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INTERACTION OF ORGANOTRANSITION METALS WITH NUCLEOSIDES. PREPARATION AND PROPERTIES OF METHYL(1,5-CYCLOOCTADIENE)-(NUCLEOSIDE)PLATINUM(II)$^+$

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Organoplatinum(II) complexes having nucleoside(Nuc) as a ligand, $[PtMe(COD)(Nuc)]^+$ (Nuc=Guo, Cyd, Ado) have been prepared by the reaction of PtMeCl(COD) with nucleoside in the presence of $AgNO_3$. The ^{1}H-NMR study of the competitive equilibrium of various nucleosides reveals the high selective binding of Guo and Cyd to the organoplatinum(II) center.

There has been considerable attention on the antitumor platinum complexes such as cis-platin.[1-3] Current investigation on the mechanism of the action suggested the importance of intrastrand binding of these platinum complexes through N7 site of guanine bases in DNA. Recently a new class of stable organoplatinum and -palladium complexes such as $Pt(RNH_2)_2$(ascorbato)[4] and palladated 6, 6'-substituted bipyridine,[5] which have an intramolecular metal to carbon bond, have been shown to possess high antitumor activity. The facts would open up the new area for exploration of antitumor reagents. Thus the increasing importance of such organometallic complexes has led us to investigate the interaction of organoplatinum(II) complexes with nucleosides. The present paper describes the preparation and properties of methylplatinum complexes having nucleoside as a stabilizing ligand.

When methylchloro(1, 5-cyclooctadiene)platinum(II),[6] 1, was treated with equimolar amounts of various nucleosides such as guanosine(Guo), cytidine(Cyd), adenosine(Ado) and thymidine(dThd) in DMSO-d_6, no significant chemical shift change both in the ^{1}H and ^{13}C NMR spectra was observed, indicating no interaction of 1 with the nucleosides. However, the cationic methylplatinum(II) complex, $[PtMe(COD)(MeOH)]^+NO_3^-$, 2, which was prepared by the reaction of 1 with $AgNO_3$ in MeOH, readily reacted with Guo to give a colorless homogeneous solution in a day at room temperature. Evaporation of volatile matters afforded a colorless solid,

Table 1. Yields, Mp and Analytical Data of Methylplatinum(II) Complexes Having a Nucleoside Ligand

Complex	Yield[a] %	Mp[b] θ_m/°C	Color	Found(Calcd) (%) C	H	N
3 [PtMe(COD)(Guo)]$^+NO_3^-$	53	155-6	white	33.22(33.18)	4.22(4.33)	12.13(12.90)
4 [PtMe(COD)(Cyd)]$^+NO_3^-$	62	146	white	34.78(34.68)	4.63(4.53)	9.07(8.99)
5 [PtMe(COD)(Ado)]$^+NO_3^-$	44	154-8	yellow	35.42(35.24)	4.19(4.30)	12.32(12.98)

a) After recrystallization. b) With decomposition.

which was recrystallized from MeOH and was characterized as a novel type of methylplatinum(II) complex having guanosine as a ligand, [PtMe(COD)(Guo)]$^+NO_3^-$, 3. Similar reactions of 2 with Cyd and Ado also gave nucleoside-coordinated organoplatinum(II) complexes 4 and 5. Table 1 summarizes the yields, mp and analytical data. These complexes are air and thermally stable. On the other hand, dThd showed no reactivity toward 2 and only starting materials were recovered.

^1H and ^{13}C NMR data of complexes 3-5 in D_2O are summarized in Tables 2 and 3. Integration of signals in ^1H NMR spectra of 3-5 also support that only one nucleoside molecule binds to the platinum center. Only slight chemical shift changes of the signals due to ribose in 3-5 by comparison with those due to free nucleosides both in ^1H and ^{13}C NMR spectra suggest the absence of significant interaction of ribose unit with the platinum complex. In the ^{13}C NMR spectra of 4, signals due to C4 and C2 resonate at 3-5 ppm higher field compared with the corresponding signals of free Cyd, suggesting the coordinaiton of Cyd to Pt through N3 atom. Similar chemical shift change is known for the soft metal complexes having N3 bonded Cyd as a ligand.[7,8] Low field coordination shift is observed for the H8 proton in 3 by 0.50 ppm, the value being slightly larger than that observed in the platinum complex coordinated with Guo through N7 atom.[9] In the case of 5, a larger coordination shift at H8 proton was observed by comparison with that at H2 proton, suggesting also preferencial coordination of Ado to Pt through N7 atom. On the other hand, signals due to the methyl-Pt in 3-5 appear as singlets at a relatively high field, accompanied by ^{195}Pt satelites both in ^1H and ^{13}C NMR spectra. The observed coupling constants with ^{195}Pt are similar to those values for known methylplatinum complexes.[10]

Table 2. ^{1}H NMR Spectral Data of Complexes 3-5 in D_2O[a)]

Complex	Chemical shift (ppm)				
	H2	H5	H6	H8	Pt-Me
3	-	-	-	4.72 (0.50)	-3.02[b)]
4	-	2.48 (0.20)	4.04 (0.16)	-	-3.13[b)]
5	4.68 (0.13)	-	-	4.80 (0.31)	-2.94[b)]

a) At 68 °C. The numbers in parentheses indicate chemical shift difference from free nucleoside. Chemical shifts are referred to internal dioxane(down field positive). Signals due to ribose and COD are omitted. b) J(Pt-H)=70 Hz.

Table 3. ^{13}C NMR Spectral Data of Complexes 3-5 in D_2O [a)]

Complex	Chemical shift (ppm)					
	C2	C4	C5	C6	C8	Pt-Me
3[e)]	87.98	84.21	48.33	89.90	71.03	-63.97[b)]
4	86.70 (-4.26)	96.57 (-2.97)	31.94 (2.36)	75.36 (0.31)	-	-67.40[c)]
5[e)]	85.45	80.93	52.42	87.06	75.04	-63.34[d)]

a) At room temperature. Chemical shifts are referred to internal dioxane. (down field positive) Numbers in parentheses indicate chemical shift difference from free nucleoside. Signals due to ribose and COD are omitted. b) J(Pt-C)= 622 Hz c) J(Pt-C)=612 Hz d) J(Pt-C)=605 Hz e) Since chemical shifts of free Nuc were not obtained due to their low solubility in D_2O, chemical shift diference was not estimated.

In the ^{1}H NMR spectrum of 1:1 mixture of 3 and Guo, signals due to coordinated and free Guo do not appear separately and only singlet for each proton is observed between both signals, indicating the existence of facile exchange between free and coordinated Guo. Similar fast ligand exchange reactions also were observed in the case of complexes 4 and 5. When an equimolar amount of Cyd was added to 3 in D_2O, equilibration between 3 and 4 immediately took place, indicating the competitive coordination of nucleosides toward the platinum center. Thus the equilibrium constant K for the following equation can be estimated from ^{1}H NMR spectroscopy.

$$[PtMe(COD)(Guo)]^{+} + Nuc \overset{K}{\rightleftharpoons} [PtMe(COD)(Nuc)]^{+} + Guo \qquad (2)$$

The values K obtained at 81 °C are 0.76 and 0.14 for Cyd and Ado, respectively. In contrast, no ligand exchange was observed for dThd. Thus the coordination ability of nucleosides to the organoplatinum(II) complex lies in the order of Guo≥Cyd>Ado≫

dThd. The observed trend is in contrast to the selective coordination of guanine base to cis-platin[3] and to that of cytidine to dimethylgold(III) complexes.[11]

Interestingly these methylplatinum(II) complexes show considerable in vitro cytotoxic activities toward P388 leukemia in mice. The present selective bonding of the organoplatinum complex to nucleosides may open up new area in the developement of antitumor reagents.

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