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cis-Dichloro(substituted *o*-phenylenediamine)-platinum(II) Compounds

B. A. HOWELL* and E. W. WALLES

Department of Chemistry, Central Michigan University, Mt. Pleasant, Mich. 48859, U.S.A.

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Various organoplatinum compounds exhibit strong antitumor activity [1]. The simplest of these *cis*-dichlorodiamineplatinum(II) (cisplatin) is now widely and effectively used both alone and in combination chemotherapy against tumors difficult to treat by other means [2]. Yet because of the debilitating side effects induced by organoplatinum drugs, the full potential which this compound and its analogs seem to offer has not been realized [3]. To permit the more general use of these compounds for the treatment of cancer, the side effects must be substantially reduced in intensity or removed. A potentially very useful approach to a solution to this problem would be to prepare noncovalent complexes of suitable organoplatinum antitumor agents and appropriate water soluble polymers. The platinum compound–polymer complex could then be administered as the chemotherapeutic agent. Hydrolysis of the complex *in vivo* might slowly release the platinum compound, *i.e.* the bound polymer would serve as a time-release agent such that the free platinum compound would never be present at concentrations sufficient to induce intolerable side effects. While several polymers are capable of forming molecular complexes with suitably-substituted organoplatinum compounds, the polymer of choice for use in a controlled-release formulation would seem to be poly(*N*-vinylpyrrolidone) (PVP). Poly(*N*-vinylpyrrolidone) (1) is readily available in medical grade and in several molecular weight ranges, (2) is water soluble, (3) has long been used as a blood extender with no known toxicity, (4) has received approval from the U.S. Food and Drug Administration for use in drug and food applications, (5) is widely used as a clarification agent in the beverage industry and (6) forms stable molecular complexes with aromatic compounds bearing polar functional groups [4–7].

In the first instance, 4-substituted *o*-phenylenediamines were selected as the ligands to be used for the preparation of suitable platinum compounds. A polar substituent at the 4-position provides a 'handle' for the complexing interaction with the polymer while the 1,2-amino functions provide the necessary *cis* amine structure for the formation of platinum compounds analogous to cisplatin.

*Author to whom correspondence should be addressed.

Experimental

In general, reactions were carried out in the absence of light and oxygen at 50 °C. Reaction mixtures were monitored by thin-layer chromatography using Eastman chromatogram sheets (silica gel with fluorescent indicator) using chloroform/methanol (7.5/2.5) as the eluting solvent mixture. The tlc plates were activated by heating in an oven at 110 °C followed by storage in a desiccator over Drierite. Melting points (m.p.) were measured using a Thomas-Hoover capillary melting point apparatus (m.p. < 250 °C) or a Mel-Temp melting point block (m.p. > 250 °C). Infrared (IR) spectra were recorded using potassium bromide (0.75–1.0 mg of platinum compound per 100 mg of Mallinckrodt infrared-grade potassium bromide) discs and a Perkin-Elmer model 597 spectrophotometer. Solutions in deuterodimethylsulfoxide (DMSO-d_6) and a Varian Associates T-60 spectrometer were used to record proton nuclear magnetic resonance (NMR) spectra. Chemical shits are reported relative to tetramethylsilane (δ 0.00) as internal reference. Analytical samples were prepared by repeated recrystallization followed by drying at 55 °C over anhydrous calcium sulfate in an Abderhalden drying pistol. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

The general procedure for the preparation of the platinum compounds is illustrated below for the synthesis of *cis*-dichloro(3,4-diaminophenol)platinum(II).

cis-Dichloro(3,4-diaminophenol)platinum(II)

A solution of 4.00 g (0.0048 mol) of potassium tetrachloroplatinate in 60 ml of 1.0 N aqueous hydrochloric acid solution was placed in a 100 ml, round-bottomed flask [8, 9]. 3,4-Diaminophenol dihydrochloride (0.86 g, 0.0048 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 50 °C (water bath) for 60 h. The pale green crystals which had formed were collected by filtration at reduced pressure, washed successively with two 100 ml portions of water, 100 ml of acetone and 100 ml of anhydrous diethyl ether, and dried at reduced pressure over Drierite (1.74 g, 93% yield): m.p. > 400 °C; IR (cm^{-1}, KBr) 3450 (m-broad, O–H), 3215(m), 3180-(m) (N–H), 1620(m) (aromatic nucleus), 1205(s) (phenolic C–O); proton NMR (δ, DMSO-d_6) 6.54, 6.64 and 7.02 (ABX pattern, J_{AB} = 7.9 Hz, J_{BX} = 3.0 Hz), 7.23–7.40 (broad singlet, exchangeable protons).

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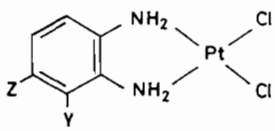
cis-Dichloro(3,4-diaminobenzenesulfonic acid)-platinum(II)

Since this compound is highly soluble in water, a modification of the procedure described above was required for its preparation. 3,4-Diaminobenzenesulfonic acid (0.25 g, 0.0016 mol) was dissolved in a solution of 0.66 g (0.0016 mol) of potassium tetrachloroplatinate in 12 ml of 1.0 N aqueous hydrochloric acid. The solvent was removed from the resulting orange–red solution by rotary evaporation at reduced pressure. The tan residue was titurated with 50 ml of dimethylformamide and the resulting solution was decanted from the insoluble potassium chloride. Treatment of the DMF solution with 400 ml of acetone afforded a clumpy red precipitate. The solid was collected by filtration at reduced pressure, washed successively with 50 ml of acetone and 50 ml of anhydrous diethyl ether, and dried at reduced pressure over Drierite (0.16 g, 64% yield).

Results and Discussion

Several *cis*-dichloro(substituted *o*-phenylenediamine)platinum(II) compounds have been prepared to serve as substrates for complex formation with water-soluble polymers [10]. The necessary substituted *o*-phenylenediamine ligands were readily synthesized from commercially available starting materials. Treatment of these ligands with potassium tetrachloroplatinate(II) in aqueous acidic solution at 50 °C afforded the corresponding platinum compounds in good yield. The platinum compounds (structures shown below), were characterized by spectroscopic methods and by elemental analysis.



Z	Y
H	H
OH	H
H	OH
COOH	H
OCH_3	H
SO_3H	H

The proton NMR spectra of all of the compounds contain complex absorption patterns due to the overlapping of the signals due to the aromatic protons and the amino protons. The infrared spectrum of each of the compounds contains a strong band at 3200 cm^{-1} attributable to the presence of the amino group in the compound. The spectrum of *cis*-dichloro(3,4-diaminobenzoic acid)platinum(II) contains a carbonyl absorption at 1730 cm^{-1} (KBr). None of the platinum compounds melt, even at 400 °C, except for *cis*-dichloro(3,4-diaminobenzoic acid)platinum(II), which decomposes at 380 °C. Elemental analyses for these compounds are reported in Table I.

TABLE I. Elemental Analysis Results for *cis*-Dichloro(substituted *o*-phenylenediamine)platinum(II) Compounds

Substituents		Actual (%)			Calculated (%)		
Z	Y	C	H	N	C	H	N
H	H	19.53	2.08	7.45	19.26	2.16	7.49
OH	H	18.57	2.20	7.14	18.47	2.06	7.18
H	OH	18.42	2.12	7.12	18.47	2.06	7.18
COOH	H	20.29	2.06	6.72	20.11	1.93	6.74
OCH_3	H	20.99	2.62	6.94	20.80	2.49	6.93

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