Synthesis, Characterization, and Structural Investigation of the First Bioinorganic Titanocene(IV) α-Amino Acid Complexes Prepared from the Antitumor Agent Titanocene Dichloride†

Thomas M. Klapötke, Hartmut Köpf, and Inis C. Tornieporth-Oetting*

Institut für Anorganische und Analytische Chemie, Technische Universität Berlin, Strasse des 17. Juni 135, Sekr. C2, D-10623 Berlin, Germany

Peter S. White*

Department of Chemistry, The University of North Carolina, Chapel Hill, North Carolina 27599

Received April 7, 1994®

Antitumor active titanocene dichloride [Cp_2TiCl_2] ($Cp = \eta^5$-C_5H_5) reacts with α-amino acids (aa = amino acid) in aqueous methanol to give the first bioinorganic titanium(IV) amino acid complexes $[Cp_2Ti(aa)_2]^{2+}[Cl]^-_2$ (aa: glycine, **1**; L-alanine, **2**; 2-methylalanine, **3**). These compounds are of great interest as the first models involving titanocene complexes with α-amino acids. The structure of **3** was determined by X-ray structure analysis. Complex **3** is monoclinic, space group $C2/c$, $a = 9.0630(11)$ Å, $b = 28.173(9)$ Å, $c = 8.8967(9)$ Å, $\beta = 96.379(9)°$, $V = 2257.5(4)$ Å^3, and $Z = 4$. It was established by X-ray analysis and vibrational spectroscopy that these compounds represent examples of very rare species in which the amino acids coordinate solely through the carboxylato group. All complexes have been characterized by chemical analyses (C/H/N/Cl), NMR (^{1}H, $^{14/15}$N), mass (EI; **3** in addition by DCI), infrared, and Raman spectroscopy.

Introduction

Many of the neutral diacido metallocene dichloride complexes of the early transition elements, Cp_2MCl_2 (M = Ti, V, Nb, Mo), exhibit antitumor activity against numerous experimental tumors, e.g. Ehrlich ascites tumor, B 16 melanoma, colon 38 carcinoma, and Lewis lung carcinoma, as well as against various human tumors heterotransplanted to athymic mice.[1] The biological features confirm that the cyclopentadienylmetal complexes are an independent group of non-platinum-group metal antitumor agents that possess unusual biological properties.[1] Application of Cp_2TiCl_2 causes cell gigantism and inhibits DNA synthesis more than protein synthesis; thus, it is reasonable to assume that inhibition of replication is responsible for the antitumor activity of metallocene compounds.[2] The first hypothesis to explain the antitumor activity of metallocene dichlorides assumed that the cytotoxicity resulted from binding with DNA similar to DNA–cisplatin.[2,3] However, the aqueous chemistries of cisplatin and Cp_2MCl_2 (M = Ti, V) differ substantially (see below) and model studies have failed to find that the Cp_2M moiety (M = Ti, V) chelates adjacent N7-guanine sites as does cisplatin.[4,6] It was therefore of great interest to investigate the coordination behavior of Cp_2TiCl_2 toward simple species that possess both oxygen and nitrogen donor functions of biological molecules.

Titanocene dichloride, Cp_2TiCl_2, has proved to be one of the most effective species in this class of compounds and is presently in the process of clinical development.[5] However, because of the limited stability of titanocene dichloride in aqueous solutions it has not been possible to synthesize titanium model complexes containing biologically important ligands under physiological conditions. It was only in nonaqueous solvents such as THF or toluene that the synthesis of a few titanium(IV) model complexes starting from Cp_2TiCl_2 (e.g. [Cp_2-TiCl(purinato)]) and some titanium(III) complexes was successful, but the latter ones are less important, because the reduction of titanium(IV) to titanium(III) in biological systems is not very likely.[6] Although there is also one report on DNA–metal binding by Cp_2MCl_2 complexes (M = Ti, Zr, Hf, V, Nb) from inductively coupled plasma studies,[7] no Cp_2Ti^{IV} complex containing

† A preliminary account of this paper has been published by the same authors: *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1518–1519.

® Abstract published in *Advance ACS Abstracts,* August 1, 1994.

(1) Köpf-Maier, P.; Köpf, H. In *Structure and Bonding*; Springer: Berlin, New York, 1988; pp 103–185, and references therein. Köpf-Maier, P. In *Complexes in Cancer Chemotherapy*; Keppler, B. K., Ed.; VCH: Weinheim, New York, 1993; pp 259–296, and references therein. Kuo, L. Y.; Kanatzidis, M. G.; Marks, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 7207–7209. Kuo, L. Y.; Kanatzidis, M. G.; Sabat, M.; Tipton, A. L.; Marks, T. J. *J. Am. Chem. Soc.* **1991**, *113*, 9027–9045. Köpf-Maier, P.; Köpf, H. *Chem. Rev.* **1987**, *87*, 1137–1152.

(2) Köpf, H.; Köpf-Maier, P. *ACS Symp. Ser.* **1983**, *No. 209*, 315–333.

(3) Rosenberg, B. *Cancer* **1985**, *55*, 2303. Sherman, S. E.; Lippard, S. *J. Chem. Rev.* **1987**, *87*, 1153–1181.

(4) Beauchamp, A. L.; Bélanger-Gariépy, F.; Cozak, D. *Inorg. Chim. Acta* 1986, *124*, L23. Pneumatikakis, G.; Yannopoulos, A.; Markopoulos, J. *Inorg. Chim. Acta* **1988**, *151*, 125–128. Toney, J. H.; Brock, C. P.; Marks, T. J. *J. Am. Chem. Soc.* **1986**, *108*, 7263–7274.

(5) Berdel, W. E.; Schmoll, H.-J.; Scheulen, M. E.; Korfel, A.; Knoche, M. F.; Harstrick, A.; Bach, F.; Baumgart, J.; Sass, G. *J. Cancer Res. Clin. Oncol.* **1994**, *120* (Suppl.), R-172.

(6) Cozak, D.; Mardhy, A.; Morneau, A. *Can. J. Chem.* **1986**, *64*, 751–759. Beauchamp, A.; Cozak, D.; Mardhy, A. *Inorg. Chim. Acta* **1984**, *92*, 191–197. Cozak, D.; Mardhy, A.; Oliver, M. J.; Beauchamp, A. L. *Inorg. Chem.* **1986**, *25*, 2600–2606. Cardin, C. J.; Roy, A. *Inorg. Chim. Acta* **1985**, *107*, L 33. Sigel, H., Sigel, A., Eds. *Metal Ions in Biological Systems*; Dekker: New York, **1984**; Vol. 30.

0276-7333/94/2313-3628$04.50/0

a biologically relevant ligand system has been isolated so far from physiological conditions or from a water-like solvent (see above). In spite of this, numerous stable Pt(II) model complexes have been synthesized in aqueous solution.[8] Some authors claimed that not titanocene complexes but cyclopentadiene formed during the decomposition of Cp_2Ti compounds is the antitumor active species.[9] Later it was unambiguously shown by in vivo experiments that neither cyclopentadiene nor its dimer is the antiproliferative active moiety in antitumor non-platinum complexes.[10] Therefore, the well-planned synthesis of a titanocene model complex containing a naturally abundant ligand system starting from the antitumor drug Cp_2TiCl_2 and working in a water-like system has been of great importance.

Since our understanding of the nature of metal binding sites in proteins owes very much to the study of models involving metal complexes with amino acids, the coordination power of α-amino acids toward the Cp_2Ti^{IV} moiety was the object of our present investigation. It is interesting to note that the coordination behavior of α-amino acids toward platinum-group metals[8,11,12] as well as toward copper(II) compounds and also toward cobalt(II), nickel(II), zinc(II), and cadmium(II) species has been extensively studied and was the subject of several reviews.[12] However, prior to our work no α-amino acid complex of a group 4 metallocene complex has been reported.

Experimental Section

General Techniques. All reactions were carried out using Schlenk techniques. Titanocene dichloride, Cp_2TiCl_2, was prepared by literature methods.[13] The amino acids (glycine, gly; L-alanine, ala; methylalanine, Meala) were used as purchased without further purification (Aldrich). Methanol (Merck, not dried) was used as supplied. Infrared spectra were recorded using a Perkin-Elmer 580 B instrument, and Raman spectra were measured with a Jobin Yvon Ramanor U 1000 spectrometer, equipped with a Spectra-Physics Kr laser (λ = 647.09 nm). ^{1}H NMR spectra were obtained from a Varian EM 360 (60 MHz) or a Varian EM 390 (90 MHz) instrument. N NMR spectra were recorded using a Varian 400 instrument operating at 40.543 MHz (^{15}N) and 28.901 MHz (^{14}N) and were referred to CH_3NO_2. Mass spectra (EI and DCI) were obtained using a Varian MAT 311 A instrument, and UV–vis spectra were obtained from a Carl Zeiss Elko III instrument. Elemental analyses were performed by Malissa & Reuter, Analytische Laboratorien, Gummersbach, Germany, or by the TU Berlin service.

Synthesis of 1. $[Cp_2TiCl_2]$ (2.00 g, 8.0 mmol) and glycine (1.20 g, 16.0 mmol) were stirred in 10 mL of CH_3OH at room temperature. After 4 h the precipitated light orange solid was filtered off and dried in vacuo (83%, T_{dec} > 160 °C). Anal. Calcd for $C_{14}H_{20}Cl_2N_2O_4Ti$ (399.11): C, 42.1; H, 5.1; N, 7.0; Cl, 17.8. Found: C, 41.5; H, 5.1; N, 7.4; Cl, 17.8. ^{1}H NMR (D_2O, relative to internal D_2O): δ 6.57 (s, Cp, 10H), 3.68 (s, CH_2, 4H). ^{14}N NMR (D_2O): δ −352.1 (s, NH_3^+). UV–vis (D_2O): λ_{max} <365 nm. MS (EI, 70 eV, 160 °C; *m/e* (I_{rel})): 248 (26), M^+ − 2 gly; 213 (25), M^+ − 2 gly − Cl; 183 (100), M^+ − 2 gly − Cp; 148 (42), M^+ − 2 gly − Cl − Cp; 75 (10), gly$^+$; 65 (21), Cp^+. IR (KBr, cm^{-1}): 3095 ms, 2970 s, sh, 2870 s, 2715 m, 2630 ms, 1655 vs, 1620 ms, 1597 m, 1535 m, 1520 ms, 1445 m, 1368 s, 1362 s, 1332 s, 1315 s, 1305 vs, 1130 ms, 1035 m, 1015 m, sh, 1020 m, 915 m, sh, 910 m, 860 m, 845 ms, 825 s, 650 ms, 523 ms, 432 ms, 415 ms, 357 m. Raman (647 nm, 22 °C, 60 mW, cm^{-1}): 3118 (<1), 3098 (<1), 2947 (<1), 1659 (1), 1443 (1), 1370 (<1), 1336 (<1), 1307 (<1), 1131 (6), 1081 (<1), 1065 (<1), 1030 (<1), 914 (<1), 858 (<1), 829 (1), 651 (<1), 605 (<1), 526 (<1), 436 (2), 360 (6), 307 (2), 265 (10), 263 (<1), 154 (1).

Synthesis of 2. $[Cp_2TiCl_2]$ (2.00 g, 8.0 mmol) and L-alanine (1.43 g, 16.0 mmol) were reacted at room temperature for 2 h as described above and yielded an orange solid (38%, T_{dec} > 100 °C). Anal. Calcd for $C_{16}H_{24}Cl_2N_2O_4Ti$ (427.16): C, 45.0; H, 5.7; N, 6.6; Cl, 16.6. Found: C, 44.5; H, 5.6; N, 6.5, Cl, 16.5. ^{1}H NMR (D_2O, relative to internal D_2O): δ 6.62 (s, Cp, 10H), 3.87 (q, CH, 2H, $^3J_{HH}$ = 7.6 Hz), 1.40 (d, CH_3, 6H, $^3J_{HH}$ = 7.6 Hz). ^{1}H NMR (SO_2, relative to TMS): δ 8.2–7.6 (s, br, NH_3^+, 6H), 6.69 (s, Cp, 10H), 3.98 (q, CH, 2H, $^3J_{HH}$ = 8 Hz), 1.61 (d, CH_3, 6H, $^3J_{HH}$ = 8 Hz). ^{14}N NMR (D_2O): δ −339.8 (s, NH_3^+). UV–vis (D_2O): λ_{max} < 365 nm. MS (EI, 70 eV, 220 °C; *m/e* (I_{rel})): 267 (13), M^+ − ala − 2 Cl; 250 (20), M^+ − ala − 2 Cl − NH_3; 248 (34), M^+ − 2 ala; 213 (42), M^+ − 2 ala − Cl; 183 (100), M^+ − 2 ala − Cp; 178 (33), M^+ − 2 ala − 2 Cl; 148 (56), M^+ − 2 ala − Cp − Cl; 89 (5), ala$^+$; 65 (25), Cp^+. IR (KBr, cm^{-1}): 3120 m, sh, 3090 m, sh, 3060 m, sh, 2890 s, br, 2790 ms, 2715 ms, 2645 ms, 2590 ms, 2515 ms, 2010 m, 1660 vs, 1625 ms, 1602 ms, 1535 ms, 1520 ms, 1447 ms, 1375 s, 1362 ms, 1335 s, 1310 ms, 1295 vs, 1205 ms, 1135 ms, 1105 ms, 1015 m, 1005 m, 925 m, 823 vs, 752 ms, 628 ms, 537 ms, 445 ms, 422 ms, sh, 405 ms, 362 m. Raman (647 nm, 22 °C, 60 mW, cm^{-1}): 3123 (<1), 3100 (<1), 3010 (<1), 2987 (<1), 2933 (<1), 2881 (<1), 1662 (<1), 1445 (<1), 1363 (<1), 1312 (<1), 1296 (<1), 1210 (<1), 1133 (5), 1107 (<1), 1075 (<1), 1006 (<1), 925 (<1), 829 (<1), 750 (<1), 629 (<1), 603 (<1), 540 (<1), 426 (3), 366 (5), 261 (10), 215 (1), 190 (<1), 143 (3).

Synthesis of 3. $[Cp_2TiCl_2]$ (2.00 g, 8.0 mmol) and 2-methylalanine (1.65 g, 16.0 mmol) were reacted for 30 min as described above, and **3** was isolated as a shiny orange solid (93%, T_{dec} > 240 °C). Compound **3** was redissolved in water, and slow evaporation of the solvent gave orange-red crystals of **3** which were suitable for X-ray diffractometry. Anal. Calcd for $C_{18}H_{28}Cl_2N_2O_4Ti$ (455.22): C, 47.5; H, 6.2; N, 6.1; Cl, 15.6. Found: C, 47.2; H, 6.2; N, 6.1; Cl, 15.6. ^{1}H NMR (D_2O): δ 6.62 (s, Cp, 10H), 1.52 (s, CH_3, 12H). ^{14}N NMR (D_2O): δ −328.8 (s, NH_3^+). ^{15}N NMR (D_2O): δ −329.5 (q, NH_3^+, $^1J_{NH}$ = 18 Hz). UV–vis (D_2O): λ_{max} < 365 nm. MS (EI, 70 eV, 240 °C; *m/e* (I_{rel})): 280 (28), M^+ − Meala − 2 Cl − H; 248 (44), M^+ − 2 Meala; 213 (30), M^+ − 2 Meala − Cl; 183 (100), M^+ − 2 Meala − Cp; 178 (60), M^+ − 2 Meala − 2 Cl; 148 (56), M^+ − 2 Meala − Cl − Cp; 65 (16), Cp^+. MS (DCI; *m/e* (I_{rel})): 384 (1), M^+ − 2 Cl; 316 (3), M^+ − Meala − Cl; 281 (19), M^+ − Meala − 2 Cl; 264 (47), M^+ − Meala − 2 Cl − NH_3; 248 (4), M^+ − 2 Meala; 213 (68), M^+ − 2 Meala − Cl − Cp; 178 (23), M^+ − 2 Meala − 2 Cl; 104 (100), Meala$^+$. IR (KBr, cm^{-1}): 3105 m, 3080 m, 3065 m, 3005 m, sh, 2975 m, 2930 ms, 2890 ms, 2820 m, 2780 m, 2770 m, 2590 m, 1655 vs, 1627 m, 1605 m, 1595 m, 1532 m, 1502 m, 1448 m, 1383 s, 1365 ms, 1345 ms, 1258 ms, 1242 s, 1200 m, 1132 vw, 1022 w, 952 w, 902 w, 872 w, 832 s, 615 m, 568 m, 447 ms, 435 m, 425 m. Raman (647 nm, 22 °C, 60 mW, cm^{-1}): 3118 (<1), 3008 (<1), 2977 (<1), 2941 (<1), 1651 (<1), 1443 (<1), 1366 (<1), 1261 (<1), 1132 (2), 1078 (<1), 947 (<1), 843 (1), 794 (<1), 596 (<1), 425 (2), 385 (2), 363 (5), 266 (10), 181 (<1), 149 (<1).

Reaction of 1–3 with HCl. A saturated solution of **1**, **2**, or **3** in D_2O/CD_3OD was reacted with an excess of HCl and

(7) McLaughlin, M. L.; Cronan, J. M., Jr.; Schaller, T. R.; Snelling, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 8949–8952.
(8) Lippard, S. J. *Science* **1982**, *218*, 1075–1082. Appelton, T. G.; Hall, J. R.; Ralph, S. F. *Inorg. Chem.* **1985**, *24*, 673–677 and references therein. Lippard, S. J. *Pure Appl. Chem.* **1987**, *59*, 731 and references therein. Howe-Grant, M. E.; Lippard, S. J. In *Metal Ions in Biological Systems*; Sigel, H., Ed.; Dekker: New York, 1980; Vol. 11, p 63.
(9) Döppert, K. *J. Organomet. Chem.* **1987**, *319*, 351–354.
(10) Köpf-Maier, P.; Köpf, H. *J. Organomet. Chem.* **1988**, *342*, 167.
(11) Appelton, T. G.; Bailey, A. J.; Bedgood, D. R., Jr.; Hall, J. R. *Inorg. Chem.* **1994**, *33*, 217–226. Pettit, L. D.; Bezer, M. *Coord. Chem. Rev.* **1985**, *61*, 97–114.
(12) Corradi, A. B. *Coord. Chem. Rev.* **1992**, *117*, 45–98 and references therein. Sheldrick, W. S.; Hauck, E.; Korn, S. *J. Organomet. Chem.* **1994**, *467*, 283–292.
(13) Wilkinson, G.; Birmingham, J. M. *J. Am. Chem. Soc.* **1954**, *76*, 4281–4284.

Table 1. Experimental Data for the X-ray Diffraction Study on Compound 3

chem formula	$C_{18}H_{24}Cl_2N_2O_4Ti$
a (Å)	9.0630(11)
b (Å)	28.173(3)
c (Å)	8.8967(9)
β (deg)	96.379(9)
V (Å^3)	2257.5(4)
Z	4
fw	455.23
cryst syst	monoclinic
space group	$C2/c$
t (°C)	20
λ (Å)	0.709 30
ϱ_{calc} (g cm^{-3})	1.339
μ (mm^{-1})	0.64
radiation	Mo K$_\alpha$, graphite monochromator
no. of reflns measd	3253
no. of unique rflns	2006
no. of data used in refinement	1487 ($I_{net} > 2.5\sigma(I_{net})$)
transmissn factor range	0.6819–0.8614
R_F[a]	0.042
R_w[b]	0.052
GOF[c]	1.67
R_F(all rflns)	0.064
R_w(all rflns)	0.056

[a] $R_F = \Sigma(F_o - F_c)/\Sigma F_o$. [b] $R_w = [\Sigma(w(F_o - F_c)^2)/\Sigma w(F_o^2)]^{0.5}$. [c] GOF = $[\Sigma(w(F_o - F_c)^2/((\text{no. of reflections}) - (\text{no. of parameters}))]^{0.5}$.

investigated by ^{1}H NMR spectroscopy. In all cases a singlet due to the generation of Cp_2TiCl_2 was detected. ^{1}H NMR (D_2O/CD_3OD, relative to TMS): δ 6.6 s.

X-ray Crystallography. An orange-red crystal of **3** with dimensions 0.40 × 0.35 × 0.20 mm was mounted on a glass fiber and investigated under atmospheric conditions. Crystal data and details associated with data collection are given in Table 1. Cell dimensions were obtained from 92 reflections with 2θ angles in the range 30.0–40.0°. Diffraction intensities were measured at 293 K on a Rigaku AFC6S diffractometer equipped with graphite-monochromated MoKα radiation (λ = 0.710 73 Å) using the $\theta/2\theta$ scan mode with $2\theta_{max}$ = 49.9°. The structure was solved and refined with 28 atoms, 123 parameters, and 1487 of the 2006 independent reflections with use of NRCVAX.[14] All non-hydrogen atoms were anisotropically refined.

Results and Discussion

One of the major problems of the reaction of titanocene dichloride with amino acids is to find a solvent that dissolves both the Ti complex and the amino acid. Whereas Cp_2TiCl_2 dissolves nicely in many organic solvents (e.g. benzene, THF, hydrocarbons, DMSO, etc.) and also in aprotic inorganic systems (e.g. SO_2), amino acids are only soluble in water and in mineral acids (e.g. hydrochloric acid); they also dissolve slightly in methanol. In pure water, however, Cp_2TiCl_2, not unlike Cp_2VCl_2, suffers from rapid and extensive chloride aquation and there is also evidence that the Cp–Ti ligation is hydrolytically unstable.[15] On the other hand, in the presence of HCl it is not possible to replace the chloride acido ligand in Cp_2TiCl_2 by any other amino acid ligand system. In fact, having succeeded in the preparation

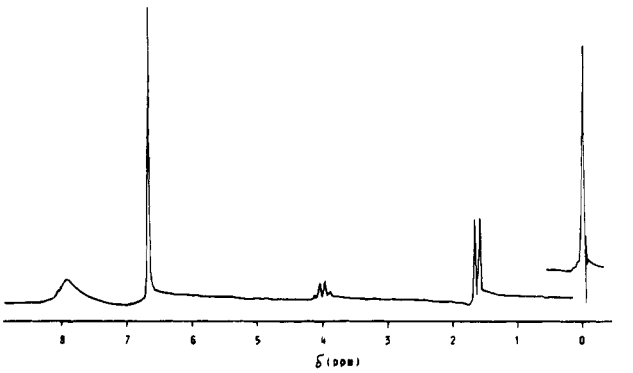

Figure 1. ^{1}H NMR spectrum of complex **2** in SO_2 solution.

of complexes of the type $[Cp_2Ti(aa)_2][Cl]_2$ (aa = amino acid) (see below), we were able to show by ^{1}H NMR spectroscopy that these species that are nearly freely soluble in water reacted back to give titanocene dichloride if HCl was added to the aqueous solution (eq 1).

$$[Cp_2Ti(aa)_2][Cl]_2 \xrightarrow{HCl} Cp_2TiCl_2 + 2aa \qquad (1)$$

aa =

amino acid = glycine, L-alanine, 2-methylalanine

Therefore, methanol was the appropriate solvent for the preparation of titanocene amino acid complexes. The reaction of Cp_2TiCl_2 with stoichiometric amounts of the corresponding amino acid in aqueous methanol (ca. 0.5–1.0% water) afforded the orange to red complexes **1**–**3** in high yields (eq 2). Compounds **1**–**3** are stable solids

$$Cp_2TiCl_2 + 2aa \xrightarrow{\text{MeOH, room temp}} \underset{\mathbf{1-3}}{[Cp_2Ti(aa)_2][Cl]_2} \qquad (2)$$

aa: glycine, $^-O_2CCH_2NH_3^+$ (**1**)

aa: L-alanine, $^-O_2CCH(CH_3)NH_3^+$ (**2**)

aa: 2-methylalanine, $^-O_2CC(CH_3)_2NH_3^+$ (**3**)

at room temperature and are nonsensitive toward air and moisture.

The ^{1}H NMR spectra were recorded in D_2O (see Experimental Section), and **1** shows a significant shift to lower field for the protons bound to the α-C atom of the coordinated amino acid in comparison with the free ligand (cf. **1**, $\delta(CH_2)$ 3.68 ppm; glycine, $\delta(CH_2)$ 3.38 ppm). Whereas the proton at the α-C atom of **2** also shows a significant shift to lower field, the methyl protons in **2** and **3** are only slightly shifted to lower field (cf. **2** δ(CH) 3.87 ppm, $\delta(CH_3)$ 1.40 ppm; alanine, δ(CH) 3.63 ppm, $\delta(CH_3)$ 1.35 ppm; **3** $\delta(CH_3)$ 1.52 ppm; 2-methylalanine $\delta(CH_3)$ 1.47 ppm). Due to fast exchange reactions with the solvent the proton NMR spectra of **1**–**3** in no case show the resonance of the N*H*$_3$ protons if the spectra were recorded in D_2O. However, in SO_2 (no proton exchange) complex **2** shows all expected ^{1}H resonances in the NMR spectrum (Figure 1). For all compounds **1**–**3** the ^{14}N NMR spectra (in D_2O solution) show resonances in agreement with the ionic ammonium ($-NH_3^+$) structures (relative to $MeNO_2$: **1**, −352 ppm; **2**, −340 ppm; **3**, −329 ppm (cf. $^-O_2CC(CH_3)_2NH_3^+$, −328 ppm)).

(14) Gabe, E. J.; Le Page, Y.; Charland, J.-P.; Lee, F. L.; White, P. S. *J. Appl. Crystallogr.* **1989**, *22*, 384–387. Le Page, Y. *J. Appl. Crystallogr.* **1988**, *21*, 983–984. Le Page, Y.; Gabe, E. J. *J. Appl. Crystallogr.* **1979**, *12*, 464–466. Scattering factors: *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, 1974; Vol. IV. ORTEP: Johnson, C. K. *ORTEP – A Fortran Thermal Ellipsoid Plot Program*; Technical Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.

(15) Toney, J. H.; Marks, T. J. *J. Am. Chem. Soc.* **1985**, *107*, 947–953. Köpf, H.; Grabowski, S.; Voigtländer, R. *J. Organomet. Chem.* **1981**, *216*, 185–190.

Table 2. Characteristic Infrared and Raman Absorptions and Assignments for Complexes 1–3 (cm^{-1})[a]

1		2		3		
IR	Raman	IR	Raman	IR	Raman	assignt
3095 ms	3098 (<1)	3090 m,sh	3100 (<1)	3105 m	3118 (<1)	ν(CH), Cp
1655 vs	1659 (1)	1660 vs	1662 (<1)	1655 vs	1651 (<1)	ν_{as}(COO)
1445 m	1443 (1)	1447 ms	1445 (<1)	1448 m	1443 (<1)	ω(CC), Cp
1368 s	1370 (<1)	1375 s	n.o.	1383 s	n.o.	ν_s(COO)
1130 ms	1131 (6)	1135 ms	1133 (5)	1132 vw	1132 (2)	δ(CH), Cp; $\varrho(NH_3^+)$
825 s	829 (1)	823 vs	829 (1)	832 s	843 (1)	γ(CH), Cp

[a] See also the Experimental Section.

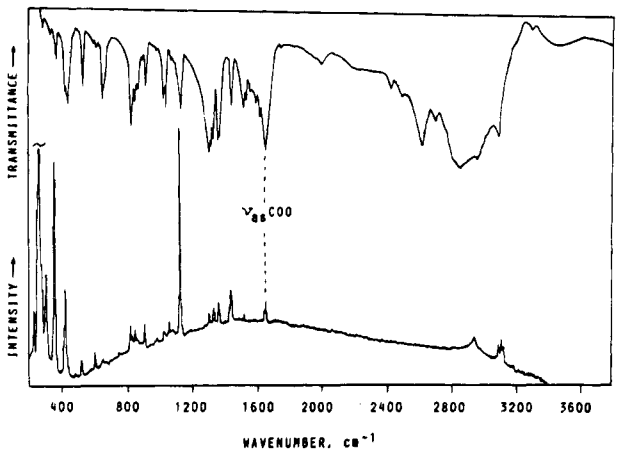

Figure 2. Infrared (top; KBr disk, 22 °C) and Raman spectra (bottom; 647 nm, 60 mW, 22 °C) of complex **1**.

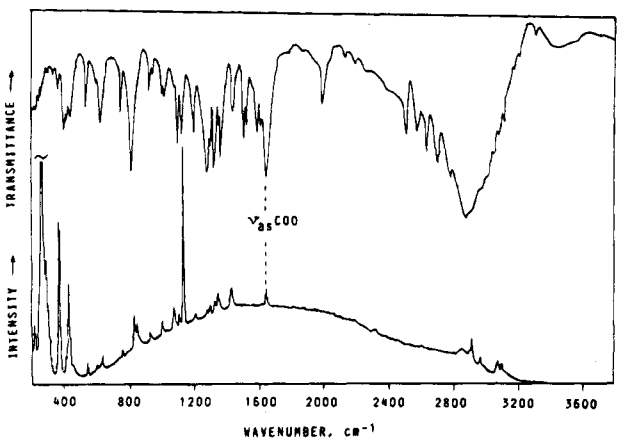

Figure 3. Infrared (top; KBr disk, 22 °C) and Raman spectra (bottom; 647 nm, 60 mW, 22 °C) of complex **2**.

The infrared spectra of **1–3** show very strong absorptions due to the asymmetric COO stretching mode and a strong band which can be assigned to the symmetric ν(COO) mode. In agreement with earlier reports on the coordination behavior of amino acids toward metals the ν_{as}(COO) vibrations are shifted to higher wavenumbers, whereas the ν_s(COO) modes are shifted to lower frequencies compared with the free amino acid ligands.[16] A full set of all observed vibrations is given in the Experimental Section; Table 2 summarizes all significant titanocene and amino acid absorptions that are characteristic for the compounds **1–3**. Figures 2–4 show both the infrared (top) and Raman spectra (bottom) of complex **1–3** and nicely demonstrate as indicated for the ν_{as}(COO) mode the reversed intensities of peaks or absorptions in the two vibrational spectra.

(16) Nakamoto, K. *Infrared and Raman Spectra of Inorganic and Coordination Compounds*; Wiley: New York, 1986; Chapter 3, and references therein.

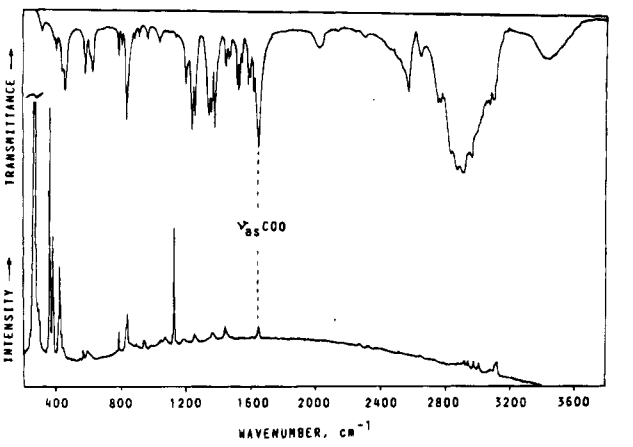

Figure 4. Infrared (top; KBr disk, 22 °C) and Raman spectra (bottom; 647 nm, 60 mW, 22 °C) of complex **3**.

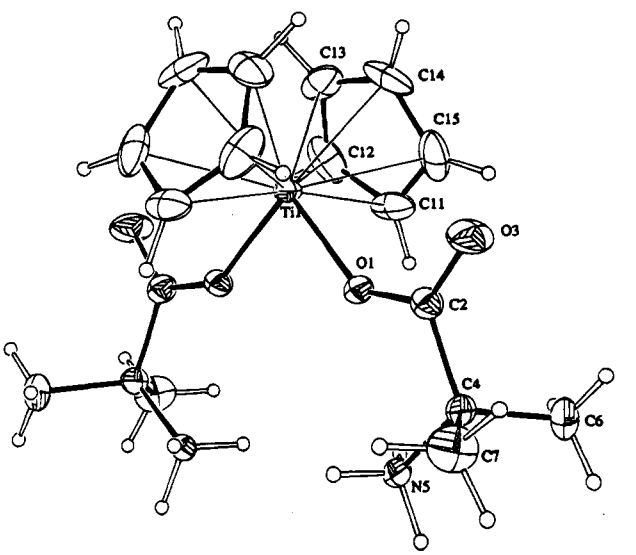

Figure 5. ORTEP presentation of the cation in complex **3**.

Slow evaporation of the solvent of an aqueous solution of **3** yielded orange-red crystals which were suitable for a X-ray structure determination. The structure of the cation in **3** is presented in Figure 5. Table 3 contains the most important bond lengths and angles of the cation in **3**. The structural features of the titanocene core are d(Cp(center)–Ti = 2.052 Å and ∠(Cp(center)–Ti–Cp(center)) = 132.3° and agree well with other titanocene compounds (cf. $Cp_2Ti(SbF_6)_2$ d(Cp–Ti) = 2.03 Å, ∠(Cp–Ti–Cp) = 133.8°; $Cp_2Ti(AsF_6)_2$, d(Cp–Ti) = 2.02 Å, ∠(Cp–Ti–Cp) = 134.0°; C_2H_4(4,5,6,7-tetrahydroindenyl)$_2$Ti(*O*-acetylmandelato)$_2$, d(Ti–O) = 1.95 Å, ∠(O–Ti–O) = 99°).[17] Moreover, the C2–O3 bond length compares nicely with the double-bond distance in R_2CO (R = H, CH_3), but the O1–C2 bond length of 1.286 Å is significantly shorter than the C–O

Table 3. Selected Bond Lengths (Å) and Angles (deg) of the $[Cp_2Ti(2\text{-methylalanine})_2]^{2+}$ Cation in 3

Ti1–O1	1.9610(19)	C4–N5	1.490(4)
Ti1–C11	2.361(4)	C4–C6	1.530(5)
Ti1–C12	2.362(4)	C4–C7	1.501(6)
Ti1–C13	2.333(4)	C11–C12	1.343(9)
Ti1–C14	2.339(4)	C11–C15	1.367(10)
Ti1–C15	2.359(4)	C12–C13	1.336(9)
O1–C2	1.286(4)	C13–C14	1.351(10)
C2–O3	1.210(4)	C14–C15	1.347(10)
C2–C4	1.531(4)	Ti1–Cp(center)	2.052
O1–Ti–O1a	90.75(8)	Ti1–O1–C2	141.21(19)
O1–C2–O3	125.1(3)	O1–C2–C4	115.12(25)
O3–C2–C4	119.7(3)	C2–C4–N5	109.59(22)
C2–C4–C6	108.5(3)	C2–C4–C7	110.1(3)
N5–C4–C6	107.5(3)	N5–C4–C7	108.2(3)
C6–C4–C7	113.0(3)	Cp–Ti1–Cp	132.28

single-bond distance in alcohols (d(C–O) = 1.42 Å).[18] Like a recently reported gold(I) complex containing an O-coordinated hippurato amino acid ligand, compound **3** represents one of the few examples in which the amino acid coordinates solely through the carboxylato group.[19] However, in the solid state there are strong cation···anion interactions, as indicated in Figure 6. Obviously, all hydrogen atoms of the NH_3^+ groups have contacts to chloride ions (in fact, the X-ray structure shows three Cl atoms very weakly coordinated to N) and each Cl atom interacts with three hydrogen atoms, two of which belong to the same cation whereas the third belongs to a neighboring titanocene cation. The mean N···Cl distance is 3.2 Å, which is substantially shorter than the sum of the van der Waals radii of N, H, and Cl (4.27 Å)[20] but still much longer than the sum of the corresponding covalent radii (2.06 Å).[21]

The X-ray structure analysis of **3** undoubtedly established that this complex represents one of the few examples[22] where the amino acids coordinate only through the carboxylato group (Figure 5). Furthermore, by a combined infrared and Raman study of all three new compounds **1**–**3** (Table 2) we have been able to show that all adopt a solely oxygen-coordinated structure. In this respect it is interesting to mention that polymeric titanocene and Pt(II) complexes with amino acids have been reported.[23] However, so far their structures have not been determined by diffraction methods.

In terms of simple HSAB considerations it is obvious that the titanocene fragment Cp_2Ti^{2+} is substantially softer than the bare Ti^{4+} cation.[24] However, the species

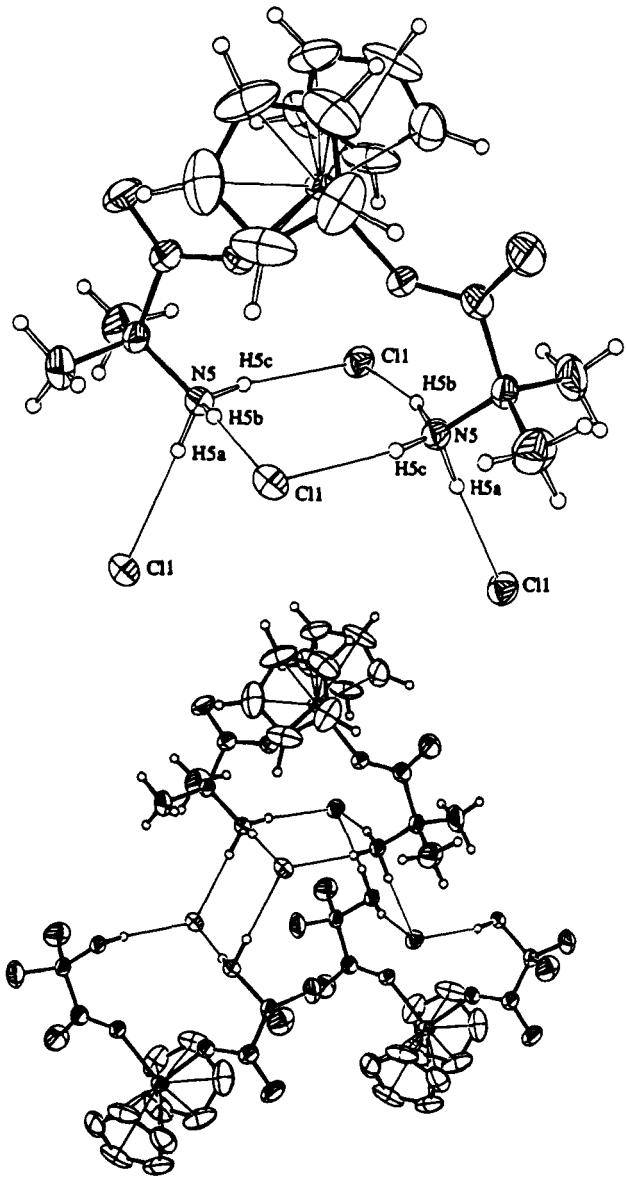

Figure 6. Top: $[Cp_2Ti(2\text{-methylalanine})_2]^{2+}$ cation with atomic numbering and cation···anion interactions. Bottom: Three $[Cp_2Ti(2\text{-methylalanine})_2]^{2+}$ cations with cation···anion interactions.

Cp_2Ti^{2+} is obviously still much harder than the $(NH_3)_2Pt^{2+}$ cation. Therefore, it is likely that, in the case of platinum, bonds to nitrogen (soft) will be thermodynamically more stable in general than bonds to oxygen (hard). This is nicely in agreement with the experimental results in platinum amino acid chemistry.[8] In the case of titanocene amino acid complexes, however, bonds to oxygen are expected to be thermodynamically more stable. This means that the initially formed O-bound complexes **1**–**3** are not only kinetically stabilized (it is difficult to see a convenient kinetic pathway while the amino group is protonated) with respect to interconversion to N-coordinated species but also thermodynamically favored. Moreover, these observations compare well with recent thermodynamic studies which derived metal–ligand bond enthalpies for a variety of metallocene complexes of the early transition ele-

(17) Klapötke, T. M.; Thewalt, U. *J. Organomet. Chem.* **1988**, *356*, 173–179. Gowik, P.; Klapötke, T. M.; Thewalt, U. *J. Organomet. Chem.* **1990**, *385*, 345–350. Schäfer, A.; Karl, E.; Zsolnai, L.; Huttner, G.; Brintzinger, H.-H. *J. Organomet. Chem.* **1987**, *328*, 87–99.

(18) Gillespie, R. J.; Hargittai, I. *The VSEPR Model of Molecular Geometry*; Allyn and Bacon: Boston, MA, 1991. Johnson, D. A. *Some Thermodynamic Aspects of Inorganic Chemistry*; Cambridge University Press: Cambridge, U.K., 1982.

(19) Jones, P. G.; Schelbach, R. *J. Chem. Soc., Chem. Commun.* **1988**, 1338–1339. Sigel, H., Ed. *Metal Ions in Biological Systems*; Dekker: New York, 1979; Vol. 8.

(20) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.

(21) Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*; Pergamon: Oxford, New York, 1984.

(22) Kaim, W.; Schwederski, B. *Bioanorganische Chemie*; Teubner: Stuttgart, Germany, 1991; pp 150–152. Lindqvist, I.; Rosenstein, R. *Acta Chem. Scand.* **1960**, *14*, 1228–1229.

(23) Carraher, C. E., Jr.; Tisinger, L. G. *Polym. Mater. Sci. Eng.* **1991**, *65*, 29–30. Carraher, C. E., Jr.; Tisinger, L. G.; Lopez, I.; Williams, M. *Biometic Polym.* **1991**, 71–80. Carraher, C. E., Jr.; Tisinger, L. G.; Tisinger, W. H. *Polym. Sci. Technol. (Plenum)* **1986**, *33*, 225–233.

(24) Pearson, R. G. *Acc. Chem. Res.* **1993**, *26*, 250–255 and references therein. Chattaraj, P. K.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1994**, *116*, 1067–1071.

ments: $E(Cp_2Ti(R)-NR_2) = 77 \pm 8$ kcal mol^{-1}; $E(Cp_2Ti(R)-OR) = 105 \pm 5$ kcal mol^{-1}.[25]

In conclusion, the successful synthesis of three titanocene amino acid complexes prepared from the antitumor drug Cp_2TiCl_2 and the free amino acids in aqueous methanol firmly established the possibility of the generation of titanocene complexes containing biologically relevant ligand systems. Moreover, compounds **1**–**3** are stable in water for several hours (**3** was recrystallized from H_2O!). They also represent the first examples of metallocene amino acid complexes in which the central metal atom is a member of group 4 (Ti, Zr, Hf).

Acknowledgment. We gratefully acknowledge continuous financial support by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the North Atlantic Treaty Organization (Grant No. CRG 920034). We thank Prof. Dr. J. Passmore for providing $^{14/15}N$ NMR facilities. We are also indebted to Dipl.-Chem. Martin Kempf for recording the DCI mass spectra.

Supplementary Material Available: A full structure report for **3**, including tables listing all bond lengths and angles, anisotropic parameters, and H atom positional parameters and figures giving stereoscopic packing diagrams (8 pages). Ordering information is given on any current masthead page. Structural details (in English) may also be obtained from Fachinformationszentrum Karlsruhe, D-76344 Eggenstein-Leopoldshafen, Germany, on quoting the deposition number CSD-58138 and the names of the authors.

OM9402628

(25) Dias, A. R.; Simoes, J. A. M. *Polyhedron* **1988**, *7*, 1531–1544.