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Water Soluble *cis*-Platinum(II) Complexes

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Abstract

The *cis*-platinum(II) complexes of 2-desoxystreptamine, D-glucosamine and 1-amino-2-methyl-2-propanol have been prepared and their synthesis is discussed in detail. The complexes were extremely water soluble, thus they were expected to be less toxic than *cis*-DDP. Their structure has been studied by elemental analysis, infrared and ^1H NMR spectra.

Introduction

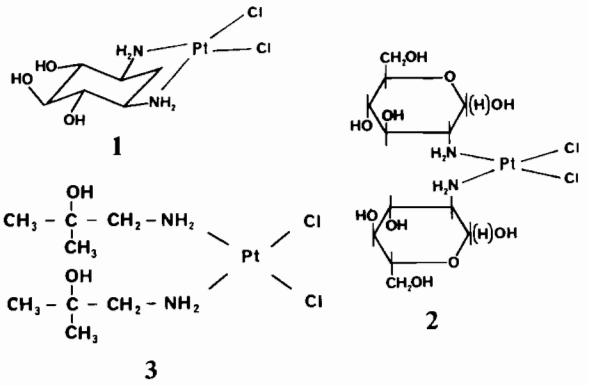
The *cis*-platinum(II)-dichlorodiamine complex (*cis*-DDP) [*cis*-$Pt(NH_3)_2Cl_2$], which has the ability to reduce or cure certain cancers [1] (testicular, ovarian, lung etc.) has been in use for some time. Its water insolubility and great toxicity, however, are serious disadvantages. Numerous dichloro platinum(II) complexes, with a variety of amine or diamine ligands have been synthesized [2], but they did not have better properties, concerning activity, solubility or toxicity, in comparison with *cis*-DDP.

Recently Kidani *et al.* [3] announced the antitumor activity of mono- and bis-D-glucuronato platinum(II) complexes of 1*R*,2*R*-cyclohexanediamine, which were water soluble and their antitumor activity was higher than *cis*-DDP. In addition they announced that the sub-acute toxicity tests were almost attenuated, while a slide side effect of pancreas was observed.

Results and Discussion

In an attempt to circumvent the *cis*-DDP disadvantages (solubility and toxicity), we used amino sugars or hydroxy amines as ligands and prepared extremely water soluble *cis*-Pt complexes. The final aim was to study the antitumor activity in relation to the structural features and the solubilities of these complexes.

Since other workers are announcing the synthesis of water soluble *cis*-Pt complexes, we are prompted to disclose our synthesis *cis*-(2-desoxystreptamine)-dichloroplatinum(II) (**1**), *cis*-dichloro[bis(D-glucosamine)]platinum(II) (**2**) and *cis*-[bis(1-amino-2-methyl-2-propanol)] dichloroplatinum(II) (**3**).



Scheme 1.

The reaction of the hydroxy amines or hydroxy diamine with K_2PtCl_4, 2:1 or 1:1 molar ratios respectively, was carried out in water. The rate of complexation was followed by monitoring the pH of the reaction medium, which was maintained at around 6.5 by addition of 0.1 N NaOH solution*. We found that maintenance of this pH is essential for good yields, short reaction times and avoidance of by-products (dimers etc.). On the other hand the time required for the formation of a *cis*-Pt complex is related to its solubility in water. As shown

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*This procedure was used for the preparation of *cis*-Pt(II) complexes using a variety of ligands, which otherwise were difficult to prepare in pure form.

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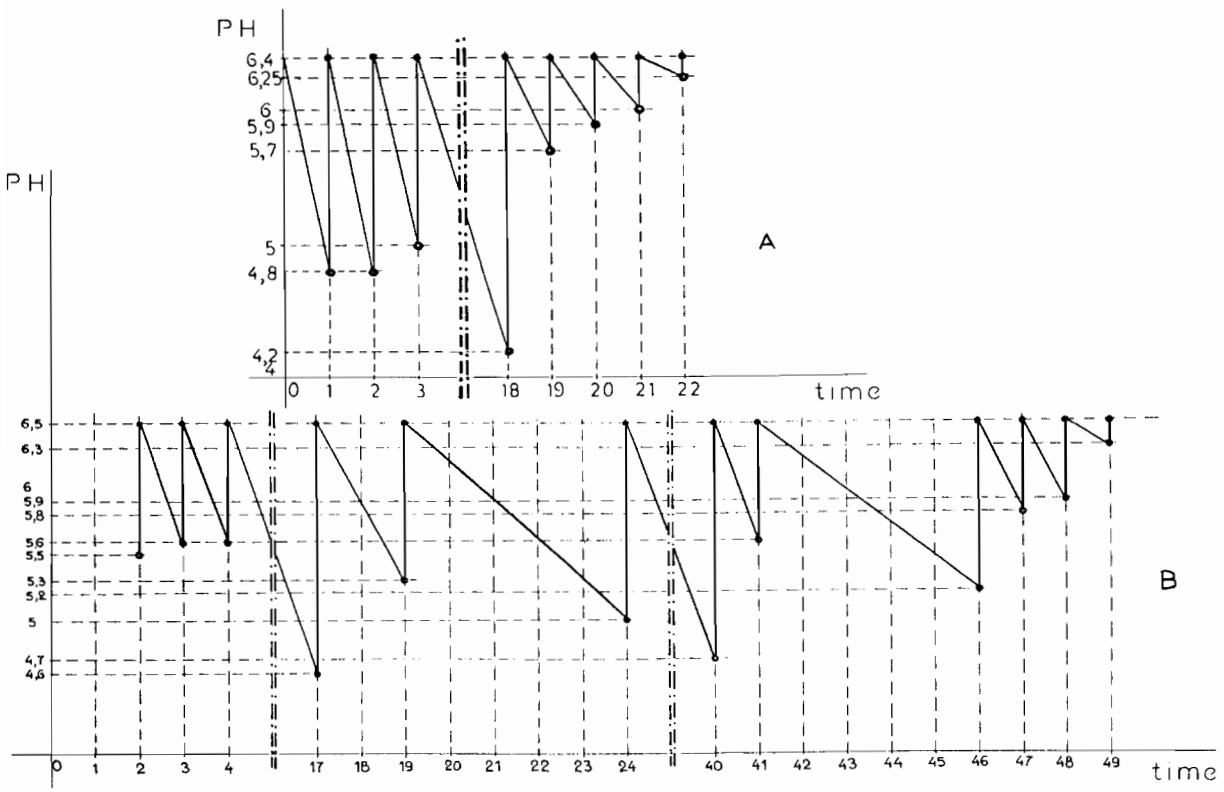

Fig. 1. pH monitoring of formation of water soluble *cis*-Pt complex.

in Fig. 1 the monitoring of the pH can serve as an indicator of the end point of the formation of a water soluble *cis*-Pt complex. In the specific example of Fig. 1 it is shown that the time required for the formation of the moderately water soluble *cis*-[3-amino-2-(*p*-methoxy phenyl)-2-methyl-tetrahydro-2H-pyran-3-yl methylamine] dichloroplatinum(II) [4], **A**, is 22 h, in contrast to the *cis*-(2-desoxystreptamine) dichloroplatinum(II), **B**, which is 49 h.

The chemical shift (^{1}H NMR) of the amino groups of 2-desoxystreptamine is downfield when the platinum complex is formed, giving a characteristic pattern. Thus the chemical shifts at 5.19 (dd, J = 3.40) and 5.54 (dd, J = 3.40) indicate the formation of a Pt–N bond. Similarly in **2** the characteristic chemical shift appears at 5.20 (dd, J = 3.44) and in **3** at 5.05(m).

The IR spectra reveal [5] that the N–H stretching vibration has changed considerably upon formation of the metal–nitrogen bond [3180 cm^{-1} (**1**), 3120 cm^{-1} (**2**), 3195 cm^{-1} (**3**)]. The very weak absorptions in the region of 530 cm^{-1} [525 cm^{-1} (**1**), 542 cm^{-1} (**2**), 535 cm^{-1} (**3**)] are characteristic of the metal–nitrogen vibration, while the two absorption bands in the far infrared close to 320 cm^{-1} [312, 320 cm^{-1} (**1**), 320, 326 cm^{-1} (**2**), 318, 325 cm^{-1} (**3**)], were used as indication of the *cis* metal–chlorine structure (two absorption bands for the *cis*-isomer in contrast with the *trans* configuration where there is only one absorption).

Experimental

Melting points were determined in open capillary tubes with a Gallenkamp apparatus, and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the University of Illinois. ^{1}H NMR spectra were obtained on a Nicolet NTC360, 360 MHz spectrometer using DMSO as solvent. Chemical shifts were measured with respect to internal TMS. IR spectra were recorded on a Perkin-Elmer Model 283 B infrared spectrophotometer from samples prepared in accordance with the KBr disk technique.

2-Desoxystreptamine Hydrobromide

It was prepared by acidic hydrolysis of Neomycin*.

*2-Desoxystreptamine hydrobromide was prepared by V. Konstadinou according to unpublished procedure of M. P. Georgiadis.

TABLE I. Analytical and Other Data

Compound	Formula	Analysis (%) (calc. (found))			Melting point (°C)	Reaction time (h)	Colour	Yield (%)
		C	H	N				
1[a]	$C_6H_{14}O_3N_2Cl_2Pt$	16.83 (17.14)	3.30 (3.56)	6.54 (6.67)	76–78 (turns yellow) 207 (dec.)	49	off white (pale tan)	66.62
2	$C_{12}H_{26}O_{10}N_2Cl_2Pt$	23.08 (23.00)	4.20 (4.60)	4.49 (4.82)	165 (turns yellow) 203 (dec.)	42	white	72.40
3	$C_8H_{22}ON_2Cl_2Pt$	22.43 (22.41)	5.18 (5.15)	6.54 (6.71)	103–105 (dec.)	68	ivory	70.51

[a]Compound 1 is moderately stable in the air, but is stable in vacuum or in solution.

D-glucosamine Hydrochloride

Aldrich, U.S.A. It was used without any further purification, melting point (m.p.) 190–194 °C (decomposition (dec.)).

1-Amino-2-methyl-2-propanol [6]

It was prepared from acetone via its cyanohydrin and subsequent hydrogenation. The product was purified by distillation (boiling point (b.p.) 151 °C) and was identified by IR and NMR spectra.

cis-(2-Desoxystreptamine) Dichloroplatinum(II)

To a solution of 2-desoxystreptamine hydrobromide (0.117 g, 0.36 mM) in 10 ml H_2O, K_2PtCl_4 (0.15 g, 0.36 mM) in 10 ml H_2O was added in one pot with stirring. The pH of the reaction was monitored (and maintained) at 6.5 until the end of the reaction. Then the solution was evaporated to dryness under a stream of air (or lyophillization) and the complex was dissolved (in contrast with the inorganic by-products) in anhydrous DMF and precipitated by the addition of anhydrous acetone.

Compounds 2 and 3 were synthesized by the same procedure. Analytical and other data are shown in Table I.

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