield) without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.36 (bs, 1H), 2.47 (t, J = 7.2 Hz, 2H), 2.32 (t, J = 7.2 Hz, 2H), 2.08 (s, 3H), 1.83 (qt, J = 7.1 Hz, 2H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3 (C), 179.0 (C), 42.3 (CH_2), 32.9 (CH_2), 29.9 (CH_3), 18.5 (CH_2). MS-ESI$^+$: $[M+Na]^+$ calcd for $C_6H_{10}NaO_3$ 153.0522; found 153.0516.

6-Oxoheptanoic acid (7c). The product was directly obtained with 72% conversion following the standard procedure after 4 days using the catalyst indicated in Scheme 2 as yellow oil (17 mg, 58% yield) after FC (1 : 1 hexane–EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (bs, 1H), 2.40 (t, J = 6.5 Hz, 2H), 2.30 (t, J = 6.6 Hz, 2H), 2.08 (s, 3H), 1.58–1.55 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9 (C), 179.4 (C), 43.2 (CH_2), 33.7 (CH_2), 29.8 (CH_3), 24.0 (CH_2), 23.0 (CH_2). MS-ESI$^+$: $[M+Na]^+$ calcd for $C_7H_{12}NaO_3$ 167.0678; found 167.0686.

General Procedure for the oxoacid deuterated compounds in aqueous media

In an ordinary vial the catalyst *cis*-$Pt(DMSO)_2Cl_2$ was added to a stirred solution of the corresponding alkyne acid (0.2 mmol) in 0.2 mL of D_2O. After complete consumption of the alkyne acid (monitored by ^{1}H NMR spectroscopy), the reaction mixture was diluted with 5 mL of HCl 10% and extracted with AcOEt (2 × 5 mL). The organic phase was dried with anhydrous Na_2SO_4.

5,5-Dideuterium-4-oxopentanoic acid (7a^D). The product was directly obtained with full conversion following the standard procedure using the catalyst indicated in Scheme 2 as yellow oil (16 mg, 71% yield) without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (bs, 1H), 2.68 (t, J = 6.3 Hz, 2H), 2.55 (t, J = 6.1 Hz, 2H), 2.12–2.08 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1 (C), 177.6 (C), 37.6 (CH_2), 29.1 (qt, J = 19.2 MHz, CH), 27.7 (CH_2). MS-ESI$^+$: $[M+Na]^+$ calcd for $C_5H_6D_2O_3$ 141.0491; found 141.0487.

6,6-Dideuterium-5-oxohexanoic acid (7b^D). The product was directly obtained with full conversion following the standard procedure using the catalyst indicated in Scheme 2 as yellow oil (20 mg, 78% yield) without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (bs, 1H), 2.52 (t, J = 7.2 Hz, 2H), 2.36 (t, J = 7.2 Hz, 2H), 2.14–2.09 (m, 1H), 1.87 (qt, J = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9 (C), 178.4 (C), 42.3 (CH_2), 33.0 (CH_2), 29.3 (qt, J = 19.3 MHz, CH), 18.6 (CH_2). MS-ESI$^+$: $[M+Na]^+$ calcd for $C_6H_8D_2NaO_3$ 155.0647; found 155.0641.

General Procedure for the oxo-alcohol ketones in aqueous media

In a ordinary vial the catalyst *cisplatin* (1 mol%, 0.002 mmol) was added to a stirred solution of pent-4-yn-1-ol or pent-4-en-1-ol (0.2 mmol) in 0.2 mL of water. After complete consumption of the alcohol (usually 5–18 days, as monitored by ^{1}H NMR spectroscopy), the reaction mixture was extracted with CH_2Cl_2 (2 × 5 mL). The organic phase was dried with anhydrous Na_2SO_4 and finally the product was purified following the procedure indicated in each case.

5-Hydroxypentan-2-one (9). The product was directly obtained with a conversion of 48% following the standard procedure using the catalyst indicated in Scheme 3 as yellow oil (conversion = 48% after 2 days, 31% yield; conversion = 100% after 7 days, 14 mg, 67% yield) without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.58 (t, J = 6.1 Hz, 2H), 2.52 (t, J = 6.9 Hz, 2H), 2.11 (s, 3H), 1.77 (tt, J = 6.9, 6.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$)

δ 209.4 (C), 62.2 (CH_2), 40.5 (CH_2), 30.0 (CH_3), 26.5 (CH_2). MS-ESI$^+$: $[M\text{-}H_2O+H]^+$ calcd for $C_5H_{10}O_2$ 85.0648; found 85.0656.

5-(2-Methyl-tetrahydrofuran-2-yloxy)pentan-2-one (9′). The product was directly obtained following the standard procedure using the catalyst indicated in Scheme 3 as yellow oil (after 2 days, 22% yield) without further purification. ^{1}H NMR (500 Hz, $CDCl_3$) δ 3.84–3.80 (m, 1H), 3.78–3.74 (m, 1H), 3.39 (dt, J = 9.3, 6.4 Hz, 1H), 3.33 (dt, J = 9.3, 6.1 Hz, 1H), 2.42 (t, J = 7.4 Hz, 1H), 2.40 (t, J = 7.2 Hz, 1H), 2.08 (s, 3H), 1.98–1.90 (m, 2H), 1.85–1.81 (m, 1H), 1.73 (tt, J = 7.3, 6.3 Hz, 2H), 1.66–1.63 (m, 1H), 1.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.9 (C), 107.4 (C), 67.5 (CH_2), 59.9 (CH_2), 40.7 (CH_2), 38.0 (CH_2), 29.9 (CH_3), 24.6 (CH_2), 24.5 (CH_2), 22.0 (CH_3). MS-ESI$^+$: $[M+Na]^+$ calcd for $C_{10}H_{18}NaO_3$ 209.1148; found 209.1154.

Pent-3-en-1-ol (11). The product was directly obtained following the standard procedure after 4 days with 72% conversion using the catalyst indicated in Scheme 3 as yellow oil inseparable from **9** and **9′** without further purification (12 mg, 59% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59–5.53 (m, 1H), 5.45–5.38 (m, 1H), 3.61 (t, J = 6.5 Hz, 2H), 2,27 (dt, J = 6.5, 1.1 Hz, 1H), 2,24 (dt, J = 6.5, 1.1 Hz, 1H), 1.69 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.1 (CH), 127.2 (CH), 62.0 (CH_2), 35.9 (CH_2), 18.0 (CH_2).

General Procedure used for the samples in the kinetic studies

The sample for the kinetic studies was prepared as follows: an aqueous solution of 4-pentynoic acid was added to another aqueous solution of *cis*-$PtCl_2(^{15}N\text{-}NHMe_2)_2$. The mixture was prepared using the ratios: $[H_2O]/[D_2O]$ = 90 : 10, platinum concentration = 2.5 mM and acid/Pt = 100 : 1. The time-dependent transformation of the mixture at 298 K was monitored by 1D ^{1}H and 2D [^{1}H, ^{15}N] HSQC NMR spectroscopy. NMR spectra were recorded on a Bruker DRX-500 spectrometer (^{1}H 500.13 MHz, ^{15}N 50.68 MHz). The ^{1}H and ^{15}N chemical shift were relative to TSP and liquid ammonia respectively. All NMR data were analyzed with the TopSpin program (Bruker). pH values were determined using a Metrohm 744 pH meter. The meter was calibrated using pH buffers at pH 7.00 and 4.01. Adjustments in pH for the titration were made at 6 and 10 using 0.1 and 0.01 M NaOH.

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