Journal of Thermal Analysis, Vol. 40 (1993) 395-403

THE THERMAL DEGRADATION CHARACTERISTICS OF SELECTED ORGANOPLATINUM ANTITUMOR AGENTS

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The thermal decomposition characteristics of representatives of three classes of organoplatinum compounds have been examined by thermogravimetry. Substituted salicylato(1,2-diaminocyclohexane)platinum(II) compounds undergo thermal decomposition by sequential loss of first the salicylato ligand and then the amine ligand to afford a residue corresponding to the platinum content of the compound. The thermal decomposition of N-arylsalicylaldimino(1,2-diaminocyclohexane)platinum(II) nitrate is more complex, but is also characterized by two major weight losses. Thermal decomposition of *bis*-(2-thiophenecarboxylato)platinum(II) is characterized by ligand fragmentation to generate a residual mass corresponding to the platinum content of the compound.

Keywords: organoplatinum antitumor agents, TG

Introduction

Since the discovery [1–3] of the remarkable therapeutic properties of *cis*-dichlorodiammineplatinum(II), cisplatin, interest in the development of more effective and, in particular, less toxic platinum antitumor compounds has remained high [4]. The need for the development of organoplatinum formulations of substantially reduced toxicity but without impaired therapeutic activity has stimulated efforts to anchor suitable platinum compounds to biocompatible carrier polymers [5–9]. Methods of attachment have included noncovalent complexation [5], covalent binding [6–8], and incorporation of the organoplatinum moiety into the polymer backbone [9]. Organoplatinum compounds containing both substitutedphthalato and substituted-catecholato ligands have previously been prepared as suitable materials for noncovalent complexation with water-soluble polymers [5–10]. A series of 5-substituted-salicylato(1,2-diamino-cyclohexane)platinum(II) compounds has now been prepared for similar purposes [11].

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Thermogravimetry has long been utilized for the characterization of organometallic compounds [12–15]. Such analysis has included a limited number of platinum compounds [13–15]. The thermal degradation characteristics of 5-substituted-salicylato(1,2-diaminocyclohexane)platinum(II) and selected other platinum compounds are reported here.

Experimental

Materials and synthesis

The necessary ligands were obtained from the Aldrich Chemical Company or were prepared by previously reported methods. In general, platinum compounds were prepared in the absence of light and oxygen at 55°–60°C. The compounds were isolated by filtration through a sintered-glass filter, washed repeatedly with a variety of organic solvents, and dried over Dririte at reduced pressure. The compounds were characterized by spectroscopic methods, principally ^1H nmr and infrared spectroscopy, and by thermogravimetry. Infrared spectra were obtained using 1% suspensions in potassium bromide or cesium iodide and a Nicolet 20 DXB FT-IR spectrophotometer. Solutions in deuterodimethyl sulfoxide (DMSO–d_6) and a General Electric QE-300 spectrometer were used to record ^1H nmr spectra. Chemical shifts are reported relative to tetramethylsilane (δ 0.00) as an internal reference.

cis-Dichloro(1,2-diaminocyclohexane)platinum(II)

A solution of 6.01 g (0.015 mol) of potassium tetrachloroplatinate in 80 ml of 1.0 *N* aqueous hydrochloric acid was placed in a 250-ml, round-bottomed flask. 1,2-Diaminocyclohexane (5.3 ml, 4.6755 g, 0.0407 mol) was added in a single portion and the contents of the flask were swirled to effect thorough mixing. The flask was flushed with nitrogen, closed with a glass stopper and wrapped with aluminum foil to exclude light. The contents of the flask were held at 55°C for 72 h and then at 7°C (refrigerator) for 10 h. The yellow crystals which had formed were collected by filtration at reduced pressure, washed repeatedly with water and dried at reduced pressure over Drierite (4.71 g, 82% yield): ir (cm^{-1}, KBr) 3272(s), 3199(s) (N–H), 2947(s), 2866(m)(aliphatic C–H), 1564(s), 757(m) (Pt–Cl), 603(w), 574(w) (Pt–N); proton nmr (δ, DMSO-d_6) 0.68–3.24 (m-broad, 10H, cyclohexyl protons), 4.62–6.93 (m-broad, 4H, amino protons).

cis-Dinitrato(1,2-diaminocyclohexane)platinum(II)

A solution of *cis*-dichloro(1,2-diaminocyclohexane)platinum(II) (0.845 g, 0.0024 mol) and silver nitrate (0.425 g, 0.0022 mol) in 150 ml of water was placed in a 250-ml, round-bottomed flask containing a magnetic stirring bar. The flask was flushed with nitrogen, closed with a glass stopper and wrapped with aluminum foil to exclude light. The mixture was stirred at room temperature for 2 h. The solution was filtered at reduced pressure through a sintered glass filter. The absence of silver nitrate in the filtrate was confirmed by treating a small aliquot with 1.0 *N* aqueous hydrochloric acid solution; no precipitate was formed. The clear colorless aqueous solution of *cis*-dinitrato(1,2-diaminocyclohexane)-platinum(II) was utilized for the preparation of compounds containing the (1,2-diaminocyclohexane)platinum(II) moiety.

Carbonato(1,2-diaminocyclohexane)platinum(II)

Carbonato(1,2-diaminocyclohexane)platinum(II) was prepared as described above for the corresponding dinitrato species except that silver carbonate rather than silver nitrate was used.

Salicylato(1,2-diaminocyclohexane)platinum(II)

Into a 100-ml, three-necked, round-bottomed flask fitted with a magnetic stirring bar, a thermometer, and a Graham condenser bearing a gas-inlet tube was placed 16.0 ml (0.13 mmole) of carbonato(1,2-diaminocyclohexane)platinum(II) solution. A solution of 0.37 g (2.68 mmole) of salicylic acid in 25 ml of ethanol was added. The resulting mixture was allowed to stir in the absence of light (aluminum foil cover) under a static nitrogen atmosphere at 80°C for five days. The gray precipitate which had formed was collected by filtration through a medium-porosity sintered-glass funnel at reduced pressure, washed successively with water, methanol, ether, and acetone, and dried over Drierite at reduced pressure (20 torr) to afford 0.025 g (43.7% yield) of the desired salicylato compound: dp 221°C; ir (cm^{-1}, CsI) 3451 (m-broad)(N–H), 1632(s) (carbonyl), 1591(s), 1484(m) (aromatic nucleus), 1251(m) (phenoxy C–O), 534(w), 442(w) (Pt–N), 391(w), 360(w) (Pt–O); proton nmr (δ, DMSO-d_6) 0.92–2.16(m) (cyclohexyl protons), 6.57(m), 6.86(m), 7.60(m) (aromatic protons). A series of 5-substituted-salicylato(1,2-diaminocyclohexane)platinum(II) compounds was prepared in an analogous fashion starting with the appropriate ligand.

N-Phenylsalicylaldimino(1,2-diaminocyclohexane)platinum(II) nitrate

An aqueous solution (40 ml) containing 0.26 mmole of *cis*-dinitrato(1,2-diaminocyclohexane)platinum(II) was treated with a solution of 0.0510 g (0.26 mmole) of N-phenylsalicylaldimine in 20 ml of ethanol. The resulting mixture was stirred in the absence of light under a static atmosphere of nitrogen at 50°C for 24 h. The solution was filtered and solvent removed by evaporation at reduced pressure to bring the volume to 5 ml. The solution was allowed to stand over Dririte in a desiccator. The yellow crystals which formed were collected by filtration through a sintered-glass funnel at reduced pressure, washed with acetone, and dried over Dririte at reduced pressure (20 torr) to afford the desired compound: dp 312°C; ir(cm^{-1}, CsI) 1605(m) (C=N), 541(w) (Pt–N), 392(w) (Pt–O); proton nmr (δ, DMSO-d_6) 0.81–2.58 (series of multiplets, cyclohexyl protons), 3.36 (m, amino protons), 6.63–7.68 (series of multiplets, aromatic protons), 8.43 (s, olefinic imine proton).

A series of N-(4-substituted-phenyl)salicyladimino(1,2-diaminocyclohexane)platinum(II) nitrates was prepared in an analogous manner.

bis-(2-Thiophenecarboxylato)platinum(II)

Into a 100-ml, round bottomed flask fitted with a magnetic stirring bar was placed an aqueous solution of 0.200 g (0.50 mmole) of potassium tetrachloroplatinate. This solution was stirred vigorously as an aqueous solution of sodium 2-thiophene carboxylate (0.150 g, 0.10 mmole) was added. The black precipitate which formed immediately was collected by filtration through a sintered-glass funnel at reduced pressure, washed with several 10-ml portions of ethanol and dried at 50°C at reduced pressure (20 torr): ir (cm^{-1}, KBr) 1630(s) (carbonyl), 475(w) (Pt–S), 320(w) (Pt–O); proton nmr (δ, DMSO-d_6) 7.18(m), 7.73(m), 7.88(m) (thiophene protons).

Thermogravimetry

The thermal decomposition characteristics of three classes of organoplatinum compounds were examined by thermogravimetry using either a TA Instruments 2100 Thermal Analyzer coupled with a 2950 TGA unit or a DuPont 9900 thermal analysis system coupled to a 951 TGA unit. In a typical run the temperature was ramped at a rate of 5 deg·min^{-1} from 35° to 450°–1000°C as appropriate for complete decomposition of the platinum compound. The TG cell was swept with nitrogen at 50 ml/min during decomposition runs and the sample, approximately 10 mg, was contained in a platinum sample pan. Decay plots, weight loss *vs.* temperature, were generated by feeding the analyzer output (TA Instruments of

DuPont software was used for all data manipulation) to a model 7440 Hewlett-Packard plotter. The temperatures for the onset and maximum of decomposition were obtained from the weight loss derivative plots.

Results and discussion

As part of an ongoing effort to develop polymer-supported organoplatinum antitumor formulations of reduced toxicity [5] platinum compounds containing a variety of ligands have been prepared and characterized. These compounds have been examined by thermogravimetry both to delienate the thermal degradation characteristics of platinum compounds and to explore the utility of thermogravimetry for the characterization of these materials. The thermal decomposition characteristics of representatives of three classes of platinum compounds are presented here.

The thermal curves for the decomposition of the simpliest of a series of 5-substituted salicylato(1,2-diaminocyclohexane)platinum(II) compounds are shown in Fig. 1.

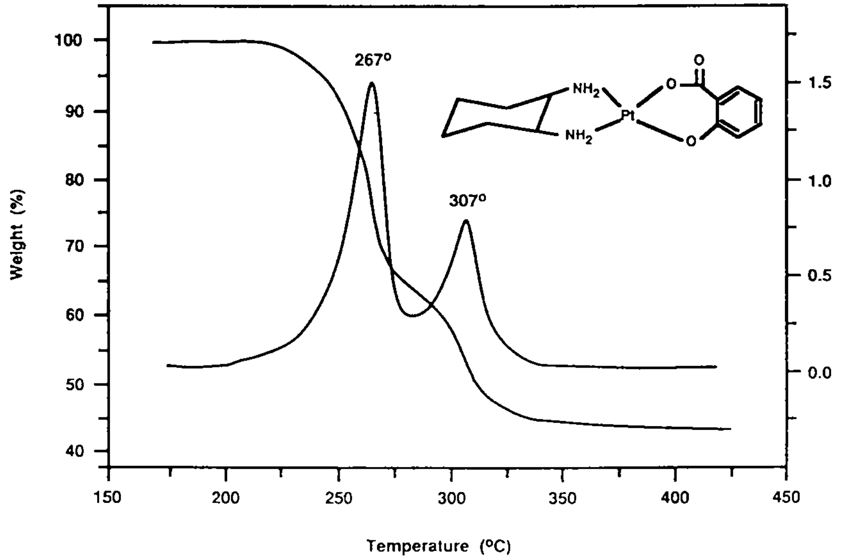

Fig. 1 Thermal decomposition of salicylato(1,2-diaminocyclohexane)platinum(II)

As can be seen, decomposition occurs in two distinct stages. The first (decomposition onset at 221°C, decomposition maximum at 267°C) corresponds to a loss of 32.4% of the initial sample weight. The second (decomposition onset at 286°C, decomposition maximum at 307 °C) corresponds to a loss of 24.0% of the initial sample weight.

A stable residue of 42.7% of the initial sample weight remains. This decomposition corresponds to the sequential loss of salicylato (30.6% of the compound mass) and amine ligand (25.6% of the compound mass) to afford a residue of platinum (43.8% the compound mass). This behaviour is observed for several analogous compounds in which the salicylato ligand bears a substituent(s). However, there are some notable exceptions. For example, 4,5-benzosalicylato(1,2-diaminocyclohexane)platinum(II) loses the total ligand mass as a single event (decomposition onset at 324°C, decomposition maximum at 355°C).

The TG and DTA curves for the decomposition of the simplest of a series of N-arylsalicylaldimino(1,2-diaminocyclohexane)platinum(II)nitrates are presented in Fig. 2.

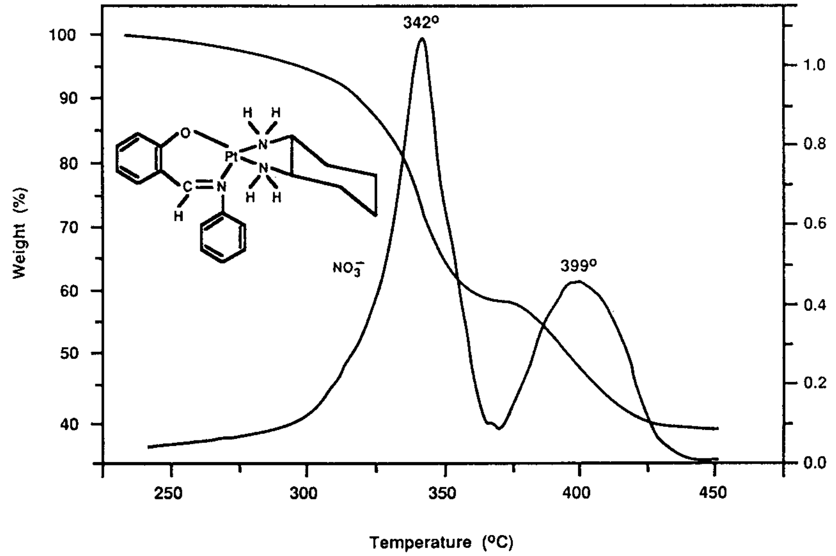

Fig. 2 Thermal decomposition of N-phenylsalicylaldimino(1,2-diaminocyclohexane)-platinum(II)nitrate

Again, the decomposition is characterized by two major losses of mass. The first (decomposition onset at 300°C, decomposition maximum at 342°C) corresponds to a loss of 37.6% of the initial sample weight while the second (decomposition onset at 372°C, decomposition maximum at 399°C) corresponds to a loss of 20.4% of the initial sample weight. The residual weight is 41.9% of the initial weight. At first this may again appear to reflect the sequential loss of ligands. The loss of the salicylaldimino ligand would represent a loss of 34.6% of the initial sample weight while a second loss corresponding to the amine ligand would represent 20.1% of the initial sample weight. However, as can be seen from the derivative plot neither of the observed weight losses (in particular, the second weight loss) may correspond to a single event. Further the residual weight (41.9% of the initial weight) does not correspond to the platinum content (34.4%) of the compound. If the residue were present as a 1:1 mixture of platinum(II) nitrate and platinum(0) it would correspond to 45.3% of the initial sample weight; if it consisted of a 1:1 mixture of platinum(II) oxide and platinum(0) it would correspond to 35.8% of the initial sample weight.

The TG and DTA curves for the decomposition for an entirely different kind of compound are displayed in Fig. 3.

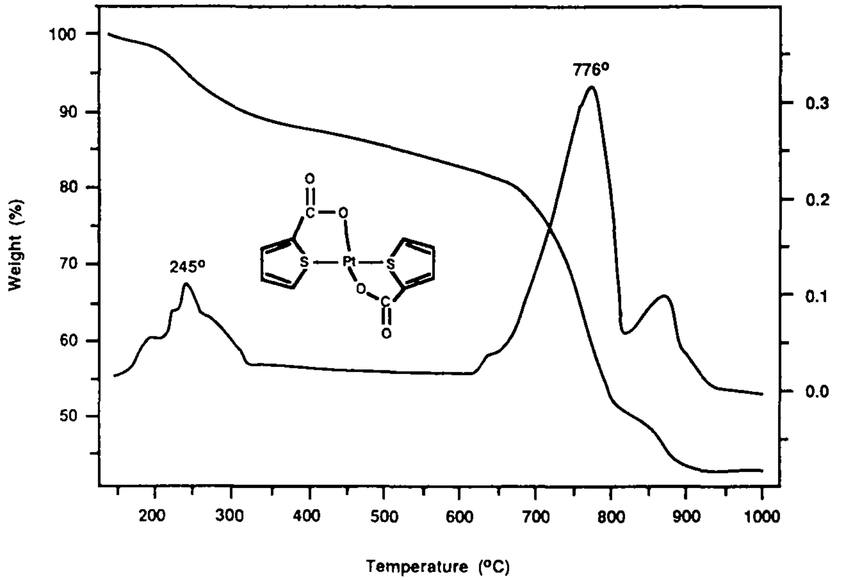

Fig. 3 Thermal decomposition of *bis*-(2-thiophenecarboxylato)platinum(II)

The decomposition pattern is also different from that observed previously. Two major weight losses (decomposition maxima at 776° and 880°C) correspond to the loss of 28.4% of the initial sample weight. However, this is preceeded by multiple events (weight loss maximum at 245°C) which corresponds to a loss of 16.0% of the initial sample weight. As has been observed previously for compounds containing sulfur ligands [15], it seems clear that ligand decomposition rather than ligand loss is the major mode of degradation in this case. The residue

(44.6% of the initial sample weight) does correspond well with that expected (43.4%) for the platinum content of the sample.

Conclusions

Several substituted-salicylato(1,2-diaminocyclohexane)platinum(II) compounds undergo thermal decomposition by sequential loss of first the salicylato ligand and then the amine ligand to afford a residue corresponding to the platinum content of the compound. The thermal decomposition of N-arylsalicylaldimino(1, 2-diaminocyclohexane)platinum(II) compounds is more complex but is characterized by two major weight losses. The thermal decomposition of *bis*-(2-thiophenecarboxylato)platinum(II) is characterized by ligand fragmentation to generate a residual mass corresponding to the platinum content of the compound. Thus, although the mode of decomposition may vary considerably from one class to another, thermogravimetry may be usefully employed in the characterization of organoplatinum compounds.

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The authors gratefully acknowledge the support of this work by the Elsa U. Pardee Foundation. Patrial support for the purchase of the GE QE-300 NMR Spectrometer used in this work was provided by NSF/ILI grant #USE-8852049. The TA Instruments 2950 thermogravimetric analyzer was made available via a grant from the Michigan Research Excellence Fund for the establishment of the Center for Applications in Polymer Science.

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Zusammenfassung — Mittels Thermogravimetrie wurden die thermischen Zersetzungsmerkmale von Vertretern dreier Klassen von Organoplatinverbindungen untersucht. Substituierte Salicylato-(1,2-diaminocyclohexan)platin(II)-Verbindungen zersetzen sich thermisch, indem zuerst die Salicylatoliganden und anschließend die Aminliganden abgegeben werden, wobei ein Rest entsteht, der mit dem Platingehalt der Verbindung übereinstimmt.Die thermische Zersetzung von N-Arylsalicylaldimino((1,2-diaminocyclohexan)platin(II)-nitrat ist komplizierter, ist aber ebenfalls durch zwei größere Masseverluste gekennzeichnet. Die thermische Zersetzung von bis-(2-Thiophencarboxylato)platin(II) ist durch eine Ligandenfragmentation gekennzeichnet, nach der eine Restmasse erhalten wird, die mit dem Platingehalt der Verbindung identisch ist.