CHEMISTRY LETTERS, pp. 457-460, 1993.

Associative Exchange of a Guanosine Ligand on Triarylphosphine-Gold(I) Complexes

Sanshiro KOMIYA,* Koji NAKADA, Mitsuru HIRATA, and Atsushi FUKUOKA

Department of Applied Chemistry, Tokyo University of Agriculture and Technology,

2-24-16 Nakamachi, Koganei, Tokyo 184

Reactions of nitrato(triarylphosphine)gold(I) complexes [Au(PR_3)(NO_3)] with nucleosides such as guanosine (Guo), adenosine (Ado), and cytidine (Cyd) give new nucleoside-containing gold(I) complexes, [Au(PR3)(Nuc)](NO_3) (R = Ph, *o*-anisyl, *p*-anisyl; Nuc = Guo, Ado, Cyd) in DMSO-d_6. NMR study reveals that the coordinated Guo ligand rapidly exchanges with free Guo by an associative mechanism.

Interaction of transition metals with nucleosides has currently attracted interests in relation to anticancer activity of transition metals such as cisplatin and enormous efforts to elucidate the mechanisms have been performed.[1] In contrast, much less attention has been paid so far to the interaction of gold(I) complexes with nucleosides, though certain gold(I) compounds containing triethylphosphine[2] and 1,2-bis(diphenylphosphino)-ethane[3] are also known to have considerable activity toward not only antiarthritic but also anticancer drugs. Coordination studies on such metal nucleoside interactions would provide further insight into understanding of metal-DNA interactions. We previously reported the dissociative exchange of nucleoside ligand on gold(III) and platinum(II) complexes by using Dynamic NMR technique.[4] We now report the formation of gold(I) complexes having a nucleoside as a ligand and its associative exchange reaction of coordinated guanosine.

When Guo (guanosine) was added to the DMSO-d_6 solution of nitrato(triphenylphosphine)gold(I), considerable down field shifts in ^1H NMR were observed for the protons on the purine ring of Guo. In contrast, only a slight change of chemical shift is observed for signals due to riborse. In the purine ring protons, the chemical shift change at H8 proton (ca. 0.9 ppm) is the largest, suggesting the coordination of Guo to gold(I) not by the riborse part but by the N7 atom in Guo. Similar chemical shift changes of Guo are known when purine bases such as Guo and GMP are coordinated to Pt by N7 atom in cisplatin derivatives.[5] The chemical shifts of the coordinated Guo do not change when the ratio of gold to Guo is less than unity to indicate the formation of a

stable 1:1 Guo-coordinated gold(I) complex under these conditions. In fact such coordination compounds can be isolated from the reaction in methanol solution. Analogous gold(I) complexes coordinated Cyd (cytidine) and Ado (adenosine) were also formed. Coordination sites of these nucleosides to Au(I) are assumed to be N7 atom for Ado and N3 for Cyd from the magnitude of chemical shift changes.[6] No reaction with thymidine took place for gold(I) complexes. ^{1}H NMR data for these complexes are summarized in Table 1.

$$Au(PR_3)(NO_3) + Nuc \longrightarrow [Au(Nuc)(PR_3)](NO_3) \quad (1)$$

R = Ph (**1**), *o*-anisyl (**2**), *p*-anisyl (**3**)
Nuc = Guo, Ado, Cyd

Table 1. Selected ^{1}H NMR Data for Gold(I) Complexes $[Au(Nuc)(PR_3)]NO_3$ Having a Nucleoside Ligand[a]

R	Nuc	H2/H5[b]	H8/H6[c]	NH_2		NH	H1'
Ph	Guo	-	8.74	6.98	-	11.34	5.85
	Ado	8.55	8.71	8.51	-	-	6.01
	Cyd	6.15	8.26	8.60	8.82	-	5.82
p-anisyl	Guo	-	8.89	7.03	-	11.42	5.83
	Ado	8.30	8.74	8.30	-	-	6.02
	Cyd	6.13	8.24	8.57	8.79	-	5.79
o-anisyl	Guo	-	8.83	d)	-	11.32	5.81
	Ado	8.37	8.74	8.13	-	-	5.97
	Cyd	6.12	8.46	8.70	8.81	-	5.82

a) Chemical shifts are referred to TMS in DMSO-d_6 at 33 °C. b) H2 for Ado and H5 for Cyd. b) H8 for Guo and Ado and H6 for Cyd. d) Signals were obscured by the large peaks of the phosphine ligand.

Interestingly, further addition of Guo to the DMSO-d_6 solution of $[Au(Guo)(PPh_3)](NO_3)$ caused the gradual upfield chemical shift change of coordinated Guo, approaching to the chemical shift value of free Guo. The results clearly indicate occurrence of the fast exchange of coordinated Guo with the added free Guo.

$$[Au(Guo)(PR_3)](NO_3) + Guo' \rightleftharpoons [Au(Guo')(PR_3)](NO_3) + Guo \quad (2)$$

Two mechanisms are conceivable for this nucleoside exchange; one being a dissociative mechanism similar to the process found in the guanosine coordinated gold(III) and Pt(II) complexes[4] and the other being an associative one including bis(Guo)gold(I) species. Figure 1 shows the spectral change of ^{1}H NMR of (tri-*o*-anisylphosphine)gold(I) complexes under various concentrations of free Guo. When the ratio of Guo/Au exceeds unity, signals of coordinated Guo extensively broadened and then they gradually sharpened again with increase in the concentration of free Guo. Although no separation of signals due to the coordinated and

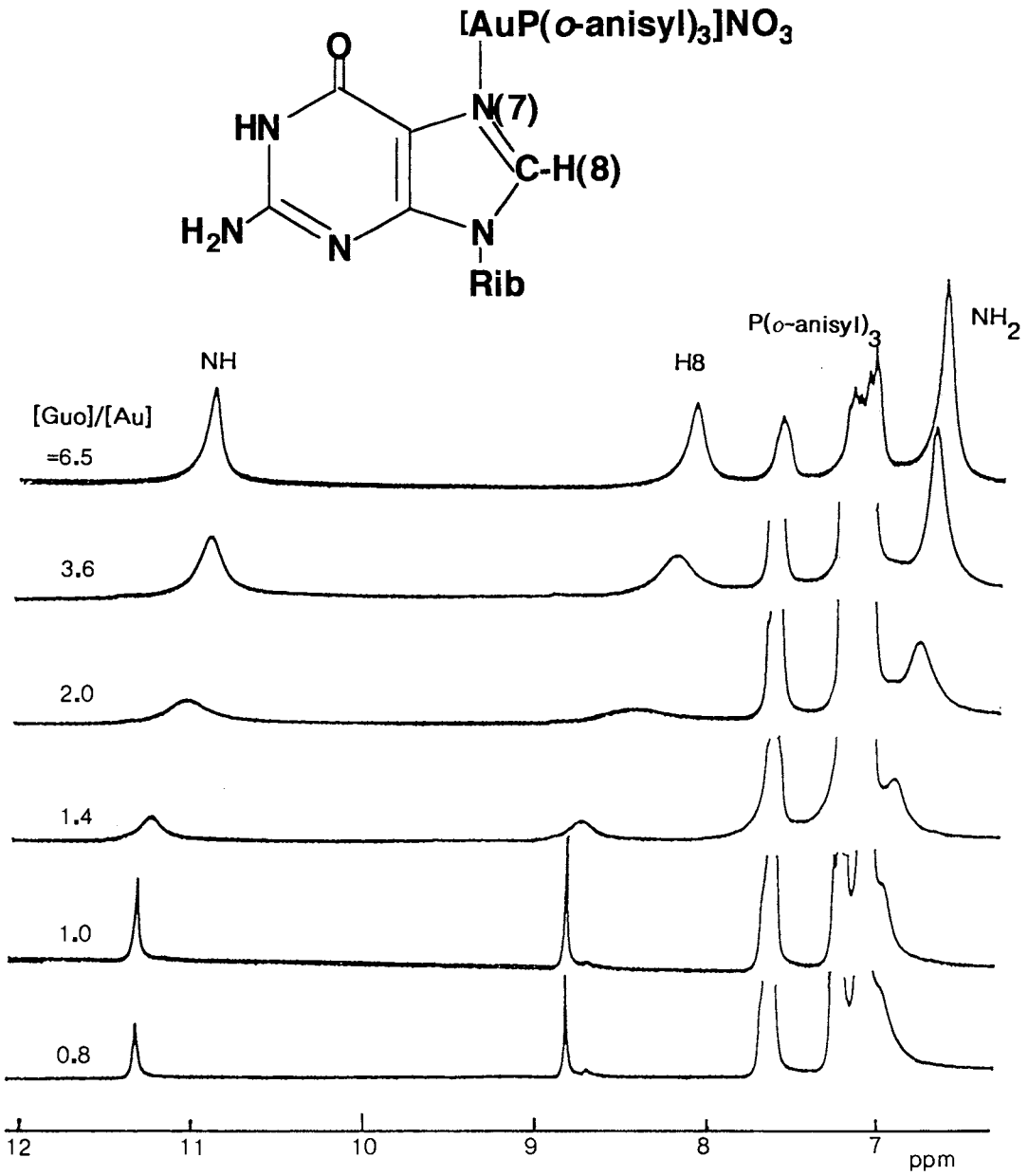

Fig. 1. ^{1}H NMR spectral change of H8, NH and NH_2 protons of **2** under various concentration of Guo in DMSO-d_6 at 33 °C.

uncoordinated Guo was observed here, such broadening of the signals and the large negative value of the estimated entropy of activation[7] suggest the occurrence of the fast associative exchange of Guo ligand in solution. On the other hand, when the less bulky triarylphosphines such as P(*p*-anisyl)$_3$ and PPh_3 rather than P(*o*-anisyl)$_3$ were employed in these ligand exchange reactions, only a slight broadening of these signals was observed. The exchange rates are considered to be faster for the gold(I) complexes having a less bulky phosphine ligand than that for **2**. The result suggests the importance of the steric demand of the tertiary phosphine ligand in this dynamic behavior.

$$[Au(Guo)(PR_3)](NO_3) + Guo \rightleftharpoons [Au(Guo)_2(PR_3)](NO_3) \qquad (3)$$

The present associative exchange of nucleoside ligand in gold(I) is in sharp contrast to the dissociative nucleoside exchange in Au(III)Me_2(Guo)Cl and [PtMe(Guo)(cod)]NO_3.[4] Further study on the kinetic and thermodynamic aspects on these processes are now in progress.

Authors are grateful for financial support to a Grant-in-Aid for Scientific Research on Priority Areas from Ministry of Education, Science and Culture, Japan.

References

1) "Metal-DNA Chemistry," ed by T. D. Tullius, ACS Symp. Ser. 402, American Chemical Society, (1989); "Platinum, Gold and Other Metal Chemotherapeutic Agents," ed by S. D. Lippard, ACS Symp. Ser. 209, American Chemical Society, (1983); "Transition Metal Complexes as Drugs and Chemotherapeutic Agents," ed by N. Farrell, Kluwer Academic Publishers, (1989).
2) T. M. Simon, D. H. Kunishma, G. J. Vibert, and A. Lorder, *Cancer Res.*, **41**, 94 (1981); C. K. Mirabelli, R. K. Johnson, C. M. Song, L. Faucette, K. Muirhead, and S. T. Crooke, *ibid.*, **45**, 32 (1985).
3) C. K. Mirabelli, R. K. Johnson, D. T. Hill, L. F. Faucette, G. R. Girard, G. Y. Kuo, C. M. Sung, and S. T. Crooke, *J. Med. Chem.*, **29**, 218 (1986); C. K. Mirabelli, D. T. Hill, L. F. Faucette, F. L. MacCabe, G. R. Girard, D. B. Bryan, B. M. Sutton, J. O'L. Bartus, and S. T. Crooke, *ibid.*, **30**, 2181 (1987).
4) S. Komiya, Y. Mizuno, and T. Shibuya, *Chem. Lett.*, **1988**, 367.
5) For example: Y.-T. Fanchiang, *J. Chem. Soc., Dalton Trans.*, **1986**, 135; P.-C. Kong and T. Theophanides, *Inorg. Chem.*, **13**, 1167 (1974).
6) S. Komiya and Y. Mizuno, *Inorg. Chim. Acta*, **125**, L13 (1986).
7) Activation parameters for the exchange reaction of **2** were obtained from the temperature dependence of the rate constants estimated by the dynamic NMR simulation: $\Delta G^{\ddagger}$ = 58 kJ mol^{-1}, $\Delta H^{\ddagger}$ = 51 kJ mol^{-1}, $\Delta S^{\ddagger}$ = -174 J mol^{-1} deg^{-1} (306 K).

(Received December 4, 1992)