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Synthesis and Characterization of Tris(β-diketonato)technetium(III) and -(IV) Complexes

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Abstract

The preparations and properties of tris(dipivaloylmethanato)technetium(III), tris(trifluoroacetylacetonato)technetium(III), and tris(hexafluoroacetonato)technetium(III) are described. The oxidation of the dipivaloyl derivative to tris(dipivaloyl)technetium(IV) hexafluorophosphate was shown to take place readily. Voltammetric studies and magnetic resonance results on the new complexes are reported. The large shifts observed for the complexes seem to be due to a contact interaction.

Introduction

Several reports have appeared recently concerning Tc(acac)$_3$ [1–4]* and other Tc(β-diket)$_3$ [2] complexes. Interest in these compounds stems from their potential as brain imaging agents [2] because they are neutral and can be prepared directly from ^{99m}TcO$_4^-$ [2–4]. However, only the preparation and properties of Tc(acac)$_3$ have appeared in the literature. Abrams found that [Tc(acac)$_3$]BF$_4$ could be prepared from Tc(acac)$_3$ [3, 4]. With the expectation that Tc(dpm)$_3$ should be easier to oxidize, we prepared [Tc(dpm)$_3$]PF$_6$. The latter compound is especially interesting because it is structurally similar to the heart imaging agent [Tc(CN t-Bu)$_6$]$^+$ [5–7]. The reduction of Tc(hfac)$_3$ to Tc(hfac)$_3^-$ was also investigated.

Experimental

Technetium as NH$_4$^{99}TcO$_4$ was obtained as a gift from New England Nuclear, Billerica, Massachusetts. Dipivaloylmethane and hexafluoroacetylacetone were obtained from Aldrich and trifluoroacetylacetone from Peninsular Chemresearch. All manipulations were carried out in laboratories approved for low-level radioactivity (^{99}Tc is a weak β-emitter with a half life of 2.12×10^5 years and a particle energy of 0.292 MeV) and all precautions followed have been described elsewhere [8, 9]. Field desorption mass spectra (FDMS) and electron impact mass spectra (EIMS) were measured with a Varian MAT 731 instrument described elsewhere [10] and ^{1}H NMR spectra were made on a Bruker 250- or 270-MHz spectrometer in either chloroform-d$_1$ or acetonitrile-d$_3$ solution with TMS as internal reference; CHCl$_3$ is at +7.25 ppm. Optical spectra were measured on a Hewlett Packard 8451 diode array spectrophotometer. Voltammetric studies, both DC polarography and cyclic voltammetry, were carried out by using a PAR model 174 polarographic analyzer with a rotating or stationary Pt electrode. All potentials were referenced to a saturated calomel electrode; ferrocene was used as an external calibrant and tetra-n-butylammonium perchlorate was used as the supporting electrolyte in dry HPLC-grade acetonitrile.

Preparation of Tris(dipivaloylmethanato)technetium(III)

A mixture of dipivaloylmethane (8.4 ml, 20 mmol), methanol (40ml), (NH$_4$)$_2$TcCl$_6$ (0.13 g, 0.37 mmol) [11], sodium methoxide (0.16 g, 3.0 mmol), and zinc powder (0.26 g, 4.0 mmol) was refluxed for 2 h. The resulting red solution was poured into 1 M sodium hydroxide (200 ml), and the mixture stirred until a uniform gel was produced. The solid was filtered, then washed with 1 M sodium hydroxide (6 × 40 ml). The product was then extracted into hexane. The hexane solution was washed in a separatory funnel with 1 M sulfuric acid (3 × 40 ml), saturated sodium bicarbonate solution (1 × 40 ml), and water (1 × 40 ml). The hexane was removed by rotary evaporation and the excess dipivaloylmethane was removed *in vacuo* using a boiling water bath.

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*Abbreviations used for ligands are: β-diket = β-diketonate ion; acac = acetylacetonate ion; dpm = dipivaloylmethanate ion; tfac = trifluoroacetylacetonate ion; hfac = hexafluoroacetylacetonate ion.

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The resulting red solid was chromatographed on alumina containing 4% water using hexane as the eluant. The first red band eluted was collected. After the hexane was removed, the residue was recrystallized from methanol. An analytically pure sample was obtained by subliming the recrystallized product at 120 °C and 0.5 mm Hg. Yield of $Tc(dpm)_3$, 48 mg, 20%; melting point 187–188 °C. *Anal.* Calc. for $C_{33}H_{57}O_6Tc$: C, 61.10; H, 8.86. Found: C, 61.05; H, 8.82%. Optical spectrum (acetonitrile): 548 nm (4.7×10^3 l mol^{-1} cm^{-1}), 530(sh), 375(sh), 356 (9.4×10^3), 290(sh), 274 (16.1×10^3), 246 (13.4×10^3). IR (KBr): 2950(s), 2900(sh), 2865(m), 1507(sh), 1495(sh), 1482(s), 1470(sh), 1370(s), 1350(s), 1340(sh), 1244(m), 1217(m), 1183(m), 1136(m), 870(m), 784(m), 751(w), 738(w), 636(w), 616(sh), 500(sh), 480(w), 447(w) cm^{-1}. ^1H NMR (chloroform-d): +10.52 ppm (γ-H), +2.40 ppm $[-C(CH_3)_3]$. (+)FDMS: *m/z* 648 (calc. for $C_{33}H_{57}O_6Tc = 648$). $E_{1/2}$ (anodic) = +0.12 V *vs.* SCE (1*e*, reversible). No other waves seen.

Preparation of Tris(dipivaloylmethanato)technetium(IV) hexafluorophosphate

To a red solution of $Tc(dpm)_3$ (69 mg, 0.11 mmol) in ether (10 ml) was added *p*-benzoquinone (23 mg, 0.21 mmol). Upon the addition of trifluoromethanesulfornic acid (8 drops, ca. 0.4 mmol), the solution immediately turned reddish-brown. Stirring was continued for 10 min. The ether was removed by careful evaporation on a steam bath, leaving an oil. This was dissolved in acetone (10 ml), then the product was precipitated by slowly adding a solution of ammonium hexafluorophosphate (2.0 g) in water (20 ml). The rust-colored needles were collected and washed several times with water then with hexane. After the product was dried, it was dissolved in methylene chloride (10 ml). When 50 ml of hexane was added in portions to this solution, a fluffy impurity precipitated which was removed by filtration through a fine-porosity fritted funnel. Another 75 ml of hexane was added to the filtrate to precipitate red needles. These were collected, dried, and recrystallized again from methylene chloride/hexane. Yield of $[Tc(dpm)_3]PF_6$, 45 mg, 54%; melting point 223–228 °C. *Anal.* Calc. for $C_{33}H_{57}F_6O_6PTc$: C, 49.94; H, 7.24; F, 14.36. Found: C, 49.43; H, 6.80; F, 14.65%. Optical spectrum (methylene chloride): 410 (6.9×10^3), 270 (29.1×10^3). IR (KBr): 2970(m), 2940(sh), 2910(sh), 2870(w), 1530(sh), 1508(sh), 1492(s), 1445(sh), 1398(vw), 1363(m), 1310(sh), 1303(s), 1248(m), 1218(m), 1142(s), 1023(w), 954(w), 935(w), 867(s), 838(s), 820(sh), 737(w), 650(m), 627(sh), 555(m), 522(w), 479(w), 448(w) cm^{-1}. ^1H NMR (acetonitrile-d_3): +54.73 ppm (γ-H), +8.56 ppm $[-C(CH_3)_3]$. Conductivity (acetonitrile, 10^{-3} M): Λ_M = 141 ohm^{-1} cm^2 mol^{-1}. Magnetic moment: (measured by the Evans NMR method in methylene chloride solution [12]) μ_{eff} (308 K) = 3.8 B.M. (+)FDMS: *m/z* 648 (calc. for $[C_{33}H_{57}O_6Tc]^+ = 648$). Electrochemistry: $E_{1/2}$ (cathodic) = +0.11 V *vs.* SCE (1*e*, reversible). No other waves seen.

Preparation of Tris(trifluoroacetylacetonato)technetium(III)

A mixture of ethanol (10 ml), 1% aqueous sodium hydroxide (8 ml), trifluoroacetylacetone (3 ml, 25 mmol), and 0.4 M NH_4TcO_4 (0.5 ml, 0.2 mmol) was brought to reflux, then a solution of sodium dithionite (0.08 g, 0.46 mmol) in 1% aqueous sodium hydroxide (5 ml) was added dropwise. The resulting solution was refluxed for 1 h. The red solution was then reduced in volume to about 20 ml, which caused product to precipitate. Water (30 ml) was added, the mixture was filtered. The solid was washed several times with water, then dried *in vacuo*. It was purified by chromatography on alumina containing 4% water with benzene as the eluant. The benzene was removed and the product was sublimed from the residue at 120 °C and 0.5 mm Hg. Yield of *cis*- and *trans*-$Tc(tfac)_3$, 36 mg, 33%; melting point 170–172.5 °C. The NMR spectrum showed that the mixture contained 14% *cis* and 86% *trans* isomers. Attempts to separate the isomers were unsuccessful. *Anal.* Calc. for $C_{15}H_{12}F_9O_6Tc$: C, 32.28; H, 2.17; F, 30.63; Found; C, 32.40; H, 2.34; F, 30.30%. Optical spectrum (acetonitrile): 554 (5.2×10^3), 524 (4.9×10^3), 385(sh), 356 (10.7×10^3), 290(sh), 274 (13.5×10^3), 238 (11.3×10^3). IR (KBr): 1565(s), 1560(sh), 1495(w), 1425(w), 1407(w), 1380(sh), 1362(m), 1290(vs), 1223(s), 1190(s), 1137(s), 1019(vw), 1002(vw), 940(w), 862(w), 805(w), 791(w), 726(m), 635(w), 628(w), 583(w), 428(w) cm^{-1}. ^1H NMR (chloroform-d): *cis* −3.67 ppm (γ-H), −12.20 ppm ($-CH_3$); *trans* −3.05 ppm (γ-H), −5.19 ppm ($-CH_3$), −6.88 ppm (γ-H), −7.51 ppm (γ-H), −12.77 ppm ($-CH_3$), −18.77 ppm ($-CH_3$). (+)FDMS: *m/z* 558 (calc. for $C_{15}H_{12}F_9O_6Tc = 558$). $E_{1/2}$ (anodic) = +1.00 V *vs.* SCE (1*e*, irreversible), $E_{1/2}$ (cathodic) = −1.16 V *vs.* SCE (1*e*, irreversible).

Preparation of Tris(hexafluoroacetylacetonato)technetium(III)

To a solution of ethanol (10 ml) and 1 M sodium hydroxide (10 ml) were added hexafluoroacetylacetone (2.8 ml, 20 mmol) and 0.44 M NH_4TcO_4 (0.5 ml, 0.22 mmol). The mixture was brought to reflux then a solution of sodium dithionite (0.07 g, 0.40 mmol) in 1 M sodium hydroxide (3 ml) was added dropwise. The product vaporized from the solution, mostly condensing on the condenser. The apparatus was disassembled 10 min after the dithionite was added and the product was extracted into methylene chloride. The methylene chloride was carefully evaporated on a steam bath so as not to vaporize product also. The residue was suspended in water, filtered, and washed several times with water. After being air-dried, the product was purified by sublimation at 60 °C and 0.5 mm Hg. Yield of Tc(hfac)$_3$, 10 mg, 7%; melting point 114–115 °C. *Anal.* Calc. for $C_{15}H_3F_{18}O_6Tc$: C, 25.02; H, 0.42; F, 47.49. Found: C, 25.30; H, 0.76; F, 47.01%. Optical spectrum (acetonitrile): 564 (6.3×10^3), 538(sh), 398(sh), 366 (13.2×10^3), 300 (13.4×10^3), 280 (12.3×10^3), 242 (9.8×10^3), IR (KBr): 1547(sh), 1540(sh), 1525(m), 1397(s), 1327(s), 1245(s), 1197(s), 1137(s), 1094(s), 942(w), 827(m), 816(s), 743(m), 716(w), 678(m), 598(m), 527(w), 338(w) cm^{-1}. ^{1}H NMR −11.96 (γ-H). EIMS: *m/z* 720 (calc. for $C_{15}H_3F_{18}O_6Tc = 720$). $E_{1/2}$ (cathodic) = +0.14 V *vs.* SCE (1*e*, quasireversible). No other waves seen.

Results and Discussion

The compounds Tc(tfac)$_3$ and Tc(hfac)$_3$ were prepared directly from pertechnetate by methods similar to that used to prepare Tc(acac)$_3$ [4]. The yield of Tc(hfac)$_3$ is low. This is probably due to the fact that the complex is unstable in solutions which contain only trace amounts of water. The ligand also reacts with water to form a dihydrate. Unfortunately, attempts to prepare the complex in nonaqueous media from $[NH_4]_2TcCl_6$ and Zn or [Tc(thiourea)$_6$][BF$_4$]$_3$ [3] were unsuccessful. By contrast, Tc(dpm)$_3$ could not be prepared directly from pertechnetate using dithionite as the reducing agent, but was prepared from $[NH_4]_2TcCl_6$ in methanol using zinc as the reducing agent.

The optical spectra of the Tc(III) complexes are similar to that found [4] for Tc(acac)$_3$ and contain two intense features in a narrow range between 500–600 nm. The Tc(IV) complexes have an intense band close to 400 nm. The ^{1}H NMR spectra of the low spin paramagnetic Tc(III) complexes show some interesting features. The line widths of the γ-CH protons are reasonably sharp *ca.* 10–20 Hz. The β-CH$_3$ protons are all shifted upfield of that found for the diamagnetic Rh(acac)$_3$ complex [13] whereas the γ-H protons are shifted to the low field for Tc(acac)$_3$ and Tc(dpm)$_3$, but experience upfield shifts in both *cis-* and *trans*-Tc(tfac)$_3$ as well as Tc(hfac)$_3$. The magnitude of the shift is greater for the β-CH$_3$ protons than for the corresponding γ-H protons. There is a correlation between the ease of oxidation *vide infra* of the complex from Tc(III) to Tc(IV) (or alternatively on the ease of reduction from Tc(III) to Tc(II)). The most easily oxidized Tc(dpm)$_3$ has γ-H + 10.52 ppm (shift from Rh(III) = +5.07 ppm) (Tc(acac)$_3$ + 7.43 ppm, from Rh(III) = +1.96 ppm) whereas Tc(hfac)$_3$ has γ-H −11.86 ppm, from Rh(III) = −17.33 ppm. The shift found for the γ-H protons in [Tc(dpm)$_3$]-[PF$_6$] +54.7 ppm is similar to that found [Tc(acac)$_3$][BF$_4$]. It is clear that the nature of the shifts found for the Tc(III) series depends upon the ligand substitution pattern. The shifts are probably governed by the contact rather than the pseudo contact term [13].

Voltammetric studies show that both the oxidation potentials Tc(III)–Tc(IV) and reduction potentials Tc(III)–Tc(II) are strongly dependent on the nature of the ring substituent of the β-diketonate ligand *cf.* the reduction potentials for ruthenium(III) tris(β-diketonates) [14]. The oxidation of Tc(dpm)$_3$ at +0.12 V and the reduction of Tc(hfac)$_3$ at +0.14 V indicated that it should be possible to isolate salts of [Tc(dpm)$_3$]$^+$ and [Tc(hfac)$_3$]$^-$ respectively.

The neutral complex Tc(dpm)$_3$ was oxidized to the cation [Tc(dpm)$_3$]$^+$ using *p*-benzoquinone/trifluoromethanesulfonic acid in ether. It was isolated as the hexafluorophosphate salt. This salt decomposed in wet solvents regenerating some of the neutral Tc(dpm)$_3$. Presumably, this decomposition accounts for the lower yields when the oxidation was performed using ferricinium hexafluorophosphate with an aqueous work up. The trifluoromethyl complexes Tc(hfac)$_3$ and Tc(tfac)$_3$ are much more difficult to oxidize and no attempts were made to obtain the Tc(IV) species.

It was not possible to isolate a salt of Tc(hfac)$_3^-$ by reducing Tc(hfac)$_3$ or by direct preparation from other technetium compounds. This may be due to the similarity of Tc(hfac)$_3$ to Co(hfac)$_3$ which immediately reduces to Co(hfac)$_2$(H$_2$O)$_2$ in wet acetone [15]. The voltammetric studies indicated that the reduction potentials for Tc(dpm)$_3$, Tc(acac)$_3$ and Tc(tfac)$_3$ were too negative for the isolation of air stable technetium(II) salts. Thus, the studies performed so far indicate that technetium(III) β-diketonates are the most attractive as potential radiopharmaceutical agents.

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