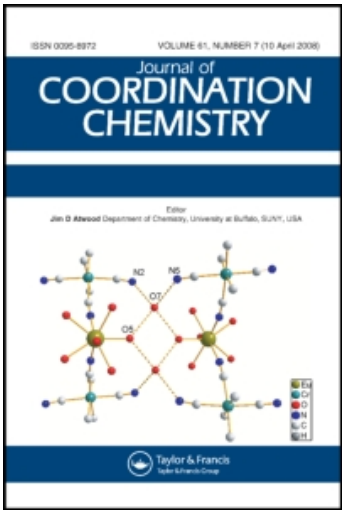


Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713455674

Au(III) interaction with Methionine- and Histidine-containing peptides

Bojidarka B. Ivanova[a]; Mariana Io. Mitewa[a]
[a] Department of Chemistry, University of Sofia, 1164 Sofia, Bulgaria

To cite this Article Ivanova, Bojidarka B. and Mitewa, Mariana Io.(2004) 'Au(III) interaction with Methionine- and Histidine-containing peptides', Journal of Coordination Chemistry, 57: 3, 217 — 221
To link to this Article: DOI: 10.1080/00958970410001671192
URL: http://dx.doi.org/10.1080/00958970410001671192

J. Coord. Chem., Vol. 57, No. 3, 15 February 2004, pp. 217–221

Au(III) INTERACTION WITH METHIONINE- AND HISTIDINE-CONTAINING PEPTIDES

BOJIDARKA B. IVANOVA* and MARIANA IO. MITEWA

Department of Chemistry, University of Sofia, 1164 Sofia, Bulgaria

(Received in final form 26 November 2003)

Mononuclear Au(III) complexes of the peptides H-His-Met-OH (D) and H-Gly-Gly-Met-OH (T) and their *N*-protected forms Ac-His-Met-OH (Ac-D) and Ac-Gly-Gly-Met-OH (Ac-T) were structurally characterized by means of IR, MS and NMR. In the complexes with dipeptides $[AuLCl_2]Cl$ (L = D or Ac-D), Au(III) is coordinated through S and imidazole N atoms from methionine and histidine fragments of the ligands forming macrochelate rings at mol ratio Au : L = 1 : 1. Additionally, Au(III) is coordinated by two terminal chloride ions in a square-planar arrangement. In complexes with the tripeptides [AuL′Cl] (L′ = T or Ac-T), however, the metal ion is coordinated in a tridentate fashion, through S and two N atoms, also at mol ratio M : L = 1 : 1. The fourth position of Au(III) is occupied by a Cl^- ligand.

Keywords: Au(III) complexes; Methionine; Histidine; Peptides

INTRODUCTION

Interest in Pt(II) and Au(III) complexes of peptides arises from proposals that these may be involved in reactions of potential antitumor agents [1,2]. A full understanding of the *in vivo* manner and mechanism of coordination of these metal ions with DNA requires the systematic investigation of their coordination with competing peptides and proteins [3,4]. Of particular interest in this respect are the thioethers and imidazole donor atoms of methionine and histidine side chains. The important role of Au(III) → Au(I) processes in organisms and the wide therapeutic use of Au(III) and Au(I) drugs to treat for example arthritis [5–7] encouraged the present investigation of the coordination of Au(III) by methionine- and histidine-containing peptides. Reactions of *cis*- and *trans*-$[PtCl_2(NH_3)_2]$ and $[Pt(L)Cl_n]$ (L = dien, en; $n = 1,2$) with the soft donor atoms of methionine- and histidine- containing di- and tripeptides were previously studied [8–13] with the goal of structurally characterizing the resulting Pt(II) complexes. Au(III) complexes with similar peptides have also been the subject of a series of papers [5,14,15].

*Corresponding author. E-mail: ahbi@chem.uni-sofia.bg

ISSN 0095-8972 print: ISSN 1029-0389 online
DOI: 10.1080/00958970410001671192

The present work deals with Au(III) complexes of histidine- and methionine-containing peptides H-His-Met-OH and H-Gly-Gly-Met-OH and their Ac-protected forms (Scheme 1). A primary goal was the isolation and structural characterization of resulting Au(III) complexes in solution and the solid state.

EXPERIMENTAL

Materials and Methods

The peptides H-Gly-Gly-Met, H-His-Met-OH were purchased from Bachem, and $HAuCl_4 \cdot 3H_2O$ from Acros Organics. The protected Ac-His-Met-OH and Ac-Gly-Gly-Met-OH forms were synthesized in accordance with procedures described in the literature [16].

Infrared spectra in the 4000–400 cm^{-1} range were obtained on a Perkin Elmer 1760 FTIR spectrophotometer; 50 scans were performed for each spectrum, with a resolution of 4 cm^{-1} (KBr pellets). FAB mass spectra were measured on a Fisons VG Autospect instrument employing 3-nitrobenzyl alcohol as the matrix. NMR measurements were made at 298 K with a Bruker DRX-400 spectrometer using 5-mm tubes and D_2O as solvent, referenced to sodium 3-(trimethylsilyi)tetradeuteriopionate.

Synthesis

All complexes were obtained according to the following general procedure. A solution of $HAuCl_4 \cdot 3H_2O$ (196.4 mg) in H_2O (5 cm^3) was added to a 5 cm^3 aqueous solution of the peptides, D (143.2 mg), Ac-D (164.2 mg), T (131.7 mg) and Ac-T (152.7 mg), respectively, the mol ratio being Au : L (or L′) = 1 : 1. Dilute aqueous NaOH was used to raise the pH from 1.0 to 3.5 in the reaction mixtures. On leaving the solutions to stand, white precipitates formed after *ca.* 10 days were filtered off, washed with H_2O and dried in air at 298 K. [$AuDCl_2$]Cl found (%): C, 22.39; H, 3.09; N, 9.47; calcd.: C, 22.41; H, 3.08; N, 9.50; yield: 14%. [AuAc-DCl_2]Cl found: C, 24.84; H, 2.70; N, 8.89; calcd.: C, 24.84; H, 2.73; N, 8.91; yield: 10%. [AuTCl] found: C, 21.91; H, 3.07; N, 8.52; calcd.: C, 21.90; H, 3.06; N, 8.51; yield: 12%. [AuAc-TCl], found: C, 25.34; H, 3.65; N, 8.07; calcd.: C, 25.32; H, 3.67; N, 8.05; yield: 22%.

RESULTS AND DISCUSSION

Infrared Spectra

The IR spectrum of D shows two bands at 3355 and 3310 cm^{-1} assigned to ν^{as}_{NH2} and ν^{s}_{NH2} stretching vibrations, while amide I and II bands are observed at 1655 and 1599 cm^{-1}, respectively [17]. The band at 1000 cm^{-1} may be assigned to the i.p. δ_{CS} vibrational mode [17]. In the 650–500 cm^{-1} region, the band at 650 cm^{-1} is assigned to the amide V (ω_{NH2}) [17–19]. The IR spectrum of the Ac-protected D is characterized by one ν_{NH} stretching vibration at 3310 cm^{-1} and amide I, II and δ_{CS} bands are observed at 1722, 1633 and 1000 cm^{-1}, respectively. In the 600–550 cm^{-1} range, the band at 622 cm^{-1} may be assigned to amide V. In contrast to the spectra of the free dipeptides, the spectra of both Au(III) complexes are characterized by a high frequency

shift of the amide II bands by 20–30 cm^{-1}, and the practical disappearance of the low intensity bands at 1000 and about 550 cm^{-1}. These results indicate that in the complexes Au(III) is coordinated through the amide and S atoms of the ligands.

Similar to the dipeptide IR spectrum, the tripeptide T is characterized by two ν^{as}_{NH2} and ν^{s}_{NH2} stretching vibrations at 3330 and 3225 cm^{-1}, amide I at 1722 cm^{-1} and amide II at 1610 cm^{-1}. The δ_{CS} and amide V bands are observed at 1111 and 699 cm^{-1}, respectively. The protected form of T is characterized by one ν_{NH} band at 3266 cm^{-1} with a shoulder at 3310 cm^{-1}. The amide I, II, δ_{CS} and amide V vibrations are at 1688, 1655, 1022 and 722 cm^{-1}, respectively. Coordination of Au(III) through the amide nitrogens and S can be inferred from the high frequency shift of the amide II and δ_{CS} bands and the disappearance of amide V modes in the 700–600 cm^{-1} range [17–19].

Mass Spectra

The most intense signals in the mass spectra of the complexes are the peaks at m/z 482.1, 561.2, 460.2 and 525.0, corresponding to the singly charged $[AuD]^+$, $[Au(Ac\text{-}D)Cl]^+$, $[AuT]^+$ and $[Au(Ac\text{-}T)Cl]^+$ ions. The data indicate a mol ratio M : L = 1 : 1 in all complexes. In the complexes with dipeptides, each metal ion is coordinated by two terminal chloride ions. In contrast, in complexes with tripeptides the presence of the one terminal Cl^- ligand can be assumed. Similar coordination geometries have been observed for Pt(III), Pd(II) and Au(III) with analogous di- and tripeptides [20–21].

NMR Data

Proton NMR data for the Au(III) complexes and the free ligands are given in Tables I and II. As reported for similar free methionine-containing peptides [22,23], δ-CH_3 singlet peaks are observed in the 2.05 to 2.15 ppm range. In all the complexes the

TABLE I Proton NMR chemical shifts δ (ppm) for D, Ac-D and corresponding Au(III) complexes

	D	*Ac-D*	$[AuD]^{3+}$	$[AuAc\text{-}DCl_2]^+$
$CH2_{his}$	8.10(s)	8.17(s)	8.55(s)	8.78(s)
$CH5_{his}$	7.09(s)	7.10(s)	7.20(d)	7.56(s)
CH-α_{his}	4.43(dd)	4.40(dd)	4.37(dd)	4.43(m)
CH_2-β_{his}	3.42(dd)	3.42(dd)	3.47(dd)	3.33(dd)
CH-α_{met}	4.60(dd)	4.56(dd)	4.62(dd)	4.63(m)
CH_2-β_{met}	2.10(m)	2.12(m)	2.10(m)	2.10(m)
CH_2-γ_{met}	2.57(m)	2.62(m)	2.58(m)	2.63(m)
CH_3-δ_{met}	2.07(s)	2.05(s)	2.42(m)	2.68(m) + 2.09(s)

TABLE II Proton NMR chemical shifts δ (ppm) for T, Ac-T and Au(III) complexes of the tripeptides

	T	*Ac-T*	$[AuT]^+$	$[AuAc\text{-}T]^+$
CH-α_{met}	4.64(dd)	4.60(dd)	4.44(m)	4.54(m)
CH_2-β_{met}	2.05(m)	2.07(m)	2.05(m)	2.04(m)
CH-γ_{met}	2.65(m)	2.56(m)	2.65(m)	2.72(m)
CH-δ_{met}	2.15(s)	2.09(s)	2.34(m)	2.68(m)
CH_2-α_{gly1}	3.90(d)	3.91(d)	3.89(d)	3.92(m)
CH_2-α_{gly2}	4.09 + 3.99(2d)	4.1 + 3.97(2d)	3.96(m)	3.95(m)

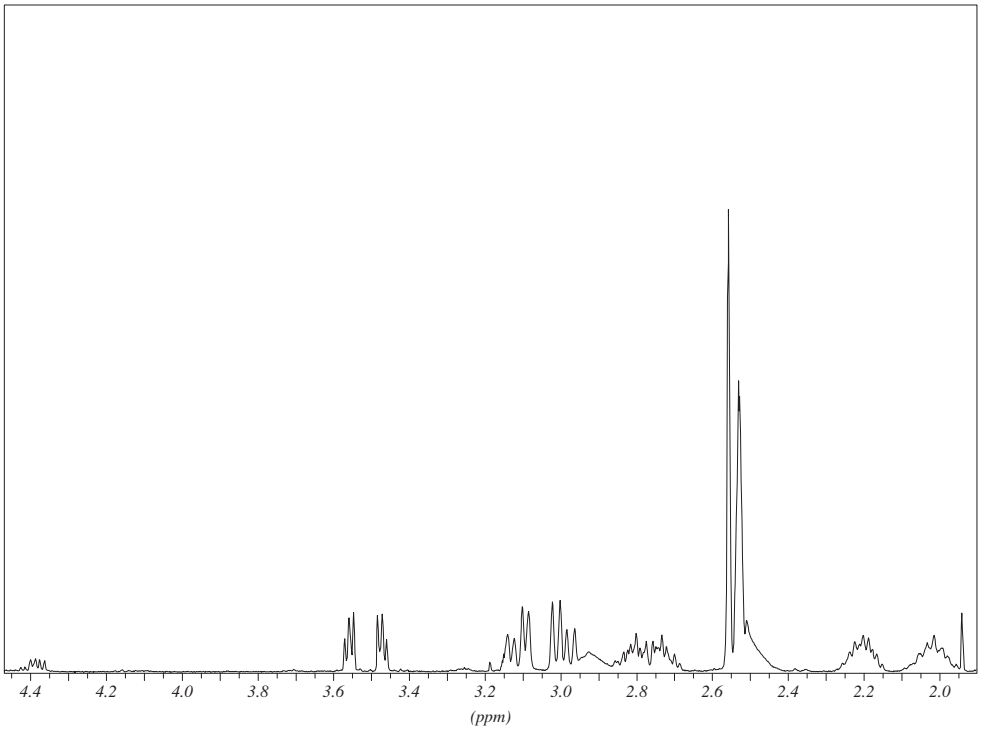


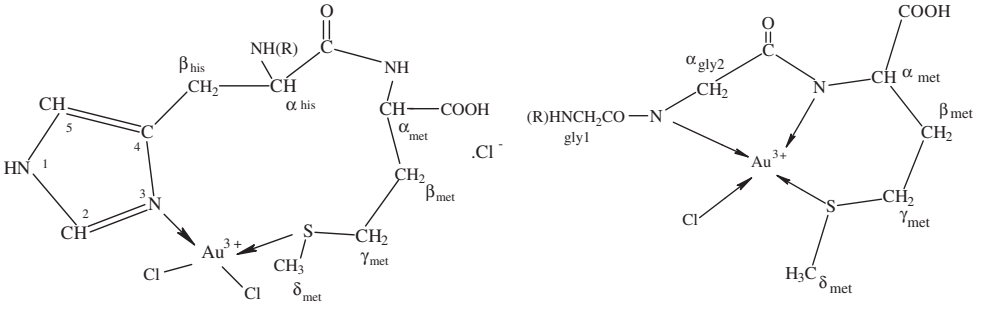
FIGURE 1 Proton NMR spectra of D (1) and [$AuDCl_2$] complex (2) in D_2O solutions.

corresponding δ-CH_3 signals are shifted to 2.34 to 3.68 ppm and two singlet peaks are observed (Fig. 1), indicating the presence of S_R and S_S isomers. These results indicate coordination of the S atom from the methionine fragments in all Au(III) compounds.

The pH-dependent CH2 signals from the histidine residues in both of the dipeptides studied are observed at about 8.15 ppm, indicating a non-protonated N3 atom in the imidazole ring. The corresponding signals in the complexes are shifted to 8.55 and 8.84 ppm, suggesting coordination of Au(III) through N3 and the formation of a macrochelate ring in both complexes. These results are in good agreement with others reported in the literature [24–27].

The multiplet α-CH methionine signals of typical tripeptides ^{1}H NMR spectra occur at around 4.60 ppm [28]. However, in both the complexes with T and Ac-T these signals are shifted to higher field. This is an indication of coordination of the methionine N atom in both the complexes. On the other hand, the αCH_2-gly_1 singlet at 3.99 ppm in the spectra of free tripeptides is observed as multiplets in the complexes, indicating coordination by the second N atoms from the gly_2 residues.

The results indicate the structures in Scheme 1. The dipeptides act as bidentate ligands joined with the Au(III) ions through the S-methionine and imidazole N3-histidine atoms forming macrochelates. In contrast, in the tripeptide complexes, the ligands coordinate in a tridentate fashion through S- and N-methionine and N-gly_2 atoms. In the first type of complex two chloride ions coordinate as terminal ligands. In the second case only one Cl^- ion is involved.



R = H, C(=O)CH_3

SCHEME 1.

Acknowledgments

The authors thank the Alexander von Humboldt Foundation for fellowships and Prof. W.S. Sheldrick for helpful discussions.

References

[1] J. Reedjik, *Chem. Commun*. 801 (1996)
[2] D.B. Zambe and S.J. Lippard, *Trends Biochem. Sci*. **20**, 435 (1995).
[3] J. Reedjik, *Inorg. Chim. Acta* **198**, 873 (1994).
[4] K.J. Barnham, M.I. Djuran, P. del Soccoro Murrdoch and P.J. Sadler, *Chem. Commun*. 721 (1994).
[5] B. Beverlz and D. Couri, *Ferd. Proc*. **46**, 854 (1987)
[6] C.F. Shaw III, S. Schaa, E. Gleichmann, Y.P. Grover, L. Dunemann and A. Jagarlamudi, *Metal Base Drugs* **1**, 351 (1994).
[7] W.E. Smith and J. Reglinski, *Prespect. Bioinorg. Chem*. **1**, 183 (1991).
[8] M. Hahn, D. Wolters, W.S. Sheldrick, F. Hulsberegen and J. Reedijk, *J. Biol. Inorg. Chem*. **4**, 412 (1999).
[9] C. Froehling and W.S. Sheldrick, *J. Chem. Soc., Dalton Trans*. 4411 (1997).
[10] A. Siebert and W. Sheldrick, *J. Chem. Soc., Dalton Trans*. 385 (1997).
[11] D. Wolters and W.S. Sheldrick, *J. Chem. Soc., Dalton Trans*. 1121 (1997).
[12] M. Hahn, M. Kleine and W.S. Sheldrick, *J. Biol. Inorg. Chem*. **6**, 556 (2001).
[13] H.C. Freeman and M.L. Golomb, *Chem Commun*. 1523 (1970).
[14] S. Best, T. Chattopadhyay, M. Djuran, R. Palmer, P. Sadler, I. Sovago and K. Varnagy, *J. Chem. Soc., Dalton Trans*. 2587 (1997).
[15] A.A. Isab and P.J. Sadler, *Biochim. Biophys. Acta* **492**, 854 (1987).
[16] L. Zhu and M. Kostic, *Inorg. Chem*. **31**, 3994 (1992).
[17] K. Nakamoto, Infrared and Raman Spectra of Inorganic and Coordination Compounds (J. Wiley & Sons, New York, 1997).
[18] R. Nyquist, Interpretation of Infrared, Raman and Nuclear Magnetic Resonance Spectra (Academic Press, New York, 2001).
[19] R. Noel, A Guide to the Complete Interpretation of the Infrared Spectra of Organic Structures (J. Wiley & Sons New York, 1994).
[20] M. Wienken, B. Lippert, E. Zangrando and L. Randaccio, *Inorg. Chem*. **31**, 1983 (1992).
[21] C.D.W. Froehling and W.S. Sheldrick, *Chem. Commun*. 1737 (1997).
[22] J. Reedjik, *Chem. Rev*. 801 (1999).
[23] N. Milovic and N. Kostic, *J. Am. Chem. Soc*. **124**, 4759 (2002).
[24] P. Tsiveriots, N. Hadjiliadis and I. Sovago, *J. Chem. Soc., Dalton Trans*. 4267 (1997).
[25] Y. Kojiima, N. Ishio and T. Yamashita, *Bull. Chem. Soc. Jpn*. **58**, 759 (1985).
[26] Y. Kojiima, N. Ishio, T. Yamashita and K. Hirotsu, *Chem. Lett*. 1365 (1983).
[27] Y. Kojiima, T. Yamashita, N. Ishio, T. Hirashima and K. Hirotsu, *Chem. Lett*. 453 (1983).
[28] D. Rabenstein, A.A. Isab and M. Shoukry, *Inorg. Chem*. **21**, 3234 (1982).