Interaction of Dimethylgold(III) Complexes with Nucleosides

YUUKO MIZUNO and SANSHIRO KOMIYA*

Department of Applied Chemistry for Resources, Tokyo University of Agriculture & Technology, 2-24-16 Nakamachi, Koganei, Tokyo 184, Japan

(Received May 2, 1986)

Attention to the mechanism of antitumor activity of organometallic compounds has been growing in recent years because of the unique antitumor properties of certain organoplatinum and gold complexes [1–3]. One specific area of interest has been the interaction of these complexes with DNA. The reactivity of isolated organotransition metal compounds toward nucleosides has been much less explored compared to that of well known *cis*-dichloro(diammine)platinum(II) and related compounds [4]. We wish to report here the selective interaction of dimethylgold(III) complexes toward nucleosides such as guanosine (Guo), cytidine (Cyd), adenosine (Ado) and thymidine (dThd), and their binding sites to gold(III).

Selected ^1H and ^{13}C NMR spectral data of the 1:1 mixture of dimethylchlorogold(III) dimer, **1**, [5] with a nucleoside such as Guo or Cyd in DMSO-d_6 are summarized in Table I. Observation of two singlets assignable to methyl–gold groups both in the ^1H and ^{13}C NMR spectra indicates that the two methyl–gold groups in the reaction product are magnetically nonequivalent. It is seen that signals due to the nucleoside shift considerably from those due to free nucleosides except for the riborse unit. Integration of these signals indicates the formation of a dimethylgold(III) complex having only one molecule of nucleoside as a ligand. Thus, the results are consistent with the instantaneous formation of square planar *cis*-dimethylhalo(nucleoside)gold(III), **2**–**4**.

$$[Me_2AuX]_2 + 2Nuc \longrightarrow 2Me{-}\overset{\overset{Me}{|}}{\underset{\underset{X}{|}}{Au}}{-}Nuc \qquad (1)$$

X = Cl, Nuc = Guo: **2**
= Cyd: **3**
= Ado: **4**

*Author to whom correspondence should be addressed.

TABLE I. ^1H and ^{13}C NMR Data for *cis*-$AuMe_2Cl$(Nuc) in DMSO-d_6 at Room Temperature[a]

Complex	Nucleoside	^1H NMR chemical shift (ppm)						
		H2	H5	H6	H8	NH	NH_2	Au–Me
2	Guo				8.57 (0.64)	11.14 (0.59)	6.76 (0.31)	1.02, 0.91
3	Cyd		6.00d (0.27) J = 7.6 Hz	8.05d (0.21) J = 7.6 Hz			7.74 8.36 (0.55) (1.17)	0.85, 0.99
3′	Cyd		6.14d (0.40) J = 7.6 Hz	8.16d (0.32) J = 7.6 Hz			7.60 8.79 (0.41) (0.29)	0.90, 0.92
4	Ado	8.24 (0.10)			8.51 (0.16)		7.42 (0.29)	0.98, 1.15
		^{13}C NMR chemical shift (ppm)[b]						
		C2	C4	C5	C6	C8	Au–Me	
2	Guo	154.56 (0.93)	150.74 (−0.56)	113.05 (−3.63)	154.83 (−1.92)	137.29 (1.61)	1.14, 7.49	
3	Cyd	151.83 (−3.56)	162.27 (−3.26)	94.89 (1.05)	142.01 (0.51)		2.62, 5.62	
3′	Cyd	153.25 (−2.14)	162.98 (−2.55)	95.72 (1.88)	[c]		1.60, 7.59	

[a]Numbers in parentheses indicate the chemical shift change from free nucleoside (down field positive). Chemical shifts are referred to internal TMS, and signals due to riborse are omitted. Yield of **3′** was *ca.* 10%. [b]Signals of **4** collapsed because of the rapid ligand exchange reaction. [c]The signal was obscured by the peaks due to **3**.

0020-1693/86/$3.50

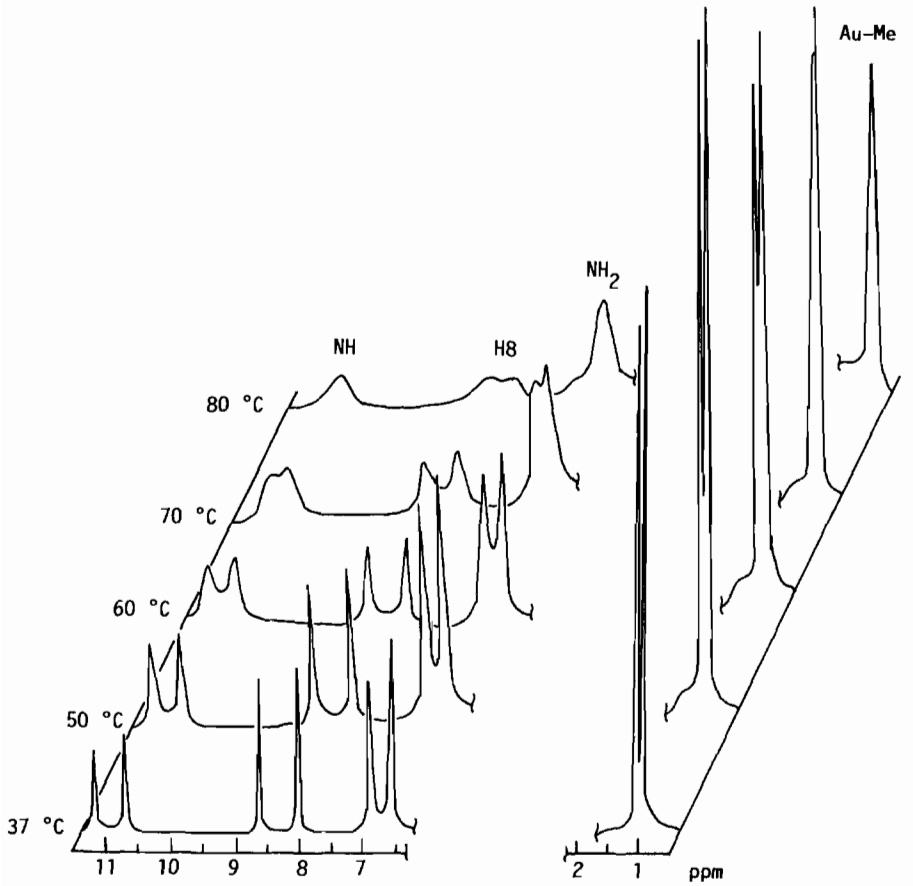
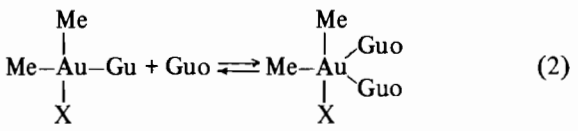


Fig. 1. Temperature dependence of ^{1}H NMR spectrum of 1:1 mixture of $AuMe_2Cl(Guo)$ and free Guo in DMSO-d_6.

Such reactions leading to the formation of stable mononuclear square planar complexes on interaction of **1** with donor ligands such as pyridine and tertiary phosphines are well known [6]. There was no significant increase of equivalent molar conductivity χ of the solution of **1** in the presence of free Guo, excluding the possible formation of cationic gold(III) complex. A slight increase of χ was observed in the reaction of **1** with Cyd and Ado. Formation of a small amount of ionic species $[Me_2Au(Cyd)_2]^+[Me_2AuX_2]^-$, **3'**, in the reaction of **1** with Cyd is responsible for the result (see Table I). In contrast, no reaction of **1** took place with thymidine (dThd). Similar dimethylgold(III) compounds having nucleoside ligands were also obtained when Cl was replaced by Br or I.

As shown in Table I, the significant low field shift of H8 by 0.6–0.7 ppm in the ^{1}H NMR and the large ^{13}C chemical shift change of C5 and C8 for **2** suggest the coordination of Guo through the N7 atom. A similar coordination shift of Guo through N7 in $Pt(Guo)_2(NH_3)_2$ has been reported [7]. For complexes **3** large upfield shifts of the C2 and C4 carbons by 3–4 ppm from free Cyd are observed in ^{13}C NMR, suggesting the coordination of Cyd to gold through the N3 atom. In the ^{1}H NMR of these complexes, protons due to the NH_2 group are magnetically nonequivalent and appeared as two singlets, also supporting this coordination. Such chemical shift changes when Cyd coordinates to a transition metal through the N3 atom seem to be general [8]. Although considerable coordination shifts at H8, H2, and NH_2 for **4** are observed, it seems to be difficult to determine the coordination site of Ado to gold. However, N7 and NH are the most probable coordination sites from their chemical shift change.

Figure 1 shows the temperature dependence of a 1:1 mixture of complex **2** and Guo. Well separated sharp signals due to coordinated and free Guo at room temperature gradually broadened with increasing temperature and finally coalesced at 80 °C. Signals of methyl–gold also coalesced at the same time. This fact is best interpreted by the fast associative exchange of the Guo ligand.



(2)

Fast intramolecular exchange in the 5-coordinated intermediate should be involved in the reaction. Kinetic parameters for the fast ligand exchange reaction are estimated by their line shape analysis: $\Delta G^{\ddagger} = 17$ kcal/mol, $\Delta H^{\ddagger} = 9$ kcal/mol and $\Delta S^{\ddagger} = -24$ e.u. at 60 °C for **2**. Similar values are also obtained for the reactions of the other complexes with Guo. Large negative values of $\Delta S^{\ddagger}$ are consistent with the above S_N2 mechanism. Such an associative exchange of the netural ligand in the square planar d^8 transition metal complexes is very common.

References

1 L. S. Hollis, A. R. Amunsen and E. W. Stern, *J. Am. Chem., Soc. 107*, 274 (1985).
2 *U.S. Pat. 4 457 926* to A. R. Amunsen and E. W. Stern.
3 Y. Yamamoto, Y. Numasaki and M. Murakami, *Nippon Kagaku Kaishi*, 625 (1985).
4 A. W. Prestayko, S. T. Crooke and S. K. Carter (eds.), 'Cisplatin', Academic Press, New York/London, 1980, and refs. therein.
5 F. H. Grain and C. G. Gibson, *J. Chem. Soc.*, 762 (1939).
6 G. C. Stocco and R. S. Tobias, *J. Am. Chem. Soc., 93*, 5057 (1971).
7 S. K. Miller and L. G. Marzilli, *Inorg. Chem., 24*, 2421 (1985).
8 L. G. Marzilli, B. de Castero, J. P. Caradonna, R. C. Stewart and C. P. Van Vuuren, *J. Am. Chem. Soc., 102*, 916 (1980); D. W. Abbott and C. Woods, *Inorg. Chem., 22*, 2918 (1983).