Mixed Ligand Complexes of *cis*-Dichloroethionine Palladium(II) with Purines, Pyrimidines and Nucleosides

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(Received August 18, 1989; revised October 20, 1989)

Abstract

Mixed ligand complexes of *cis*-dichloroethionine palladium(II) with adenine, adenosine, guanine, guanosine, hypoxanthine, inosine, cytosine and cytidine were synthesised and characterised by elemental analysis, conductivity data, IR and ^1H NMR spectral studies. In all these mixed ligand complexes the ethionine molecule coordinates to the palladium through the amino nitrogen and sulphur atoms, thus leaving a free carboxylic acid group. In the complexes of purines and their corresponding nucleosides, the ligand binding site to the metal ion is N_7, whereas in the case of pyrimidine and their corresponding nucleosides it is N_3.

Introduction

Since the discovery of anticancer effects of *cis*-dichlorodiammineplatinum(II) (cisplatin) [1], studies had been undertaken to determine the relationships between chemical structure and antitumor activity [2, 3]. Because of the higher antitumor activity of the *cis* as compared to *trans* compounds [4], efforts were made to synthesise various platinum(II) complexes with *cis* geometry. This is because of the fact that cisplatin exhibits its biological activity by binding to interstrand purine bases of DNA and inhibiting replication [5–7]. The platinum group complexes of nucleic acid constituents were found to possess antitumor and antibacterial activity [8–12]. We have, therefore, undertaken a study of the ternary complexes of platinum group metals with amino acids and nucleic acid constituents [13–18], which may serve as models for metallo-enzyme reactions in biological system.

Even though considerable work has been done on the complexes of S-containing amino acids with palladium(II) [19–25], very little is, however, reported on ethionine complexes [26–28]. In this paper, we report the mixed ligand complexes of *cis*-dichloroethionine palladium(II) with adenine, adenosine, guanine, guanosine, hypoxanthine, inosine, cytosine and cytidine.

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Experimental

Chromotagraphically pure DL-ethionine, adenine, adenosine, guanine, guanosine, hypoxanthine, inosine cytosine and cytidine were obtained from Sigma Chemical Company, U.S.A. Palladium chloride was purchased from Johnson Mathey, U.K. *cis*-Dichloroethioninepalladium(II) was prepared by the published procedure [26].

All solvents used were of high purity and distilled in the laboratory before use. Elemental analysis were obtained from Central Drug Research Institute, Lucknow, India. Conductivity measurements were carried out on conductivity meter No. DL 909. The IR spectra were recorded in KBr pellets on a Shimadzu 435 spectrophotometer. The ^1H NMR spectra of the complexes were recorded on a JEOL 100 MHz spectrometer at the Central Salt & Marine Chemicals Research Institute, Bhavnagar. All the ^1H NMR spectra were recorded in D_2O solvent.

Preparation of Complexes: cis-Dichloroethioninepalladium(II), [Pd(DL-ethionine)Cl$_2$] (1); Chloroadenineethioninepalladium(II) Chloride, [Pd(DL-ethionine)(ade)Cl]Cl (2); Chloroadenosineethioninepalladium(II) Chloride Monohydrate, [Pd(DL-ethionine)(adenos)Cl]Cl·H$_2$O (3); Chloroguanineethioninepalladium(II) Chloride Monohydrate, [Pd(DL-ethionine)(gua)Cl]Cl·H$_2$O (4); Chloroguanosineethioninepalladium(II) Chloride Monohydrate, [Pd(DL-ethionine)(guanos)Cl]Cl·H$_2$O (5); Chlorohypoxanthineethioninepalladium(II) Chloride, [Pd(DL-ethionine)(hypo)Cl]Cl (6) Chloroinosineethioninepalladium(II) Chloride Dihydrate, [Pd(DL-ethionine)(inos)Cl]Cl·2H$_2$O (7); Chlorocytosineethioninepalladium(II) Chloride Monohydrate, [Pd(DL-ethionine)(Cyt)Cl]Cl·H$_2$O (8); Chlorocytidineethioninepalladium(II) Chloride Dihydrate, [Pd(DL-ethionine)(Cyd)Cl]Cl·2H$_2$O (9)

For the preparation of complex **1**, DL-ethionine (0.250 g, 1.5 mM) was dissolved in 10 ml of warm water and to this a solution of K_2PdCl_4 (0.490 g, 1.5 mM) was added. The solution was warmed on a water bath with stirring when the dark brown colour of the solution changed to orange. The heating was continued for a further 20 min. On cooling

0020-1693/90/$3.50

(0 °C), an orange crystalline solid separated out, which was filtered, washed with cold water, alcohol, ether and dried *in vacuo*.

In a general method for the preparation of complexes **2–9**, *cis*-dichloroethioninepalladium(II) (0.587 mM) in water was added to an aqueous solution of purine, pyrimidine or nucleoside (0.587 mM). The resulting solution was refluxed on a water bath for 3 h and the solution concentrated to half of its volume, cooled and filtered. When kept overnight in the refrigerator, the complex separated out. It was washed with acetone and dried *in vacuo*.

Results and Discussion

The conductivity of complex **1** in DMSO (5 mhos) indicates that it is a non-electrolyte. For complexes **2–9**, the conductivity values vary from 20–30 mhos (Table 1) indicating that these complexes are 1:1 electrolytes.

In the IR spectra of all these mixed ligand complexes, the presence of the COOH band around 1700 cm^{-1} indicates a free carboxylic acid group of ethionine. The important ligational frequencies of purines, pyrimidines and nucleosides are the ν(C=C), ν(C=N) and ν(C=O) modes. The ν(C=C) and ν(C=N) frequencies of purines, pyrimidines and nucleosides are observed around 1450–1600 cm^{-1} and undergo a significant shift (~80 cm^{-1}) on complexation compared to the frequencies in the free ligands indicating the involvement of ring nitrogen in coordination to the metal ion. There is no significant shifts in the ligational frequencies of ν(C=O) and δNH_2 modes observed around 1710 and 1680 cm^{-1}, respectively, excluding the coordination of C=O or NH_2 groups of the ligands to the metal ion. The ν(OH) mode of coordinated water appears as a medium band around 3300 cm^{-1}.

The ^1H NMR spectrum of DL-ethionine gives a triplet centered at 1.50 ppm corresponding to the methyl protons. The quartet centered at 2.95 ppm and a triplet centered at 2.85 ppm can be attributed to the S-CH_2 protons. The resonance peak observed as a triplet of doublets centered at 2.38 ppm arises due to the methylene (–CH_2–) protons. The resonance peak observed as a triplet at 4.10 ppm corresponds to the –CH– protons.

In complex **1**, the S-CH_2 and –CH resonance peaks are shifted downfield by 0.25 and 0.40 ppm, respectively, indicating that the sulphur and NH_2 groups of ethionine are coordinated to the metal ion. This is also supported by the reported [27] crystal structure of complex **1**.

In the ^1H NMR spectrum of complex **2**, the signals observed at 8.27 and 8.54 ppm are assigned to C_2H and C_8H protons of coordinated adenine, respectively. The peak corresponding to the C_8H proton is shifted more downfield (0.22 ppm) than that of C_2H (0.07 ppm) indicating that N_7 of adenine is

TABLE 1. Characterisation and conductivity data of mixed ligand complexes of palladium(II) ethionine

Complex	Analysis: Calculated (found) (%)			Conductivity in DMSO[a] (mho cm^2 mol^{-1})
	Carbon	Hydrogen	Nitrogen	
[Pd(DL-ethionine)Cl_2] (1)	21.16 (21.33)	3.84 (3.91)	4.11 (4.14)	5
[Pd(DL-ethionine)(ade)Cl]Cl (2)	27.77 (27.52)	4.23 (4.19)	17.66 (17.80)	28
[Pd(DL-ethionine)(adenos)Cl]Cl·H_2O (3)	30.70 (30.89)	4.50 (4.43)	13.42 (13.31)	26
[Pd(DL-ethionine)(gua)Cl]Cl·H_2O (4)	25.91 (25.74)	3.95 (3.92)	16.49 (16.68)	20
[Pd(DL-ethionine)(guanos)Cl]Cl·H_2O (5)	30.80 (31.02)	4.20 (4.14)	13.47 (13.65)	21
[Pd(DL-ethionine)(hypo)Cl]Cl (6)	27.72 (27.83)	3.60 (3.57)	14.69 (14.78)	22
[Pd(DL-ethionine)(inos)Cl]Cl·$2H_2O$ (7)	29.80 (29.58)	4.53 (4.60)	10.85 (10.72)	27
[Pd(DL-ethionine)(cyt)Cl]Cl·H_2O (8)	25.57 (25.42)	4.29 (4.36)	11.92 (11.70)	23
[Pd(DL-ethionine)(cyd)Cl]Cl·$2H_2O$ (9)	29.04 (29.25)	4.87 (4.82)	9.02 (8.97)	24

[a] 1×10^{-3} molar solutions.

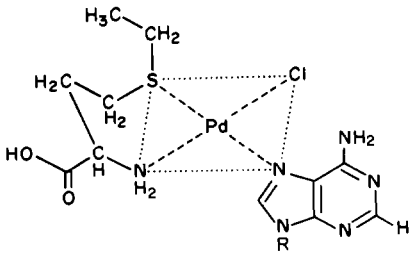

Fig. 1. Structure of [Pd(DL-ethionine)(ade)Cl]Cl, R = H and [Pd(DL-ethionine)(adenos)Cl]Cl·H_2O, R = ribose.

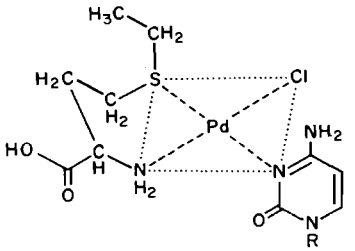

Fig. 2. Structure of [Pd(DL-ethionine)(cyt)Cl]Cl·H_2O, R = H and [Pd(DL-ethionine)(cytd)Cl]Cl·$2H_2O$, R = ribose.

coordinating site to the metal ion. Such a situation also exists for complex **3** where the C_8H proton is shifted more downfield (0.23 ppm) than the C_2H proton indicating N_7 as the coordinating site in adenosine. Based on the above discussions the tentative structures of complexes **2** and **3** are given in Fig. 1. In the ^1H NMR spectrum of complex **4**, the peak at 8.35 ppm for the C_8H proton of coordinated guanine shows a downfield shift of about 0.67 ppm indicating that N_7 of guanine is the metal binding site. In the ^1H NMR spectrum of complex **5** the peak for the C_8H proton of coordinated guanosine at 8.42 ppm also shows a downfield shift of about 0.54 ppm, which is evidence for the coordination of N_7 of guanosine to the metal ion.

The ^1H NMR spectrum of complex **6** exhibits a downfield shift of 0.78 ppm for the C_8H proton of hypoxanthine which shows N_7 as the site of coordination to the metal ion. In the ^1H NMR spectrum of complex 7, the signals observed at 8.88 and 8.34 ppm are assigned to C_8H and C_2H protons of coordinated inosine, respectively. Since the signal due to the C_8H proton is shifted more (0.66 ppm) than that for the C_2H proton (0.23 ppm), N_7 of inosine is proposed as the binding site to the metal ion. In the ^1H NMR spectrum of complex **8**, the signals at 6.08 and 7.57 ppm correspond to the C_5H and C_6H resonances of coordinated cytosine. The C_5H proton has a downfield shift of 0.20 ppm as compared to the C_6H proton (0.10 ppm) indicating N_3 of cytosine as the site of coordination. Such a situation also exists for complex **9** where the C_5H proton is shifted to downfield (0.58 ppm) more than the C_6H proton (0.20 ppm) indicating N_3 as the coordinating site in cytidine. The tentative structures of complexes **8** and **9** are given in Fig. 2.

Acknowledgements

K. Najmuddi, S. Shamsuddin (Junior Research Fellows) and S. M. Zakeeruddin (Research Associate) are grateful to CSIR, New Delhi for financial assistance.

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