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Reaction of 2-Amino-5-nitrothiazole with Palladium Salts

NICHOLAS FARRELL* and T. M. GOMES CARNEIRO

Departmento de Quimica-ICEx, Universidade Federal de Minas Gerais Belo Horizonte, MG 30000, Brasil

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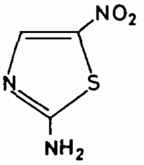
Abstract

The complexation of 2-amino-5-nitrothiazole, (ANT), a radiosensitizing drug has been studied with palladium. In methanol, the product is the square-planar complex, *trans*-$[PdCl_2(ANT)_2]$ with the binding site being the ring nitrogen. In water, however, the product is the chelate, $[Pd(ANT)_2]Cl_2$, the chelation being from the ring nitrogen and the exocyclic amine.

Introduction

Recently we have been interested in the study of metal complexes as radiosensitizers in cancer treatment [1]. Radiosensitization refers to the enhancement of radiation damage by drugs, especially in hypoxic (oxygen-deficient) cells, and may occur by a variety of mechanisms [2]. A major area of study is that of the 'electron-affinic' approach using nitroimidazoles [3] and nitrofurans [4], which may interact with the ultimate target of radiation damage, DNA, in a manner similar to oxygen. The strong binding of platinum, in its complexes, to purine and pyrimidine bases suggested to us [1], and others [5, 6], the possibility of targetting the nitroimidazoles by complexation to metals such as platinum. As part of our general studies on metal complexation of radiosensitizer ligands we have also studied 2-amino-5-nitrothiazole (ANT)



As with nitroimidazoles [1] we have found it useful to study both palladium and platinum complexes and this paper reports on our studies with palladium. A recent article summarised complexes of this ligand with some first row metals [7].

Experimental

The sodium tetrachloropalladate used was a gift from Johnson-Matthey and Co. Ltd. The 2-amino-5-nitrothiazole was from Aldrich and was recrystallized from methanol before use.

Physical Methods

IR spectra were recorded as KBr discs on a Perkin-Elmer 467 instrument. UV–Vis spectra were run on a Cary-17D spectrophotometer. Conductivity measurements were made on a Metrohm E-527 meter. Elemental analyses were from CETEC, Belo Horizonte.

Preparation of the Complexes

The complex *trans*-$[PdCl_2(ANT)_2]$ (**I**) was prepared by adding a solution of the ligand (29.0 mg, 2 mmol), in MeOH (5 ml) to a solution of Na_2PdCl_4 (29.0 mg, 1 mmol) in MeOH (10 ml). An immediate orange precipitate was obtained and after 1h the precipitate was filtered off, washed with cold methanol and diethylether, yield 72%. *Anal.* Calc. for $C_6H_6Cl_2N_6O_4PdS_2$: C, 15.41; H, 1.29; N, 17.96. Found: C, 14.85; H, 1.39; N, 18.44%.

The complex $[Pd(ANT)_2]Cl_2$ (**II**) was obtained in an identical manner using water as the reaction medium and the brick-red precipitate was washed with cold water and dried *in vacuo*, yield 63%. Found: C, 16.03; H, 1.50; N, 17.60%.

The tetrafluoroborate and nitrate complexes were prepared by metathesis from **I** or **II** using the appropriate silver salt in MeOH. The hot solutions were filtered to remove insoluble silver chloride and upon evaporation to half-volume and cooling red–brown products precipitated out. *Anal.* Calc. for $C_6H_6B_2F_8N_6O_4PdS_2$: C, 12.62; H, 1.05; N, 14.70. Found: C, 12.32; H, 1.24; N, 15.00%. Calc. for $C_6H_6N_8O_{10}PdS_2$: C, 13.84; H, 1.15; N, 20.15. Found: C, 14.16; H, 1.20; N, 21.03%.

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*Author to whom correspondence should be addressed at Department of Chemistry, University of Vermont, Burlington, Vt. 05404, U.S.A.

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TABLE I. Selected Spectroscopic and Physical Properties of Palladium Complexes of 2-Amino-5-nitrothiazole (ANT)

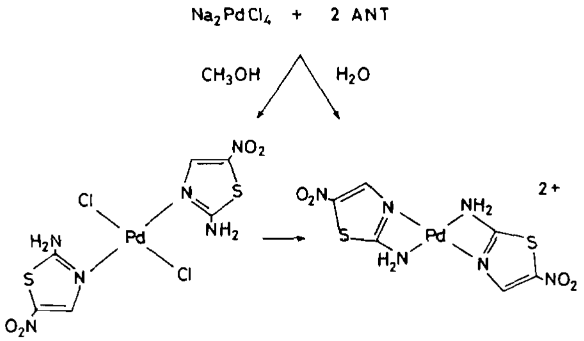
Complex	IR (cm^{-1})		UV–Vis (nm) (log ϵ)		Λ_m (ohm^{-1} cm^2 mol^{-1})	
	ν(NH)	ν(Pd–Cl)	H_2O	CH_3OH	$MeNO_2$	CH_3OH
ANT	3430, 3400 3150, 3100		380 (4.7)	380 (4.7)		
$PdCl_2(ANT)_2$ (orange, I)	3390, 3280 3200, 3110	360	385 (4.3)	370 (4.5) 450	63.0	44.0
$[Pd(ANT)_2]Cl_2$ (brick red, II)	3300, 3110	–	385 (4.3)	370 (4.5) 450	100	240
$[Pd(ANT)_2](BF_4)_2$	3300, 3110	–	–	370 (4.5) 445	103	206
$[Pd(ANT)_2](NO_3)_2$	3300, 3110	–	–	375 (4.4) 445	–	177

Results and Discussion

The reaction of Na_2PdCl_4 with two equivalents of ANT in MeOH gave a bright-orange solid analysing for $[PdCl_2(ANT)_2]$ (**I**). The IR data indicated the *trans* configuration with only one strong ν(Pd–Cl) (Table I). The free ANT ligand shows four bands in the ν(NH) region of the IR spectrum, indicative of inequivalent N–H bonds. The IR spectrum of the product also shows four bands; the two high frequency bands being downshifted in comparison to the free ligand. The nature of the bands was confirmed by deuteration. The major binding sites of ANT are the ring nitrogen and exocyclic amine and the absence of any major perturbations of the N–H frequencies may be considered to be indicative of binding through the ring nitrogen. This is also in accord with previous results for nickel and cobalt complexes with methanol as solvent [7] and the product from methanol can be considered to be the simple square-planar adduct *trans*-$[PdCl_2L_2]$, with L being ring-bound ANT.

A different reaction, however, occurs between these two reactants in aqueous medium. We noticed that upon dissolution of the methanol product, *trans*-$[PdCl_2(ANT)_2]$, in water an immediate colour change occurred and a dark brick-red product was isolated. To ascertain the nature of this product we carried out the reaction between Na_2PdCl_4 and ANT in water. The brick-red product also analysed for $PdCl_2(ANT)_2$ (**II**) but the IR spectrum showed only two N–H bands, one being very broad, and ν(Pd–Cl) was absent. Reaction of product **II** with two equivalents of $AgBF_4$ gave a red-brown product analysing for $[Pd(ANT)_2](BF_4)_2$, and the same salt was also isolated from the reaction of **I**, *trans*-$[PdCl_2(ANT)_2]$, with $AgBF_4$; the IR spectra being identical. Similar chemistry occurred with $AgNO_3$ instead of the tetrafluoroborate.

In agreement with the arguments previously developed for assignment of ANT binding sites, and also the simpler 2-aminothiazole [8–11], the exocyclic amine is indicated as a binding site in the case of product **II** from aqueous solution. However, the absence of ν(Pd–Cl) in the latter case indicates that the different products are not simply linkage isomers. Conductivity studies in MeOH show that **II** is a 1:2 conductor, like its BF_4 and NO_3 analogues, although in nitromethane the values are intermediate. The best explanation for these facts, then, is that a chelate is being formed and a scheme may be written



I **II**

and

$$\underset{\mathrm{I}}{trans\text{-}[PdCl_2(ANT)_2]} \underset{CH_3OH}{\overset{H_2O}{\rightleftharpoons}} \underset{\mathrm{II}}{[Pd(ANT)_2]Cl_2}$$

$$\begin{matrix} trans\text{-}[PdCl_2(ANT)_2] \\ \text{or} \\ [Pd(ANT)_2]Cl_2 \end{matrix} \xrightarrow{AgBF_4} [Pd(ANT)_2](BF_4)_2$$

An interesting fact is that the nature of these products is easily reversible and is dependent on the solvent. Thus, dissolution of **I** in H_2O gives **II** and dissolving **II** in MeOH readily gives back **I** after a few minutes. This can be seen in the UV–Vis spectrum, where increasing the % MeOH in aqueous solution causes a distinctive shoulder at 440 nm to grow in. Also, the conductivity of **II** in MeOH decreases as the colour changes back to the orange of the *trans* isomer **I**. The complexes with weakly coordinating anions such as NO_3 and BF_4 do not undergo this change in MeOH as expected.

The binding sites of aminothiazoles and its substituted derivatives such as ANT have generally been discussed in terms of solid state structures [7–12], and the ready conversion from one form to another in solution has not been observed previously. The ease of conversion on palladium is probably due to a number of factors including the labile nature of palladium complexes. Differences in binding site for Ni and Co complexes were observed when DMF was used as solvent instead of MeOH, the more polar solvent favouring amine coordination [7]. The explanation that greater solvation in DMF will essentially hinder sterically the ring nitrogen is probably also valid in the present case but rapid hydrolysis of the chloride ligands can permit chelation. The rapid isomerisation of the *trans* complex in H_2O reflects this. In MeOH, as for Ni, coordination of the ring nitrogen is favoured. Four-membered chelate rings are rarer than the more stable 5-membered rings, but do exist; a relevant example is 2-aminopyridine [13].

The deactivating nitro group does not make ANT a strong ligand and HPLC studies indicate extensive dissociation. The complexes give only radiosensitization equivalent to the free ligand [14], as was the case for the Pd-nitroimidazole complexes [15]. The activity of platinum–ANT complexes has been studied by ourselves and others [15, 16] but it is clear that similar chemistry to that described here must prevail and the results must be understood in this context. The observation of a very clear isomerisation has in fact helped in our elucidation of the Pt system and these results will be presented shortly.

Acknowledgements

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