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Benchtop synthesis and characterization of air-stable titanocene(IV) complexes from phosphorous- and sulfur-based amino acid analogs

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Abstract

Four new air-stable titanocene(IV) salt complexes were synthesized by reacting titanocene dichloride with phosphorous- and sulfur-based β-amino acid analogs in standard chemical glassware open to atmospheric conditions. Each new titanocene(IV) complex contained two identical ligands with a terminal ammonium chloride group and either the phosphorous- or sulfur-based ester group bonded directly to the central titanium atom. Each complex was characterized by ^{1}H, ^{13}C, and ^{31}P NMR, IR, UV, and MS analyses. Initial data revealed the titanocene(IV) complexes with sulfonate or sulfate amino ester ligands to be far more stable to hydrolysis than the analogous phosphonate or phosphate amino ester complexes. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Four new titanocene(IV) complexes **1**, **2**, **3**, and **4** containing phosphorous and sulfur-based β-amino acid ligands were quantitatively synthesized from titanocene dichloride (Scheme 1) in standard chemical glassware open to the atmosphere. These new ligands bond to the central titanium atom through phosphoroxy or sulfoxy ester groups, and could be models for more complex ligands of bioorganic interest. Titanocene(IV) complexes bearing α-amino acid ligands were reported using Schlenk techniques devoid of air (Scheme 2).[1a–d] In this case, the ligand was bonded to the central titanocene atom through its carboxylate ester group.

Metallocene dichlorides possess a unique chemical structure where substituents at three very different sites can be used to tailor diverse physical, chemical, and biological properties. Fig. 1 illustrates this structural flexibility for chemical synthesis design. The central atom can be varied using different metal

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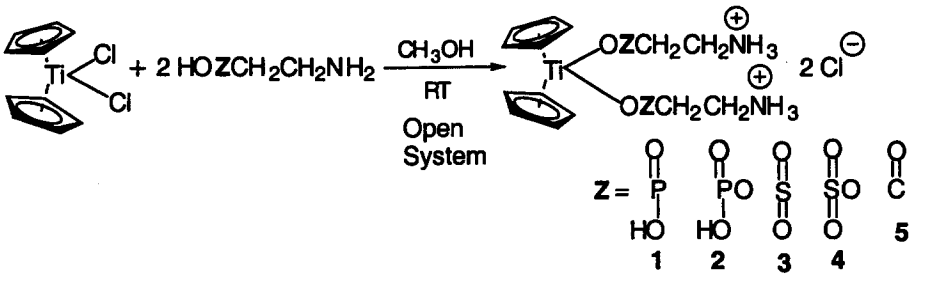
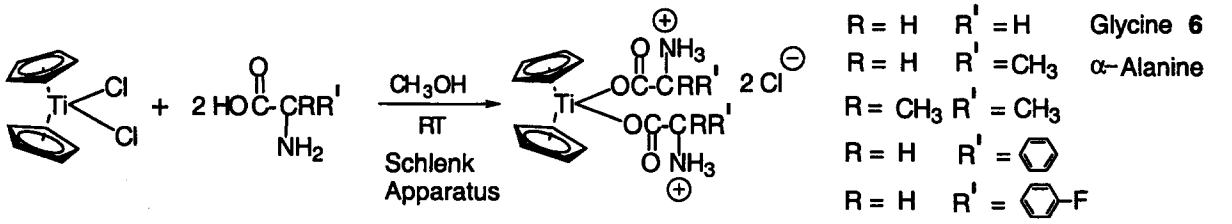


Scheme 1.



Scheme 2.

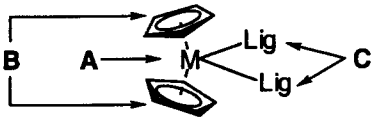


Figure 1.

ions (A). Various pendant substituents can be introduced into the cyclopentadienyl rings prior to forming the metallocene dihalide (B), and different ligands can replace the two Cl atoms at the central metal atom (C). All three synthetic strategies have been used with metallocene and half-metallocene compounds in the design and evaluation of potential antitumor and human imaging pharmaceutical compounds.[1a–d,2a,b] Possibly, the same compound could provide both antitumor and imaging functions.[2a,b] Ferrocene can exhibit antitumor activity[2b] and has been used as a terminal hydrophobic moiety through covalent cyclopentadienyl ring bonding in double-tailed cationic surfactants, $R_2N^+[(CH_2)_nCp_2Fe)]_2$ Br^- (n=5 and 11). These give spontaneously self-assembling vesicles above a 1×10^{-7} mol/L concentration.[3] Such vesicles could be useful in pharmaceutical applications. The antitumor activity of metallocene dichloride complexes encouraged the first synthesis (Scheme 2) and characterization of titanocene(IV) complexes that incorporated biological α-amino acid ligands (lig) from glycine, L-alanine, 2-methylalanine, DL-phenylalanine, and DL-4-fluorophenylalanine. These ligands bonded to the central titanium atom through the carboxylate group.[1a–c] With a good water solubility and a low toxicity potential, the titanocene(IV) complexes with the DL-phenylalanine and DL-4-fluorophenylalanine displayed antimicrobial behavior towards *Escherichia coli*.[1c] These syntheses were conducted at room temperature in methanol using Schlenk techniques. An Ar or SO_2 atmosphere in a two-bulb glass vessel with PTFE valves was used. The titanocene dichloride was synthesized by literature methods.

2. Results and discussion

Because bioorganic pharmaceutical compounds often contain thioester and phosphoroester structures, it seemed reasonable to react metallocene dichlorides with sulfur and phosphorous-based β-amino

acid analogs to form new complexes where sulfur and phosphorous esters, rather than carboxylate esters, were bonded to the central metal atom. Taurine (2-aminoethanesulfonic acid), 2-aminoethyl hydrogen sulfate, 2-aminoethyl-phosphonic acid, or 2-aminoethyl dihydrogen phosphate, when reacted at room temperature in methanol solvent (HPLC reagent grade) with commercial titanocene dichloride (Aldrich), produced new compounds **1**, **2**, **3**, and **4**, respectively, as cherry red solids in quantitative yield (Scheme 1). Like their pumpkin orange carboxylate analogs,[1b] they undergo slow hydrolysis. Preliminary proton NMR solvolysis data in D_2O with 0.05 M solutions revealed the phosphorous-based complexes **1** and **2** are depleted over six weeks, but the sulfur-based complexes **3** and **4** required more than six months, or greater than 17 times longer. Attempts to synthesize the analogous β-alanine carboxylate complex **5** for comparison to the analogous sulfur and phosphorous complexes **1**, **2**, **3**, and **4** failed because this titanocene(IV) complex **5** proved to be extremely hygroscopic. Therefore, the glycine complex **6** was synthesized by our open-air benchtop method in an overnight reaction (18 hours). The Schlenk-based method required four hours to synthesize complex **6**.[1b]

Proton and ^{13}C NMR spectra were taken in D_2O solvent using acetone as a reference at δ 2.22[4] and 29.92 ppm, respectively. New IR peaks not observed in the sulfoxy or phosphoroxy amino acid analogs, but which are characteristic of titanocenyl group incorporation,[1b] are listed. Exact masses could only be obtained for phosphoroxy titanocene(IV) complexes **1** and **2**. The sulfoxy complexes **3**, **4** and the glycine complex **6** were not compatible with exact mass spectral conditions. The DIP MS fragmentation pattern of the sulfoxy complexes **3** and **4** matched those reported for glycine complex **6**.[1b]

3. Experimental

3.1. General procedure

Reactions were conducted in a fumehood using a 14/20 jointed 5 mL single-necked round bottom flask containing a Teflon®-coated magnetic stirring bar. A condenser was fitted to the reaction flask. The condenser top was fitted with a Drierite®-containing drying tube. The condenser was not cooled during the reaction. The reaction flask was charged with 0.452–0.515 g (1.76–2.00 mmol) 97% titanocene dichloride, 0.5–1.5 mL methanol, 2 equivalents S- or P-amino acid analog, and another 0.5–1.0 mL methanol. After stirring at room temperature for 72 hours (S-compounds) or 48 hours (P-compounds), 1.5 to 2.0 mL diethyl ether were added to the stirred suspension. Suction filtration, washing the solid product with 1.5 to 9.0 mL diethyl ether, and room temperature drying 30 to 90 minutes in a vacuum dessicator (1.2 mm Hg) provided the solid product.

3.1.1. Compound 1

$Cp_2Ti[OP(O)(OH)CH_2CH_2NH_3]^{2+}$ $2Cl^-$ (FW=499.2): stirred 0.452 g (1.76 mmol) 97% Cp_2TiCl_2; 0.5 mL MeOH; 0.441 g (3.49 mmol) 99% $HOP(O)(OH)CH_2CH_2NH_2$; 1.0 mL MeOH for 48 h. Obtained 1.068 g of a cherry red solid (100% yield within balance variance). ^1H NMR: δ 6.78 & 6.73 (2s, 10H, Cp), δ 3.75 (m, 4H, PCH_2), δ 2.08 (m, 4H, CH_2).[5] ^{13}C NMR: 3 peak sets (6 peaks) at 120.72, 120.62, 34.88, 34.65, 26.01, and 24.88 ppm. ^{31}P NMR: 1 peak set (3 multiplets) at 20.08, 18.12, and 16.38 ppm in a 10/8.8/1.7 ratio that 200 MHz ^1H decoupling simplified. IR (KBr, cm^{-1}): 3105 (Cp CH), 822 (Cp CH). MS (FAB, H_2O/glycerine matrix): exact mass determined at *m/z*=427 from M^+–2HCl with actual *m/z*=427.066100 being 1.5 ppm within the theoretical value (actual Ti isotope ratios matched the predicted distribution pattern at *m/z*=457.7, 458.1, 459.1 (major), 460.1, and 461.1); 362, M^+–2HCl–Cp; 328, M^+–2HCl–Cp–$2NH_3$; 303, M^+–HCl–Cl–lig; 302, M^+–2HCl–lig; 251, M^+–2HCl–lig–$2NH_3$–OH;

237, M^+–2HCl–lig–Cp; 218, M^+–2HCl–lig–HCp–H_2O; 126 ($Hlig^+$). UV–vis (D_2O): 210 nm, m; 248 nm, s; 320 nm, w.

3.1.2. Compound 2

$Cp_2Ti[OP(O)(OH)OCH_2CH_2NH_3]^{2+}$ $2Cl^-$ (FW=531.2): stirred 0.515 g (2.01 mmol) 97% Cp_2TiCl_2; 0.5 mL MeOH; 0.574 g (3.99 mmol) 98% $HOP(O)(OH)OCH_2CH_2NH_2$; 0.5 mL MeOH for 48 h. Obtained 0.870 g of a cherry red solid (99.9% yield). ^1H NMR: δ 6.75 (s, 10H, Cp), δ 4.15 (m, 4H, OCH_2), δ 3.32 (m, 4H, CH_2). ^{13}C NMR: 3 peak sets (4 peaks) at 120.91 with shoulder at slightly higher ppm, 61.84, 61.26, and 39.65 ppm. ^{31}P NMR: 1 peak set (3 multiplets) at –2.02, –2.71, and –3.47 ppm in a 10/8.6/1.4 ratio that 200 MHz ^1H decoupling simplified. IR (KBr, cm^{-1}): 3105 (Cp CH), 822 (Cp CH). MS (FAB, H_2O/glycerine matrix): exact mass determined at *m/z*=459 from M^+–2HCl with actual *m/z*=459.060900 being 0.4 ppm within the theoretical value and actual Ti isotope ratios matching predicted distribution pattern; 418, M^+–Cl–NH_3–$HOCH_2CH_2NH_2$; 394, M^+–2HCl–Cp; 344, M^+–lig–$CH_3CH_2NH_2$; 326, M^+–lig–$CH_3CH_2NH_2$–H_2O; 318, M^+–HCl–Cl–lig; 283, M^+–2HCl–lig–NH_3–OH; 234, M^+–2HCl–lig–Cp–H_2O; 142 ($Hlig^+$). UV–vis (D_2O): 210 nm, m; 248 nm, s; 314 nm, w.

3.1.3. Compound 3

$Cp_2Ti[OS(O)_2CH_2CH_2NH_3]^{2+}$ $2Cl^-$ (FW=499.4): stirred 0.515 g (2.01 mmol) 97% Cp_2TiCl_2; 1.5 mL MeOH; 0.504 g (3.99 mmol) 99% $HOSO_2CH_2CH_2NH_2$; 1.0 mL MeOH for 72 h. Obtained 0.999 g of a cherry red solid (100% yield). ^1H NMR: δ 6.73 & 6.53 (2s, 10H, Cp), δ 3.33 (m, 8H, CH_2). ^{13}C NMR: 3 peak sets (4 peaks) at 119.84, 117.73, 47.08, and 35.04 ppm. IR (KBr, cm^{-1}): 3105 (Cp CH), 828 (Cp CH). MS (EI, 70 eV, DIP): 248, M^+–2 lig; 213, M^+–2 lig–Cl; 183, M^+–2 lig–Cp; 148, M^+–2 lig–Cl–Cp; 65 (Cp^+). UV–vis (D_2O): 196 nm, m; 242 nm, s; 320 nm, w.

3.1.4. Compound 4

$Cp_2Ti[OS(O)_2OCH_2CH_2NH_3]^{2+}$ $2Cl^-$ (FW=531.4): stirred 0.515 g (2.01 mmol) 97% Cp_2TiCl_2; 1.5 mL MeOH; 0.580 g (3.98 mmol) 97% $HOSO_3CH_2CH_2NH_2$; 1.0 mL MeOH for 72 h. Obtained 1.062 g of a cherry red solid (100% yield within weighing variance). ^1H NMR: δ 6.72 & 6.52 (2s, 10H, Cp), δ 4.30 (m, 4H, OCH_2), δ 3.34 (m, 4H, CH_2). ^{13}C NMR: 3 peak sets (4 peaks) at 119.80, 117.77, 64.175, and 38.62 ppm. IR (KBr, cm^{-1}): 3105 (Cp CH), 822 (Cp CH). MS (EI, 70 eV, DIP): 248, M^+–2 lig; 213, M^+–2 lig–Cl; 183, M^+–2 lig–Cp; 148, M^+–2 lig–Cl–Cp; 65 (Cp^+). UV–vis (D_2O): 198 nm, m; 242 nm, s; 320 nm, w.

3.1.5. Compound 6

$Cp_2Ti[OC(O)CH_2NH_3]^{2+}$ $2Cl^-$ (FW=399.0): stirred 0.514 g (2.00 mmol) 97% Cp_2TiCl_2; 1.5 mL MeOH; 0.299 g (3.99 mmol) 97% $HOC(O)CH_2CH_2NH_2$; 1.0 mL MeOH for 18.33 h. Obtained 0.750 g of a pumpkin orange solid (94.0% yield). Reaction run for 44.0 h gave a 75.1% yield. ^1H NMR: δ 6.63 (s, 10H, Cp), δ 3.73 (m, 4H, CH_2). ^{13}C NMR: 2 peak sets (4 peaks) at 118.67, 117.747, 117.28, and 40.25 ppm. IR (KBr, cm^{-1}): 3081 (Cp CH), 837 (Cp CH).[6] MS (Flow Inj., APCI): 288, M^++1–H–HCl–lig; 247, M^++1–2Cl–Cp–H_2O; 237, M^++1–2HCl–lig–NH_3; 213, M^++1–H–HCl–2 lig. UV–vis (D_2O): 200 nm, m;[7] 244 nm, s; 308 nm, w.

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References

1. (a) Klapötke, T. M.; Köpf, H.; Tornieporth-Oetting, I. C.; White, P. S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1518–1519; (b) Klapötke, T. M.; Köpf, H.; Tornieporth-Oetting, I. C.; White, P. S. *Organometallics* **1994**, *13*, 3628–3633; (c) Tornieporth-Oetting, I. C.; White, P. S. *Organometallics* **1995**, *14*, 1632–1636; (d) Ritter, S. K. *Fluorine Chemistry Branches Out From Its Traditional Focus*; *Chem. & Eng. News*, Feb. 27, 1995, pp. 39–44, which discusses the work in Refs. 1a–c.
2. (a) Jaouen, G.; Vessieres, A.; Butler, I. S. *Acc. Chem. Res.* **1993**, *26*, 361–369; (b) Dagani, R. *Organometallic Chemistry Opens New Vistas in Medicine, Materials Science*; *Chem. & Eng. News*, Apr. 10, 1995, pp. 32–36, which discusses the work in Ref. 2a.
3. Shoji, H.; Kondo, Y.; Yoshino, N. *Langmuir* **1996**, *12*, 921–924.
4. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.
5. The acetone reference peak interferes with the higher field CH_2 multiplet. Integrating this multiplet was done by noting the chemical shift of temperature-dependent HOD peak, then running a second sample without the acetone reference, and using the HOD peak as the reference peak.
6. Another sample with two different KBr pellets prepared on two consecutive days gave 841 and 833 cm^{-1}.
7. On two separate runs, this showed as a double peak at 198 and 212, or 198 and 214 nm.