Inorganica Chimica Acta, 66 (1982) L1–L2

Potential Anti-Cancer Complexes: Binding Site Determination-II

ADEGVOYE ADEYEMO*

Department of Chemistry, Howard University, Wash, D.C. 20059, U.S.A.

and RAJENDRA P. RAVAL

Department of Chemistry, Virginia Union University, Richmond, Va. 23220, U.S.A.

Received September 21, 1981

Introduction

The discovery of Rosenberg *et al.* more than two decades ago that *cis*-diamin complexes of platinum-(II) and platinum(IV) could be effective against tumor laid down an immortal foundation for cancer research that has turned out to be a multi-billion dollar project throughout the world today. Although, there are numerous reports on potential anti-tumor complexes, not many have been found very satisfactorily effective, a situation which has led to a great disappointment both within and outside the scientific world. While the high hope to find a permanent solution to cancer problems, still lingers on, most of whatever has been done to this end, so far, remains a matter of academics. In an effort to find the most satisfactory anti-cancer complexes, we report here the synthesis and characterization of Pd(II) complexes with 4-amino-2,5-dimethylpyrimidine (ADMPY).

Experimental

The organic ligands, 4-amino-2,5-dimethylpyrimidine and 1-methyl-(4-amino-2,5-dimethyl) pyrimidinium iodide were prepared as described earlier [1, 2]. The Pd(II) complexes of these ligands were prepared by mixing aqueous solutions of the ligands and metal salt, K_2PdCl_4 (4:1 mole ratio). There was no immediate formation of precipitate upon mixing aqueous solutions of ADMPY and metal salt. On the contrary, there was an immediate formation of precipitate upon mixing aqueous solutions of M-ADMPY and metal salt. The precipitate formed in each case was thoroughly washed with cold distilled water, acetone and ether, and then air-dried.

*Author to whom correspondence should be addressed.

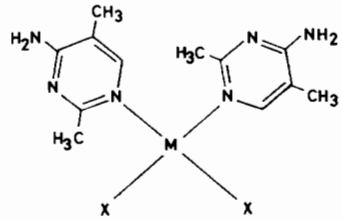

Fig. 1. Possible *Cis* Structure of $PdADMPYCl_2$.

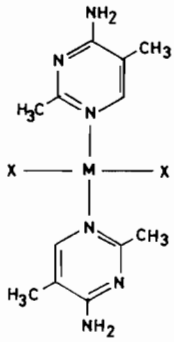

Fig. 2. Possible *Trans* Structure of $PdADMPYCl_2$.

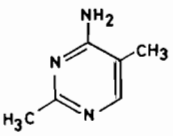

Fig. 3. Numbering Scheme of ADMPY.

The IR, ^1H and ^{13}C NMR spectra were run on Perkin-Elmer IR No 297, Varian A-60 and Varian FT-80A 20 MHZ, respectively. Deuterated dimethyl sulfoxide was used as solvent with TMS as internal reference standard. *Anal.* Calcd. for $C_{12}H_{18}N_6$-$PdCl_2$: C, 34.02; H, 4.28; N, 19.85%. Found: C, 33.79; H, 4.26; N, 19.77%.

Results and Discussions

The ligand, ADMPY, is a simple ligand with three possible coordination sites (N1, N3 and NH_2). The question which arises quite naturally is whether this ligand would act as unidentate, bidentate or tridentate under our experimental conditions. This question has been satisfactorily resolved by elemental and spectroscopic analysis. Elemental analysis indicates 1:2 (metal:ligand) stoichiometry. The possible *cis* and *trans* structures are shown in Figs. 1 and 2. This result is consistent with earlier studies [3]. Both the proton and carbon-13 NMR chemical shifts have

TABLE I ^{1}H NMR Chemical Shifts of ADMPY, M-ADMPY[a] and Metal Complexes.

Proton	ADMPY	$PdADMPYCl_2$	M-ADMPY[a]	$M\text{-}ADMPYPdCl_2$[b]
5-CH_3	1.91	1.96	2 02	2.02
2-CH_3	2.26	3.04	3.69	3.70
C-6-H	7.79	8.08	8.12	8.10
C-4-NH_2	6.51	7.35	8.81	8.80

[a,b]See Table II

TABLE II. ^{13}C NMR Chemical Shifts of ADMPY, M-ADMPY[a] and Metal Complexes (ppm).

Carbon	ADMPY	$PdADMPYCl_2$	M-ADMPY[a]	$M\text{-}ADMPYPdCl_2$[b]
2-CH_3	13.53	11.97	13.43	13.23
5-CH_3	25.11	25 69	21.92	21.51
C-5	109.81	110 3	112.65	112.52
C-6	154.06	[c]	146.00	145 81
C-4	162.48	160.95	160.99	160.76
C-2	164.41	163 24	163.37	163.19

[a]M-ADMPY. 1-Methyl-(4-amino-2,5-dimethyl) pyrimidinium iodide. [b]$M\text{-}ADMPYPdCl_2$: Precipitate obtained upon mixing aqueous solutions of M-ADMPY and K_2PdCl_4. [c]Too broad to be observed.

supported the assumption that the only binding site is N1 position of this ligand. Complexation causes downfield shifts of protons and upfield shifts of carbons adjacent to the coordination site [4]. The most downfield shifted proton peaks are those of 2-CH_3 (0.78 ppm), C-6-H (0.29 ppm) and C-4-NH_2 (0.84 ppm), while the most upfield shifted carbon peaks are those of 2-CH_3 (1.55 ppm), C-4 (1.53 ppm), and C-2 (1.17 ppm) with C-6 being too broad to be observed. This observation may be ascribed to very strong interaction. It has been reported that coordination of the amino group significantly shifts $\nu(NH_2)$ and $\delta(NH_2)$ bands [5, 6]. We have not observed any detectable difference in these bands upon complexation of ADMPY.

In order to further prove that the N1 position of this ligand is the only binding site, we have blocked the N1 position through methylation. Our results (Tables I and II) have clearly shown that once the N1 position of this ligand is blocked, there is no interaction between the methylated ligand and the metal salt. Meanwhile, X-ray studies are in progress to confirm the structures proposed in this paper.

Acknowledgements

This work was partly supported by Department of Chemistry of Howard University. The authors wish to express their thanks to Dr. Larry Jacques of A. H. Robins Co., Richmond, Virginia for helping with elemental analysis and NMR spectra.

References

1 R P Raval, Ph.D. Dissertation, Howard University, 1978.
2 G. Bonicino and D. Hennessy, *J. Org. Chem., 24,* 779 (1959).
3 A. Adeyemo and A. Shodeinde, *Inorg. Chim. Acta, 54,* L105 (1981).
4 A. Adeyemo, Y. Teklu and T. Williams, *Inorg Chim. Acta, 51,* 19 (1981)
5 D. Brodzki and G. Pannetier, *J. Organometal Chem., 104,* 241 (1976).
6 S. Haghighi, C. A. McAuliffe, W. E. Hill, H. H. Kohl and M. E. Friedman, *Inorg. Chim Acta, 43,* 113 (1980).