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Modeling Novel Radiopharmaceuticals: Mono-C6-Substituted PnAO Ligands (PnAO = 3,3,9,9-Tetramethyl-4,8-diazaundecane-2,10-dione Dioxime)

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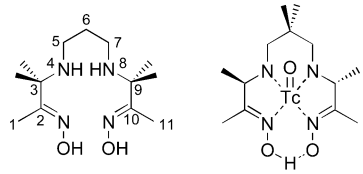
The solid-state behavior of six novel 6-substituted PnAO (propylene amine oxime) complexes (**6**–**11**) involving Tc(V), Co(III), and Cu(II) salts is reported. Each of the Tc complexes **6**–**8** has the C6-substituent located equatorially in a six-membered chelate ring involving a Tc═O unit which has the expected boat geometry. The C6-substituent therefore has little effect on the conformational behavior of the PnAO complex and thus provides an attractive site for further modification. The Co(III) complex **9** has the expected octahedral geometry, while the Cu(II) complexes **10** and **11** form square-based pyramids capped by water molecules. One Cu(II) system (**10**) contains two unique complexes in the asymmetric unit which are associated via multiple hydrogen bonds to a BF_4 anion, the remaining BF_4 anion being loosely hydrogen bonded to a coordinating water molecule. The cobalt and copper complexes **9**–**11** each exhibit a chair conformation for the six-membered chelate ring.

Introduction

As a result of a combination of its favorable nuclear properties (γ, E_γ = 140 keV, $t_{1/2}$ = 6.02 h) and its ready availability from an on-site generator, the metastable isotope ^{99m}Tc is used in approximately 90% of all diagnostic nuclear medical scans performed annually.[1] However, as a metal ion, this radionuclide must be bound by an appropriate ligand into a complex which is suitable for administration to the patient. For the current generation of radiopharmaceuticals localization in vivo tends to result from the physiological properties of the complex as a whole rather than any specific receptor-binding interactions.[1] To improve control over the distribution of radiopharmaceuticals in the body, investigations have been made into the attachment of suitable technetium-binding ligands to biologically active molecules.[2] In such cases the chelation of the radionuclide must not interfere with biological receptor interaction.

3,3,9,9-Tetramethyl-4,8-diazaundecane-2,10-dione dioxime (**1**), known as PnAO (from propylene amine oxime), and related ligands form stable, lipophilic complexes such as **2**



1 **2**

with oxotechnetium(V), $[TcO^{3+}]^{3-5}$ and charged complexes with nitridotechnetium(IV), $[TcN^{2+}]$.[6] These complexes are neutral as a result of the deprotonation of both amine groups and of one of the oxime hydroxyl groups. The former process is indicative of the acid-inducing effect of the high-valent Tc(V) species which causes the deprotonation of the amine ligands. The resulting amides may then further stabilize the metal center by π-donation. The latter facilitates the formation of an intramolecular hydrogen bond to give a pseudomacrocyclic complex. Since the development of the commercial cerebral perfusion agent Ceretec[7,8] (**2**), attention has turned

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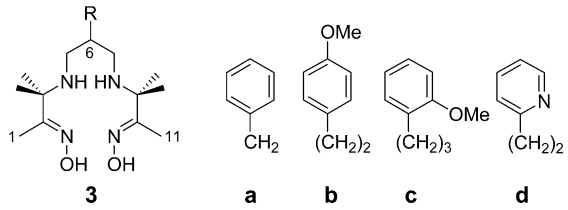
to the further modification of the PnAO skeleton to fine-tune the properties of its complexes. The effect of two identical substituents at the 6-position[4,9] and that of the attachment of a bioactive targeting group at the 1-position[10] have been investigated, and synthetic routes to mono-6-substituted ligands have been described.[11] However, there has as yet been no systematic study of the behavior of mono-6-substituted ligands or the structural characterization of their corresponding metal ion complexes.[12] Nonetheless, for reasons of synthetic ease and minimal interference with the complexation process, the 6-position would appear to be the most logical choice for the point of attachment of a targeting group. Furthermore, elaboration at this position would avoid stereochemical complexity arising from the formation of racemic products upon complexation in addition to any stereoisomerism present in the C6-substituent.

All isotopes of technetium are radioactive, and as such the study of all of its complexes is necessarily limited. However, there is a wealth of information regarding the complexation behavior of PnAO and related ligands with more easily accessible metal ions such as Co(III),[13,14] Cu(II),[15−20] Cu(III),[19] Pd(II),[21] Ni(II),[18,22] and Rh(III).[23] The results of these crystallographic studies indicate that it would be possible for nonspecialists to investigate the effect of 6-substitution upon the complexing behavior of the PnAO ligand and ultimately on complex stability.

In the work reported here a series of ligands (**3a**−**d**) bearing simple model groups in the 6-position have been synthesized to investigate the effect of such substitution upon their coordination behavior with TcO^{3+}, Cu(II), and Co(III). Single-crystal X-ray diffraction studies of the resulting complexes have provided an insight into the effect of such ligand modification on the nature of the resulting complexes.



3 **a** **b** **c** **d**

Experimental Section

General Procedures. All solvents were purified and dried using standard techniques. All other chemicals were of reagent grade and used without further purification. Melting points were recorded using open-ended capillary tubes on an electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed by Microanalytical Service, Department of Chemistry, Imperial College of Science, Technology and Medicine, London. Low-resolution electrospray mass spectrometry was performed on a Micromass Platform quadrupole mass analyzer (capillary 3.50 kV, HV lens 0.5 kV, cone voltage 20 V, source temperature 110 °C, 100% acetonitrile eluent). High-resolution electrospray mass spectrometry was performed on a Bruker Apex III FT-ICR-MS high-resolution electrospray mass spectrometer (ES eluent 50:50 MeOH/water). Infrared spectrometry was performed on a Perkin-Elmer 1600 series FTIR spectrometer. ^{1}H and ^{13}C NMR data were acquired at room temperature on a Bruker AC300 spectrometer (^{1}H, 300.135 MHz; ^{13}C, 75.469 MHz) with the chemical shifts referenced to the peak for the deuterated solvent.

Radiation Protection. ^{99}Tc is a low-energy (292 keV) β-particle emitter with a half-life of 2.12×10^5 years. When handled on the milligram scale, ^{99}Tc does not present any significant health hazards and bremsstrahlung is avoided as a result of the low energy of the β-particle emission. However, routine radiological practices were observed at all times to prevent contamination. This requirement extended to the characterization of the ^{99}Tc-containing complexes, which were therefore characterized by single-crystal X-ray diffraction alone.

Ligand Synthesis. The general synthetic route is outlined in Scheme 1. Elaboration at the 6-position of the PnAO backbone (**1**) was achieved by the suitable modification of an established pathway.[24] Alkylation was achieved by substitution at the central carbon of diethyl 1,3-propanedioate followed by conversion of the diester to the corresponding 2-substituted 1,3-diamine. The oxime functionality was then added by substitution of an α-haloketone followed by conversion to the dioxime. The synthesis of the parent PnAO ligand **3a** has been reported elsewhere.[25]

Synthesis of 2-Benzyl-1,3-propanediamine (5a). 2-Benzyl-1,3-propanediamide[26] (7.28 g, 38.0 mmol) was slowly added in portions to a solution of borane in THF (1 mol dm^{-3}, 288 mL, 290.0 mmol). The mixture was refluxed for 24 h, carefully acidified at 0 °C with concentrated HCl to pH 1, and then concentrated by evaporation at reduced pressure. The residue was repeatedly coevaporated with methanol (5×100 mL) to remove borane residues as the trimethyl borate ester and then neutralized with 10% NaOH. The aqueous solution was then saturated with NaCl and extracted into DCM. The combined organic phases were dried over Na_2SO_4, and the solvents were evaporated at reduced pressure. The crude oil was

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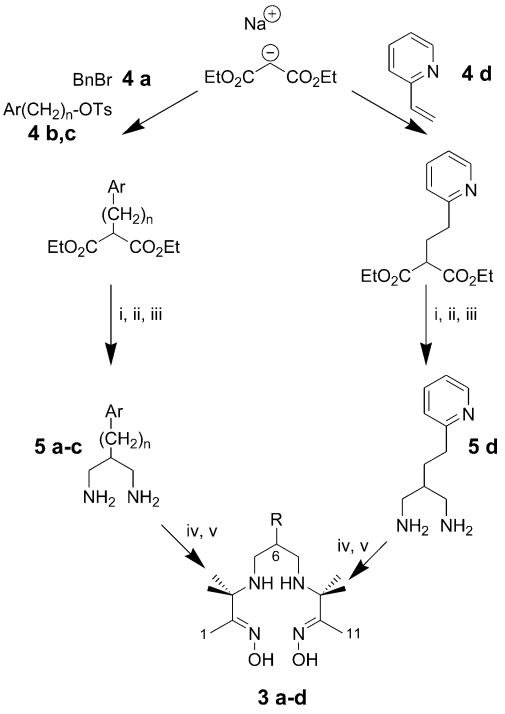
Scheme 1. General Synthetic Route to 6-Derivitized PnAO Ligands[a]



[a] Reagents and conditions: (i) NH_3, MeOH, MeONa; (ii) B_2H_6, THF; (iii) H_2O, H^+; (iv) 3-bromo-3-methyl-2-butanone, DMF, K_2CO_3; (v) NH_2OH, MeOH.

distilled on a Kugelrohr apparatus at reduced pressure to provide the product diamine **5a** as a colorless oil. Yield: 4.13 g (66%). IR (film, cm^{-1}): 3371, 3289, 1974, 1878, 1811, 1602. ^1H NMR ($CDCl_3$): δ 1.58 (s, 4 H, NH_2), 1.73 (sep, $J = 6.2$ Hz, 1 H, CH), 2.61 (d, $J = 7.4$ Hz, 2 H, CH_2), 2.69 (dd, $J = 6.1$ Hz, $J = 12.7$ Hz, 2 H, CH_2), 2.74 (dd, $J = 5.5$ Hz, $J = 12.5$ Hz, 2 H, CH_2), 7.17−7.31 (m, 5 H, ring). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 36.8 (t, CH$_2$CH), 43.6 (t, CH$_2$NH$_2$), 46.1 (d, CH), 126.0 (d, ring), 128.4 (d, ring), 129.1 (d, ring), 140.7 (s, ring).

Synthesis of 2-(2-(4-Methoxyphenyl)ethyl)-1,3-propanediamine (5b). 2-(2-(4-Methoxyphenyl)ethyl)-1,3-propanediamide[27] (3.00 g, 13.0 mmol) was slowly added in portions to a solution of borane in THF (1 mol dm^{-3}, 100 mL, 100.0 mmol). Otherwise the method for the synthesis of **5a** was followed to provide the product diamine **5b** as a colorless oil. Yield: 1.95 g (72%). ES-MS: *m*/*z* 209 ($M + H^+$). IR (film, cm^{-1}): 3371, 3292, 1611, 1583, 1512. ^1H NMR ($CDCl_3$): δ 1.24 (br s, 4 H, NH_2), 1.44 (sep, $J = 5.9$ Hz, 1 H, CH), 1.59 (dt, $J = 7.6$ Hz, $J = 7.6$ Hz, 2 H, CH_2), 2.59 (t, $J = 7.6$ Hz, 2 H, CH_2), 2.73 (dd, $J = 5.5$ Hz, $J = 15.8$ Hz, 2 H, CH_2), 2.78 (dd, $J = 5.9$ Hz, $J = 16.2$ Hz, 2 H, CH_2), 3.78 (s, 3 H, OCH_3), 6.82 (d, $J = 8.1$ Hz, 2 H, ring), 7.11 (d, $J = 8.8$ Hz, 2 H, ring). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 32.1 (t, CH_2CH_2CH), 32.6 (t, CH$_2$CH$_2$CH), 43.6 (d, CH), 43.9 (t, CH$_2$NH$_2$), 55.4 (q, OCH_3), 114.0 (d, ring), 129.3 (d, ring), 134.7 (s, ring), 157.9 (s, ring).

Synthesis of 2-(3-(2-Methoxyphenyl)-1-propyl)-1,3-propanediamine (5c). Diethyl 1,3-propanedioate (8.06 g, 5.0 mmol) was carefully added dropwise to a suspension of NaH (1.83 g, 4.60 mmol) in THF (100 mL), and the mixture was stirred for 1 h. 3-(2-Methoxyphenyl)-1-propyl 4-methylbenzenesulfonate[28] (14.66 g, 4.60 mmol) in THF (100 mL) was added dropwise, and the mixture was stirred for a further 1 h and then refluxed for a sufficient time to neutralize the solution (moist litmus paper). Water was carefully added to neutralize any remaining NaH, and then the organic phase was washed with water (3 × 100 mL), dried ($MgSO_4$), and evaporated at reduced pressure. The residue was distilled at reduced pressure to provide the intermediate substituted diester as a colorless oil. Yield: 11.59 g (82%). Bp: 215−220 °C at 18 mmHg. IR (film; cm^{-1}): 1749, 1600, 1588, 1494. ^1H NMR ($CDCl_3$): δ 1.25 (t, $J = 7.4$ Hz, 6 H, CH_2), 1.62 (quin, $J = 7.7$ Hz, 2 H, CH_2), 1.94 (q, $J = 7.6$ Hz, 2 H, CH_2), 2.64 (t, $J = 7.4$ Hz, 2 H, CH_2), 3.37 (t, $J = 7.4$ Hz, 1 H, CH), 3.80 (s, 3 H, OCH_3), 4.18 (q, $J = 7.1$, 4 H, CH_2), 6.81−6.89 (m, 2 H, ring), 7.10−7.19 (m, 2 H, ring). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 14.2 (q, CH$_3$CH$_2$), 27.7 (t, CH$_2$), 28.7 (t, CH$_2$), 29.9 (t, CH$_2$), 52.1 (d, CH), 55.3 (q, OCH_3), 61.4 (t, CH$_3$CH_2), 110.3 (d, ring), 120.5 (d, ring), 127.3 (d, ring), 130.0 (d, ring), 130.3 (s, ring), 157.6 (s, ring), 169.7 (s, C═O).

Diethyl 2-(3-(2-methoxyphenyl)-1-propyl)-1,3-propanedioate (4.05 g, 16.3 mmol) was dissolved in 2-propanol/toluene (1:1, 50 mL) and saturated with ammonia gas at 0 °C. The mixture was left overnight at room temperature, again saturated with ammonia gas, and then placed in a freezer for 48 h. The precipitated solid was filtered, and the filtrate was concentrated to yield more solid. The combined solids were recrystallized from hot toluene/60−80 petroleum ether to provide the intermediate diamide as a colorless crystalline solid. Yield: 1.38 g (32%). Mp: 159−169 °C. Anal. Calcd: C, 62.4; H, 7.3; N, 11.2. Found: C, 62.5; H, 7.0; N, 11.0. ES-MS: *m*/*z* 251 ($M + H^+$). IR (Nujol mull, cm^{-1}): 3394, 3184, 1674. ^1H NMR (DMSO-d_6): δ 1.48 (m, 2 H, CH_2), 1.67 (m, 2 H, CH_2), 2.53 (q, $J = 7.7$ Hz, 2 H, CH_2), 2.98 (t, $J = 7.4$ Hz, 1 H, CH), 3.76 (s, 3 H, OCH_3), 6.85 (t, $J = 7.4$ Hz, 1 H, ring), 6.95 (d, $J = 8.1$ Hz, 1 H, ring), 7.04 (br s, 2 H, NH_2), 7.09−7.19 (m, 2 H, ring), 7.27 (br s, 2 H, NH_2). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 29.3 (t, CH$_2$), 30.0 (t, CH$_2$), 30.6 (t, CH$_2$), 52.9 (d, CH), 55.1 (q, OCH_3), 110.5 (s, ring), 120.1 (d, ring), 127.1 (d, ring), 129.5 (d, ring), 129.7 (d, ring), 157.0 (s, ring), 171.8 (s, C═O).

2-(3-(2-Methoxyphenyl)-1-propyl)-1,3-propanediamide (1.37 g, 5.47 mmol) was slowly added in portions to a solution of borane in THF (1 mol dm^{-3}, 43.8 mL, 43.8 mmol). Otherwise the method for the synthesis of **5a** was followed to provide the product diamine **5c** as a colorless oil. Yield: 1.05 g (86%). ES-MS: *m*/*z* 223 ($M + H^+$). IR (film, cm^{-1}): 3370, 3290, 1600, 1587. ^1H NMR ($CDCl_3$): δ 1.34 (m, 2 H, CH_2), 1.44 (m, 5 H, NH_2, CH), 1.60 (m, 2 H, CH_2), 2.60 (t, $J = 7.4$ Hz, 2 H, CH_2), 2.67 (dd, $J = 5.9$ Hz, $J = 16.9$ Hz, 2 H, CH_2), 2.71 (dd, $J = 5.9$ Hz, $J = 16.9$ Hz, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 6.81−6.89 (m, 2 H, ring), 7.10−7.19 (m, 2 H, ring). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 27.0 (t, CH_2CH_2CH), 29.5 (t, CH$_2$CH$_2$CH), 30.4 (t, ArCH_2CH$_2$), 43.5 (d, CH), 43.7 (t, CH$_2$NH$_2$), 55.1 (q, OCH_3), 110.0 (d, ring), 120.2 (d, ring), 126.8 (d, ring), 129.6 (d, ring), 130.7 (s, ring), 157.2 (s, ring).

Synthesis of 2-(2-(2-Pyridinyl)ethyl)-1,3-propanediamine (5d). Diethyl 2-(2-(2-pyridinyl)ethyl)-1,3-propanedioate[29] (11.00 g, 41.0 mmol) was dissolved in methanol (50 mL), treated with sodium methoxide (0.01 g, 0.255 mmol), and saturated with ammonia gas at 0 °C. The mixture was left overnight at room temperature, again saturated with ammonia gas, and then placed in a freezer for 48 h. The precipitated solid was filtered, and the filtrate was concentrated to yield more solid. The combined solids were recrystallized from hot ethanol to provide the intermediate diamide as colorless needles. Yield: 6.54 g (76%). Mp: 215−216 °C. Anal. Calcd: C, 58.0; H,

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6.3; N, 20.3. Found: C, 58.3; H, 6.1; N, 20.4. ES-MS: *m*/*z* 207 ($M + H^+$). IR (Nujol mull, cm^{-1}): 3383, 3168, 1671. ^1H NMR (DMSO-d_6): δ 2.06 (q(app), $J = 7.8$ Hz, 2 H, CH_2), 2.66 (t(app), $J = 7.7$ Hz, 2 H, CH_2), 3.03 (t, $J = 7.7$ Hz, 1 H, C*H*), 7.10 (br s, 2 H, NH_2), 7.20 (m, 2 H, ring), 7.30 (br s, 2 H, NH_2), 7.70 (dd, $J = 7.4$ Hz, $J = 7.7$ Hz, 1 H, ring), 8.48 (d, $J = 5.1$ Hz, 1 H, ring). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 29.5 (t, *C*H_2), 35.2 (t, *C*H_2), 52.5 (d, *C*H), 121.2 (d, ring), 122.7 (d, ring), 136.4 (d, ring), 148.9 (d, ring), 160.7 (s, ring), 171.3 (s, *C*═O).

2-(2-(2-Pyridinyl)ethyl)-1,3-propanediamide (3.00 g, 14.0 mmol) was slowly added in portions to a solution of borane in THF (1 mol dm^{-3}, 100 mL, 100.0 mmol). Otherwise the method for the synthesis of **5a** was followed to provide the product diamine **5d** as a yellow oil. Yield: 1.35 g (52%). ES-MS: *m*/*z* 179 ($M + H^+$). IR (film, cm^{-1}): 3364, 3282, 1591, 1568. ^1H NMR ($CDCl_3$): δ 1.50 (sep(app), $J = 6.1$ Hz, 1 H, C*H*), 1.64 (br s, 4 H, NH_2), 1.75 (m, 2 H, CH_2), 2.80 (m, 6 H, CH_2), 7.11 (dd, $J = 5.5$ Hz, $J = 7.0$ Hz, 1 H, ring), 7.17 (d, $J = 8.1$ Hz, 1 H, ring), 7.59 (dd, $J = 7.4$ Hz, $J = 7.7$ Hz, 1 H, ring), 8.52 (d, $J = 4.0$ Hz, 1 H, ring). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 29.9 (t, CH_2CH_2CH), 35.7 (t, CH_2CH_2CH), 43.3 (d, *C*H), 43.7 (t, *C*H_2NH_2), 121.1 (d, ring), 122.7 (d, ring), 136.4 (d, ring), 149.2 (d, ring), 162.0 (s, ring).

Synthesis of 3,3,9,9-Tetramethyl-4,8-diaza-6-benzyl-2,10-undecanedione Dioxime (3a). To a suspension of K_2CO_3 (8.71 g, 63.0 mmol) in dry DMF (32 mL) were added diamine **5a** (4.13 g, 25.0 mmol) and 3-bromo-3-methyl-2-butanone[30] (10.40 g, 63.0 mmol). The mixture was stirred for 18 h at 45 °C, after which time DCM (50 mL) was added. The mixture was filtered, and the solvent was removed under reduced pressure. The residue was chromatographed (silica column, 5% methanol in DCM) to provide the intermediate diketone as a slightly impure pale yellow wax which was used directly in the next reaction step. Yield: 5.86 g (71%). IR (film; cm^{-1}): 3321, 2961, 1708s. ^1H NMR ($CDCl_3$): δ 1.22 (s, 12 H, CH_3), 1.91 (m, 1 H, C*H*), 2.12 (s, 6 H, CH_3), 2.31 (br s, 2 H, N*H*), 2.38 (dd, $J = 7.0$ Hz, $J = 11.4$ Hz, 2 H, CH_2), 2.47 (dd, $J = 4.4$ Hz, $J = 11.0$ Hz, 2 H, CH_2), 2.60 (d, $J = 7.4$ Hz, 2 H, CH_2), 7.14−7.29 (m, 5 H, ring). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 24.5 (q, *C*H_3), 24.8 (q, *C*H_3CO), 38.0 (t, *C*H_2CH), 41.8 (d, *C*H), 46.6 (t, *C*H_2NH_2), 63.1 (s, *C*), 126.1 (d, ring), 128.4 (d, ring), 129.1 (d, ring), 140.5 (s, ring), 213.6 (s, *C*═O).

Hydroxylamine hydrochloride (7.82 g, 113.0 mmol) was added to NaOH (4.20 g, 105.0 mmol) in methanol (115 mL), and the resulting solution was stirred for 2 h at 0 °C. The solution was filtered directly onto 3,3,9,9-tetramethyl-4,8-diaza-6-benzyl-2,10-undecanedione (4.96 g, 15.0 mmol), and the resulting solution was stirred at room temperature for 18 h. After removal of the solvent under reduced pressure the residue was triturated with water and recrystallized from hot ethyl ethanoate/ethanol to provide the product **3a** as fine, colorless needles. Yield: 1.77 g (33%). Mp: 176−177 °C. ES MS: *m*/*z* 363 ($M + H^+$). HR-ES-MS: $C_{20}H_{35}N_4O_2$, *m*/*z* calcd 363.2755, found *m*/*z* 363.2753 ($M + H^+$). IR (Nujol mull, cm^{-1}): 3316, 3173, 1636, 1600, 1495. ^1H NMR (DMSO-d_6): δ 1.33 (s, 12 H, CH_3), 1.79 (s, 6 H, CH_3), 2.22 (m, 1 H, C*H*), 2.59 (m, 8 H, CH_2, N*H*), 7.21−7.35 (m, 5 H, ring), 10.88 (s, 2 H, NO*H*). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 10.9 (q, *C*H_3), 25.1 (q, *C*H_3), 37.8 (t, *C*H_2CH), 38.6 (d, *C*H), 46.8 (t, *C*H_2NH_2), 60.5 (s, *C*), 127.4 (d, ring), 129.6 (d, ring), 130.2 (d, ring), 140.6 (s, ring).

Synthesis of 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-(4-methoxyphenyl)ethyl)-2,10-undecanedione Dioxime (3b). To a suspension of K_2CO_3 (3.23 g, 23.0 mmol) in dry DMF (10 mL) were added diamine **5b** (1.95 g, 9.36 mmol) and 3-bromo-3-methyl-2-butanone[30] (3.86 g, 23.0 mmol). Otherwise the method for the synthesis of **3a** was followed. Yield: 2.07 g (59%). ES-MS: *m*/*z* 377 ($M + H^+$). IR (film, cm^{-1}): 3323, 1706s, 1675, 1612, 1584, 1513. ^1H NMR ($CDCl_3$): δ 1.25 (s, 12 H, CH_3), 1.58 (m, 3 H, C*H*, CH_2), 1.97 (br s, 2 H, N*H*), 2.18 (s, 6 H, CH_3), 2.40 (m, 2 H, CH_2), 2.53 (m, 4 H, CH_2NH), 3.78 (s, 3 H, OCH_3), 6.82 (d, $J = 8.8$ Hz, 2 H, ring), 7.08 (d, $J = 8.1$ Hz, 2 H, ring). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 24.3 (q, *C*H_3), 24.5 (q, *C*H_3), 24.8 (q, *C*H_3CO), 32.5 (t, *C*H_2), 33.4 (t, *C*H_2), 39.2 (d, *C*H), 46.9 (t, *C*H_2NH_2), 55.2 (q, OCH_3), 62.9 (s, *C*), 113.8 (d, ring), 129.2 (d, ring), 134.4 (s, ring), 157.7 (s, ring), 213.4 (s, *C*═O).

Hydroxylamine hydrochloride (2.87 g, 41.2 mmol) was added to NaOH (1.54 g, 38.5 mmol) in methanol (40 mL), and the resulting solution was stirred for 2 h at 0 °C. Otherwise the method for the synthesis of **3a** was followed with recrystallization from hot ethanol to provide the product **3b** as very fine, colorless needles. Yield: 0.89 g (40%). Mp: 200−201 °C. ES-MS: *m*/*z* 407 ($M + H^+$). HR-ES-MS: $C_{22}H_{39}N_4O_3$, calcd *m*/*z* 407.3017, found *m*/*z* 407.3013 ($M + H^+$). IR (Nujol mull, cm^{-1}): 3356, 3300, 3194, 1612, 1585, 1513. ^1H NMR (DMSO-d_6): δ 1.33 (s, 12 H, CH_3), 1.53 (br s, 3 H, C*H*, CH_2), 1.82 (s, 6 H, CH_3), 2.42−2.67 (m, 6 H, CH_2), 3.72 (s, 3 H, OCH_3), 5.95 (br s, 2 H, N*H*), 6.84 (d, $J = 8.1$ Hz, 2 H, ring), 7.15 (d, $J = 8.1$ Hz, 2 H, ring), 10.94 (s, 2 H, NO*H*). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 9.7 (q, *C*H_3), 23.9 (q, *C*H_3), 31.5 (t, *C*H_2), 32.7 (t, *C*H_2), 46.0 (t, *C*H_2NH_2), 55.0 (q, OCH_3), 59.3 (s, *C*), 113.7 (d, ring), 129.2 (d, ring), 133.8 (s, ring), 157.4 (s, ring).

Synthesis of 3,3,9,9-Tetramethyl-4,8-diaza-6-(3-(2-methoxyphenyl)-1-propyl)-2,10-undecanedione Dioxime (3c). To a suspension of K_2CO_3 (1.66 g, 12.2 mmol) in dry DMF (10 mL) were added diamine **5c** (1.05 g, 4.72 mmol) and 3-bromo-3-methyl-2-butanone[30] (1.94 g, 12.0 mmol). Otherwise the method for the synthesis of **3a** was followed. Yield: 0.93 g (50%). ES-MS: *m*/*z* 391 ($M + H^+$). IR (film, cm^{-1}): 3400, 3318, 1706s, 1674, 1600, 1588. ^1H NMR ($CDCl_3$): δ 1.26 (m, 12 H, CH_3), 1.33 (m, 2 H, CHCH_2CH$_2$), 1.56 (m, 2 H, CHCH$_2$CH_2), 1.64 (m, 1 H, C*H*), 2.17 (s, 6 H, CH_3), 2.47−2.60 (m, 6 H, CH_2, CH_2NH), 3.81 (s, 3 H, OCH_3), 6.82−6.89 (m, 2 H, ring), 7.09−7.19 (m, 2 H, ring). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 24.3 (q, *C*H_3), 24.5 (q, *C*H_3), 24.9 (q, *C*H_3CO), 27.4 (t, CH_2), 30.6 (t, *C*H_2), 31.4 (t, *C*H_2), 39.4 (d, *C*H), 47.3 (t, *C*H_2NH_2), 55.3 (q, OCH_3), 63.2 (s, *C*), 110.3 (d, ring), 120.5 (d, ring), 127.1 (d, ring), 130.0 (d, ring), 130.9 (s, ring), 157.5 (s, ring), 213.5 (s, *C*═O).

Hydroxylamine hydrochloride (21.65 g, 23.8 mmol) was added to NaOH (0.89 g, 22.2 mmol) in methanol (15 mL), and the resulting solution was stirred for 2 h at 0 °C. Otherwise the method for the synthesis of **3a** was followed with recrystallization from hot ethanol to provide the product **3c** as shiny, colorless needles. Yield: 0.39 g (39%). Mp: 198 °C. ES-MS: *m*/*z* 421 ($M + H^+$). HR-ES-MS: $C_{23}H_{41}N_4O_3$, calcd *m*/*z* 421.3173, found *m*/*z* 421.3176 ($M + H^+$). IR (Nujol mull, cm^{-1}): 3317, 3194, 1588, 1492. ^1H NMR (DMSO-d_6): δ 1.31 (s, 12 H, CH_3), 1.49 (br s, 3 H, C*H*, CH_2), 1.80 (s, 6 H, CH_3), 2.56−2.61 (m, 6 H, CH_2), 3.78 (s, 3 H, OCH_3), 4.48 (br s, 2 H, N*H*), 6.84−6.96 (m, 2 H, ring), 7.12−7.21 (m, 2 H, ring), 10.87 (s, 2 H, NO*H*). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 10.2 (q, *C*H_3), 24.4 (q, *C*H_3), 27.1 (t, *C*H_2), 30.2 (t, *C*H_2), 30.8 (t, *C*H_2), 46.8 (t, *C*H_2NH_2), 55.7 (q, OCH_3), 59.7 (s, *C*), 111.1 (d, ring), 120.7 (d, ring), 127.6 (d, ring), 130.1 (d, ring), 130.3 (s, ring), 157.5 (s, ring).

Synthesis of 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-(2-pyridinyl)-ethyl)-2,10-undecanedione Dioxime (3d). To a suspension of K_2CO_3 (2.50 g, 19.0 mmol) in dry DMF (10 mL) were added diamine **5d** (1.35 g, 7.53 mmol) and 3-bromo-3-methyl-2-butanone[30]

(30) Pfleiderer, W.; Zondle, H. *Chem. Ber.* **1966**, *99*, 3008−3021.

(3.10 g, 19.0 mmol). Otherwise the method for the synthesis of **3a** was followed. Yield: 1.03 g (39%). ES-MS: *m*/*z* 347 ($M + H^+$). IR (film, cm^{-1}): 3304, 1705s, 1668, 1592, 1568. ^1H NMR ($CDCl_3$): δ 1.32 (s, 12 H, C*H*$_3$), 1.70 (m, 2 H, C*H*$_2$), 1.83 (m, 1 H, C*H*), 2.20 (s, 6 H, C*H*$_3$), 2.46 (dd, $J = 8.1$ Hz, $J = 11.0$ Hz, 2 H, C*H*$_2$), 2.65 (dd, $J = 3.7$ Hz, $J = 11.0$ Hz, 2 H, C*H*$_2$), 2.80 (m, 2 H, C*H*$_2$), 3.17 (br s, 2 H, N*H*), 7.11 (dd, $J = 5.5$ Hz, $J = 7.0$ Hz, 1 H, ring), 7.16 (d, $J = 8.1$ Hz, 1 H, ring), 7.59 (dd, $J = 7.7$ Hz, $J = 7.7$ Hz, 1 H, ring), 8.50 (d, $J = 3.7$ Hz, 1 H, ring). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 23.8 (q, *C*H$_3$), 24.2 (q, *C*H$_3$), 24.7 (q, *C*H$_3$CO), 31.5 (t, *C*H$_2$), 35.7 (t, *C*H$_2$), 38.2 (d, *C*H), 47.3 (t, *C*H$_2$NH$_2$), 63.3 (s, *C*), 121.1 (d, ring), 122.9 (d, ring), 136.5 (d, ring), 138.6 (d, ring), 149.2 (d, ring).

Hydroxylamine hydrochloride (1.54 g, 22.2 mmol) was added to NaOH (0.83 g, 20.7 mmol) in methanol (22 mL), and the resulting solution was stirred for 2 h at 0 °C. Otherwise the method for the synthesis of **3a** was followed with recrystallization from ethyl ethanoate to provide the product **3d** as a sticky, low-melting-point, yellow solid. Yield: 0.30 g (27%). Mp: 49 °C. ES-MS: *m*/*z* 378 ($M + H^+$). HR-ES-MS: $C_{20}H_{36}N_5O_2$, calcd *m*/*z* 378.2864, found *m*/*z* 378.2862 ($M + H^+$). IR (film, cm^{-1}): 3168, 1644, 1594, 1569. ^1H NMR ($CDCl_3$): δ 1.21 (s, 12 H, C*H*$_3$), 1.56 (m, 1 H, C*H*), 1.68 (m, 2 H, C*H*$_2$), 1.77 (s, 6 H, C*H*$_3$), 2.38 (br s, 4 H, C*H*$_2$), 2.72 (m, 2 H, C*H*$_2$), 3.72 (br s, 2 H, N*H*), 7.21 (dd, $J = 5.1$ Hz, $J = 6.6$ Hz, 1 H, ring), 7.28 (d, $J = 8.1$ Hz, 1 H, ring), 7.72 (dd, $J = 7.4$ Hz, $J = 8.1$ Hz, 1 H, ring), 8.49 (d, $J = 3.7$ Hz, 1 H, ring), 10.59 (br s, 2 H, NO*H*). $^{13}C\{^1H\}$ NMR (DMSO-d_6): δ 9.3 (q, *C*H$_3$), 25.1 (q, *C*H$_3$), 30.5 (t, *C*H$_2$), 34.9 (t, *C*H$_2$), 39.7 (d, *C*H), 45.6 (t, *C*H$_2$NH$_2$), 121.1 (d, ring), 122.6 (d, ring), 136.4 (d, ring), 148.8 (d, ring), 161.7 (s, ring).

Synthesis of Oxo(6-benzyl-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximato(3−)-*N*,*N*′,*N*″,*N*‴)technetium(V) (6). Preparation of the Tc complex was carried out by adaptation of a previously described method.[4] **3a** (20.0 mg, 55.2 μmol) was dissolved in 0.9% saline (5 mL) and 5 M HCl (1 drop). NH_4TcO_4 (4.98 mg, 27.6 μmol), 1 M sodium hydrogen carbonate solution (3 mL), and ether (20 mL) were added with stirring. Tartaric acid (9.06 mg, 60 μmol) in 0.9% saline (1 mL) was added followed by $Sn^{II}Cl_2 \cdot 2H_2O$ (13.5 mg, 60 μmol) in 0.9% saline (1 mL), whereupon the aqueous phase changed from colorless to yellow. The mixture was stirred at room temperature for 20 min, during which time the yellow color moved into the organic phase. The layers were separated, and the aqueous phase was extracted with ether (10 mL aliquots) until no further yellow color was observed in the extract. The organic layers were combined, dried (Na_2SO_4), and then concentrated to 2 mL under reduced pressure. The resulting orange organic solution was chromatographed (5 g silica column, 10 mL of ether to wash, methanol to elute orange product). Fractions containing the orange product were pooled and evaporated under reduced pressure. The orange solid was dissolved in the minimum volume of ether at room temperature and crystallized at −20 °C (24 h). Characterization of this radioactive product was by single-crystal X-ray diffraction alone.

Synthesis of Oxo(6-(3-(2-methoxyphenyl)propyl)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximato(3−)-*N*,*N*′,*N*″,*N*‴)technetium(V) (7) and Oxo(6-(2-(2-pyridyl)ethyl)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximato(3−)-*N*,*N*′,*N*″,*N*‴)technetium(V) (8). X-ray-quality crystals of complexes **7** and **8** were prepared using a procedure identical with that used for complex 6 except for the period allowed for crystallization (14 and 3 days, respectively) and, in the case of **8**, the solvent (methanol/ether). Characterization of these radioactive products was by single-crystal X-ray diffraction alone.

Synthesis of (6-Benzyl-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximato(1−)-*N*,*N*′,*N*″,*N*‴)cobalt(III) Dinitrite (9). Preparation of the intermediate dichloride complex and subsequent anion substitution to provide the required dinitrite complex was carried out by adaptation of a previously described method.[31] **3a** was dissolved in hot ethanol and filtered. To this was added an excess of $CoCl_2$, resulting in a purple solution. On cooling, the solution turned green, and after 1 h a light green microcrystalline solid had deposited which was separated by filtration and dried under vacuum. This precursor salt was not purified further but was used directly to prepare the product. The cobalt dichloride complex of **3a** (1.0 g) was dissolved in water (50 mL) by the addition of dilute KOH solution. KNO_2 (1.0 g) was added with stirring, and the solution was brought to pH 5 with dilute HCl. The solution was warmed for 30 min at 50 °C, during which time it turned orange and precipitated a brown solid. The brown solid was separated by filtration and recrystallized from an excess of hot water to provide crystalline orange plates. Mp: 215 °C. ES-MS: *m*/*z* 420 (M^+). HR-ES-MS: $C_{20}H_{33}N_4O_2Co$, calcd *m*/*z* 420.1930, found *m*/*z* 420.1931 (M^+). ^1H NMR (CD_3CN): δ 1.02 (d, $J = 4.5$ Hz, 6 H, C*H*$_3$), 1.52 (d, $J = 4.5$ Hz, 6 H, C*H*$_3$), 2.10 (s, 4 H, C*H*$_2$), 2.12 (s, 1 H, C*H*), 2.17 (s, 6 H, C*H*$_3$), 2.64 (m, 2 H, N*H*), 2.84 (d, $J = 6.8$ Hz, 2 H, CH$_2$), 7.24−7.38 (m, 5 H, ring). ^{13}C NMR (CD_3CN): δ 13.2 (q, *C*H$_3$), 19.9 (q, *C*H$_3$), 24.7 (q, *C*H$_3$), 38.3 (t, *C*H$_2$), 40.3 (d, *C*H), 45.8 (t, *C*H$_2$), 67.6 (s, *C*), 126.49 (d, ring), 128.8 (d, ring), 129.8 (d, ring), 139.0 (s, ring), 160.0 (s, *C*≡N).

Synthesis of (6-Benzyl-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximato(1−)-*N*,*N*′,*N*″,*N*‴)copper(II) Hydrate Tetrafluorborate (10). The following procedure was based on the preparation of a similar perchlorate salt.[17] **3a** (20.0 mg) and $Cu(BF_4)_2$ (10.0 mg) were separately dissolved in hot methanol (2 mL) and filtered. The solutions were mixed and allowed to cool, resulting in the precipitation of a dark purple microcrystalline solid. The solid was separated and recrystallized from water by slow evaporation to provide crystalline dark purple blocks. Mp: 185−185 °C. ES-MS: *m*/*z* 424 (M^+). HR-ES-MS: $C_{20}H_{33}N_4O_2$-Cu, calcd *m*/*z* 424.1894, found *m*/*z* 424.1895 (M^+). NMR gave poor results due to the paramagnetic nature of Cu(II).

Synthesis of (6-(2-(4-Methoxyphenyl)ethyl)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximato(1−)-*N*,*N*′,*N*″,*N*‴)-copper(II) Hydrate Tetrafluoroborate (11). The following procedure was based on the preparation of a similar perchlorate salt.[17] **3b** (20.0 mg) and $Cu(BF_4)_2$ (12.0 mg) were separately dissolved in hot methanol (2 mL) and filtered. The solutions were mixed and allowed to cool. Slow evaporation provided crystalline dark purple needles. Mp: 170−173 °C. ES-MS: *m*/*z* 468 (M^+). HR-ES-MS: $C_{22}H_{37}N_4O_3Cu$, calcd *m*/*z* 468.2156, found *m*/*z* 468.2157 (M^+). NMR gave poor results because of the paramagnetic nature of Cu(II).

Synthesis of (6-(2-(2-Pyridinyl)ethyl)-3,3,9,9-tetramethyl-4,8-diazaundecane-2,10-dione dioximato(1−)-*N*,*N*′,*N*″,*N*‴)copper-(II) Hydrate Tetrafluoroborate (12). 3c (20.0 mg) and $Cu(BF_4)_2$ (10.0 mg) were separately dissolved in hot methanol (2 mL) and filtered. The solutions were mixed and allowed to cool, resulting in the formation of a brown solid. The solid was separated and recrystallized from water in the presence of excess $Cu(BF_4)_2$ by slow evaporation to provide crystalline orange-brown fine plates. Very little material was recovered with which to attempt characterization other than by single-crystal X-ray crystallography.

Single X-ray Crystallographic Studies. Details of the crystal data and a summary of the intensity data collection parameters for

(31) Goff, H.; Kidwell, S.; Lauher, J.; Murmann, R. K. *Inorg. Chem.* **1973**, *12*, 2631−2640.

Table 1. Crystal Data, Intensity Measurements, and Structure Refinements for **6**−**11**

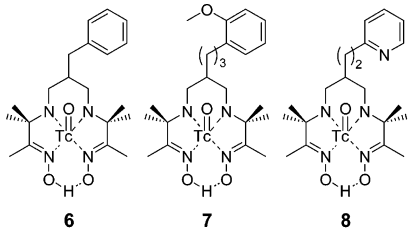
	6	**7**	**8**	**9**	**10**	**11**
empical formula	$C_{20}H_{31}N_4O_3Tc$	$C_{23}H_{37}N_4O_4Tc$	$C_{20}H_{32}N_5O_3Tc$	$C_{20}H_{33}CoN_6O_6$	$C_{20}H_{35}BCuF_4N_4O_3$	$C_{22}H_{39}BCuF_4N_4O_4$
fw	473.49	531.57	488.51	512.45	529.87	573.92
temp (K)	293	293	293	293	150	150
cryst dimens (mm)	0.2 × 0.05 × 0.05	0.5 × 0.15 0.1	0.25 × 0.15 × 0.05	0.5 × 0.2 × 0.07	0.75 × 0.35 × 0.30	0.65 × 0.15 × 0.15
cryst syst	monoclinic	Monoclinic	Triclinic	triclinic	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/n$	$P\bar{1}$	$P\bar{1}$	$P2_1/c$	$C2/c$
a (Å)	7.957(2)	12.963(3)	10.678(2)	10.867(2)	14.336(3)	22.067(4)
b (Å)	11.979(2)	7.577(2)	10.852(2)	12.248(2)	18.443(4)	19.047(4)
c (Å)	22.914(5)	25.431(5)	11.052(2)	9.617(2)	18.931(4)	12.928(3)
α (deg)			92.05(3)	103.64(3)		
β (deg)	91.00(3)	91.89(3)	113.21(3)	93.66(3)	99.52(3)	104.04(3)
γ (deg)			109.55(3)	71.47(3)		
V (Å^3)	2183.8(8)	2496.5(10)	1088.2(3)	1179.3(4)	4936.4(18)	5271.4(19)
Z	4	4	2	2	8	8
μ (cm^{-1})	6.86	6.11	6.92	7.76	9.43	8.92
d(calcd) (g cm^{-3})	1.440	1.414	1.491	1.443	1.426	1.446
F(000)	984	1112	508	540	2216	2408
θ range (deg)	1.92−27.57	2.92−30.00	3.15−30.56	2.18−25.00	2.64−25.04	2.69−25.00
scan type	$2\theta-\theta$	$2\theta-\theta$	$2\theta-\theta$	$2\theta-\theta$	$2\theta-\theta$	$2\theta-\theta$
no. of reflns collected	32236	14941	12741	4484	9226	4877
no. of indep reflns	5025	6036	5467	4149	8662	4646
R(int)	0.1728	0.0672	0.0419	0.0361	0.0423	0.0235
GOF on F^2	0.985	1.037	1.051	0.965	1.068	0.970
R1[a] [$I > 2\sigma(I)$]	0.0610	0.0462	0.0367	0.0388	0.0575	0.0355
wR2[b] [$I > 2\sigma(I)$]	0.1383	0.1026	0.0790	0.0880	0.1560	0.0817
largest difference peak and hole (e Å^{-3})	1.1012 and −1.684	0.834 and −1.022	1.037 and −0.906	0.323 and −0.443	1.175 and −1.127	0.346 and −0.410

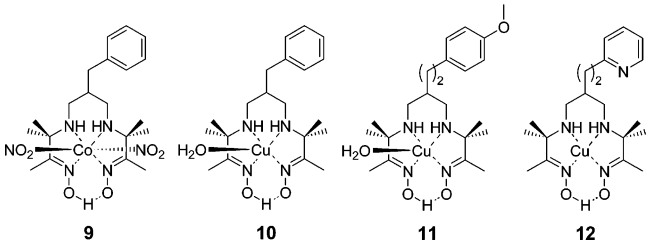
[a] $R1 = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $wR2 = \{\sum[w(|F_o|^2 - |F_c|^2)^2]/\sum[w(|F_o|^2)^2]\}^{1/2}$, where $w = 1/[\sigma^2(|F_o|^2) + (0.0717P)^2 + (1.4086P)]$ for **6**, $w = 1/[\sigma^2(|F_o|^2) + (0.0557P)^2]$ for **7**, $w = 1/[\sigma^2(|F_o|^2) + (0.0422P)^2]$ for **8**, $w = 1/[\sigma^2(|F_o|^2) + (0.0488P)^2]$ for **9**, $w = 1/[\sigma^2(|F_o|^2) + (0.0971P)^2 + (13.4682P)]$ for **10**, and $w = 1/[\sigma^2(|F_o|^2) + (0.0403P)^2]$ for **11**; $P = (|F_o|_2 + 2|F_c|_2)/3$.

6−**11** are given in Table 1. Data for **6**−**8** were collected on an Enraf-Nonius FR591 rotating anode diffractometer, and those for **9**−**11** on a Rigaku AFC7S diffractometer. Both machines used graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). The structures were solved by direct methods and refined by full-matrix least squares on F^2 using SHELX97[32] through the WinGX interface.[33] All non-hydrogen atoms were refined with anisotropic thermal parameters in the latter stages of refinement. In the case of **9** and **11** all hydrogen atoms were located by difference Fourier maps and refined isotropically. In the case of **6**−**8** and **10** all non-methyl hydrogen atoms were located and refined as described above whereas methyl hydrogen atoms were placed in idealized positions and refined using general isotropic temperature factors. Final values of the atomic positional parameters for **6**−**11** are available as Supporting Information. Although **12** appeared to provide good-quality diffraction data, attempts to solve its structure by numerous methods failed, there being consistently high disorder in the majority of non-hydrogen atoms.

Results and Discussion

Synthesis of Ligands 3a−**d.** The 6-substituted PnAO ligands **3a**−**d** were prepared as outlined in Scheme 1 following established literature methodology.[24] While benzyl bromide (**4a**) was used in the preparation of **3a**, the simple purification of tosylates **4b** and **4c** favored their use as the malonate alkylating agents for the preparation of methoxyphenyl derivatives **3b** and **3c**. Initial attempts to add the pyridylethyl ligand using 2-(2-chloroethyl)pyridine were hampered by in situ conversion of the latter to 2-vinylpyridine under the basic reaction conditions. However, 2-vinylpyridine itself (**4d**) was found to react efficiently with the malonate anion. Use of sodium metal in ethanol was favored for the alkylations involving benzyl bromide and 2-vinylpyridine, whereas sodium hydride in THF was preferred for the methoxyphenyl derivatives. Each diester was then converted to its corresponding diamine **5a**−**d** before alkylation to the corresponding PnAO analogue **3a**−**d**. Metal complexes **6**−**11** with Tc,[3,4] Co,[31] and Cu[17] were then





prepared by suitable modifications of established literature procedures. The technetium complexes were formed via the in situ reduction of pertechnetate using Sn(II); the Co and Cu complexes were formed directly from the easily accessible salts $CoCl_2$ and $CuBF_4$. Oxidation to Co(III) occurred during the heating required for anion substitution with KNO_2.

(32) SHELX97 Suite—Programs for Crystal Structure Analysis (Release 97-2): Sheldrick, G. M., Institüt für Anorganische Chemie der Universität, Tammanstrasse 4, D-3400 Göttingen, Germany, 1998.
(33) Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837−838.

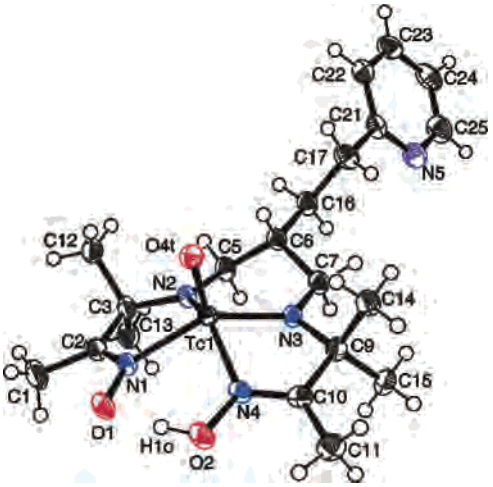


Figure 1. ORTEP representation of **8**.

Table 2. Comparison of Selected Bond Lengths and Distances (Å)

	6	**7**	**8**	**2**[a]
Tc(1)−O(4t)	1.679(3)	1.6758(13)	1.6722(17)	1.679(3)
Tc(1)−N(1)	2.084(4)	2.0672(15)	2.0848(19)	2.086(3)
Tc(1)−N(2)	1.905(4)	1.9190(14)	1.910(2)	1.917(3)
Tc(1)−N(3)	1.911(4)	1.9121(13)	1.9213(19)	1.908(3)
Tc(1)−N(4)	2.081(4)	2.0770(15)	2.079(2)	2.093(4)
Tc(1)−N_4 plane	0.667(22)	0.667(9)	0.664(20)	0.678(1)

[a] Reference 3.

Technetium Complexes. In each technetium complex **6**−**8** (e.g., Figure 1) the observed structure is analogous to that of the known parent TcO−PnAO complex (**2**[3]) as summarized in Table 2. Each adopts a square-pyramidal geometry in which the base is defined by the plane of the four nitrogen donors with the oxo ligand occupying the apical position. The technetium ion sits approximately 0.67 Å above the plane of the nitrogen atoms. The ligand is deprotonated at both amine groups and at one of the oxime hydroxyl groups, thereby affording a neutral complex of oxotechnetium(V) [TcO^{3+}]. The shorter N(amide)−Tc bond lengths (ca. 1.91 Å) compared with the N(oxime)−Tc distance (ca. 2.08 Å) reflect the multiple bond character of the former caused by π-donation stabilizing the high formal charge of the oxotechnetium core. Such high bond character from the ligand leads to a slight weakening and hence lengthening of the Tc═O bond (ca. 1.68 Å), a value which lies at the upper end of the range observed for oxotechnetium(V) complexes (1.610−1.672 Å),[3] in common with the complexes previously observed with this ligand class.[4] In each complex the C6-substituent occupies a pseudoequatorial position which places it at the greatest distance from the metal-binding site. Such a conformation is desirable for the application of a PnAO ligand as a radioactive-metal-chelating agent attached to a bioactive targeting group via a functionalized side arm.

In each of the structures **6**−**8** the non-methyl hydrogen atoms were located from a difference map including the proton of the O···H−O hydrogen bond, which has previously proved somewhat difficult to detect in similar complexes.[3,4] The disorder of the methyl hydrogen atoms suggests that intra- or intermolecular hydrogen-bonding of the type CH···X involving the methyl groups is unimportant in these

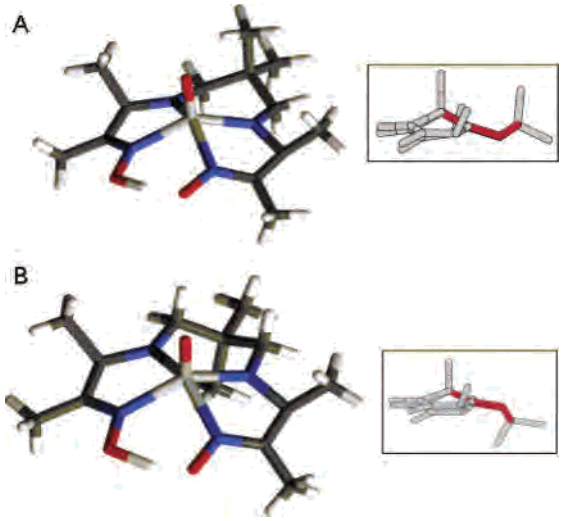
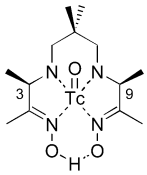


Figure 2. Boat (A) and chair (B) conformations of **13**[4] (with ring conformations highlighted in the insets).

structures. Further evidence for this comes from the examination of the tables of inter- and intramolecular close contacts for each structure.

Technetium complexes **6**−**8** clearly illustrate that the TcO−PnAO complex is a robust pseudocrown which is insensitive to the nature of the C6-substituent. In particular, since the TcO−PnAO complex can be regarded as an 18-electron species featuring a strong multiple bond, the absence of coordination from the additional pyridyl group in complex **8** is not surprising. Such a coordination would also require some distortion of the geometry of the complex since the pyridine ring is tethered to the PnAO skeleton by a short ethyl chain.

Conformation of the Six-Membered Chelate Ring. In each of the TcO complexes reported here the six-membered chelate ring adopts the pseudoboat conformation common to the majority of TcO−PnAO complexes. A survey of the Cambridge Crystallographic Database[12] reveals that the only exception is displayed by complex **13**,[4] where the asymmetric unit contains one molecule of the complex in a boat conformation (Figure 2A) and, uniquely, a second independent molecule in a chair conformation (Figure 2B).



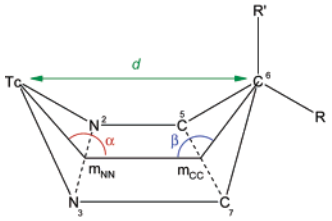
13

Complex **13** appears to be the only example in which the relative energies of the two conformations are close enough for the chair conformation to compete with the boat, leading to the presence of both conformers. One possible explanation for this behavior centers around the conformation of the methyl substituents at C3 and C9; in most other examples of this ligand class at least one of these groups occupies the lower face of the complex *anti* to the TcO core. The consequent steric bulk may force the lower face C6-substituent

Table 3. Six-Membered Chelate Ring Conformational Data (α, *β*, and *d* Being Defined in Figure 3)

complex	R	R′	α/deg	*β*/deg	*d*/Å
1[a]	−H	−H	158.61	121.48	3.134
14[b]	$-(CH_2)_3-$		165.78	123.48	3.249
13[c]	−Me	−Me	168.90	128.01	3.341
6	$-CH_2Ph$	−H	159.64	123.87	3.179
7	$-(CH_2)_3$-*o*-C_6H_4OMe	−H	158.68	123.44	3.171
8	$-(CH_2)_2$-*o*-C_5H_4N	−H	159.53	123.52	3.169

[a] Reference 3. [b] Reference 9. [c] Reference 4.



$\alpha = Tc\text{-}m_{NN}\text{-}m_{CC}$

$\beta = C6 - m_{CC} - m_{NN}$

$d = Tc - C6$

where

m_{CC} is the midpoint of C5 and C7

m_{NN} is the midpoint of N2 and N3

Figure 3. Definitions of α, *β*, and *d*.

to adopt a pseudoequatorial position which pushes the propylene bridge up toward the oxo ligand and hence a boat conformation. However, in **13** both methyl groups are *syn* to the core (Figure 2B), leaving the lower face relatively unhindered. This may permit the lower face C6-substituent to reside in a pseudoaxial position and consequently the chelate ring to adopt the chair conformation.

The TcO−PnAO complexes presented here adopt the boat conformation exclusively with the C6-substituents residing in pseudoequatorial positions. Since each complex exhibits C3- and C9-substituents on the lower face of the complex, such a conformation might therefore have been predicted. The alternative chair conformation was not observed. This may indicate that the methyl groups at C3 and C9 have sufficient steric bulk to encourage the adoption of the boat conformer alone, even though the chair conformer would require only that the sterically unfavorable pseudoaxial position were occupied by a hydrogen atom.

In support of this theory a closer examination of the precise geometry of the six-membered chelate ring in complexes **6**−**8** and in representative examples of technetium−PnAO complexes reported previously was also undertaken. This revealed that the conformational sensitivity may be more dependent upon a steric clash between the oxo ligand and the upper face C6-substituent regardless of the substitution at C3 and C9. It appears that flattening of the boat conformation can be quantified (Table 3) by measurement of the distance *d* and the angles of fold α and *β* (Figure 3). The shortest distance *d* is observed with R = R′ = H (**1**), while the introduction of bulkier methyl groups, R = R′ = Me (**13**), produces the greatest flattening of the ring with *d* increasing by ca. 0.2 Å, a significant increase in the distance between the technetium and C6. If the boat conformation is energetically more favorable because of the fundamental nature of the TcO−PnAO complex, then the partial population of the less favorable chair conformer in **13** can be explained by the need to reduce the steric overlap of the

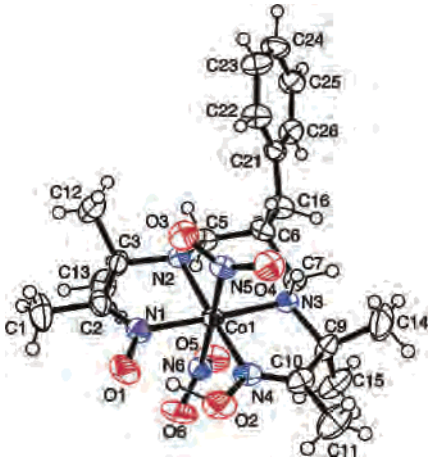
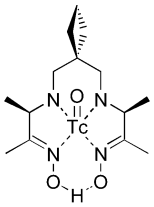


Figure 4. ORTEP representation of **9**.

oxo ligand and upper face pseudoaxial C6-substituent. The corresponding values for the cyclobutane derivative **14** lie



14

between these extremes as might be predicted for smaller methylene substituents which are further constrained by their restricted cyclic conformation. Clearly the steric overlap in **14** is not sufficient to force the adoption, partial or otherwise, of the less favorable chair conformer. Since **14**, like **13**, has no lower face substituents but does not exhibit a chair conformer, it can be concluded that the initially observed boat−chair dependence upon C3- and C9-substitution is a more fundamental rather than specific contributor to the conformation of the chelate ring. This is further confirmed by analysis of the data for the complexes presented here bearing a single substituent at C6. The values for the distance *d* and the angles α and *β* are very close to those found in the complex unsubstituted at C6 (i.e., R ≃ R′ = H, **1**) as would be expected for ligands which also bear the same small hydrogen atom in the key, sterically unfavorable pseudoaxial position.

Non-technetium Complexes. We have also prepared the cobalt and copper complexes **9**−**11**. Once again these form pseudomacrocycles via the deprotonation of one oxime hydroxyl group. However, in keeping with all other reported PnAO complexes involving metals other than technetium, the amine functions remain protonated in each case. This leads to a number of important changes in the overall properties of the complexes when compared to their technetium analogues.

The cobalt complex **9** (Figure 4) displays the expected Co(III) octahedral geometry comprising the four approximately planar nitrogen atoms from the PnAO skeleton with two nitrite ligands occupying the remaining vertexes. The nitrite ligands are mutually orthogonal, an arrangement that

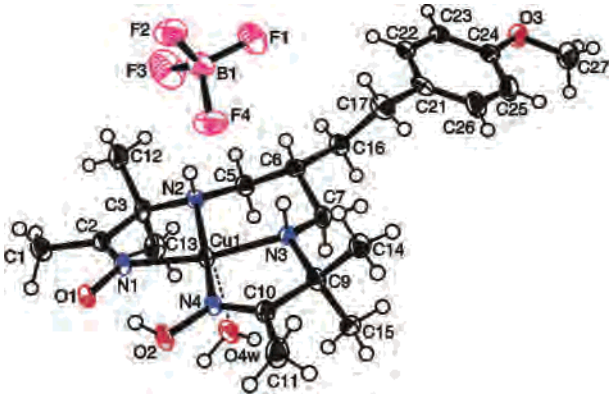


Figure 5. ORTEP representation of **11**.

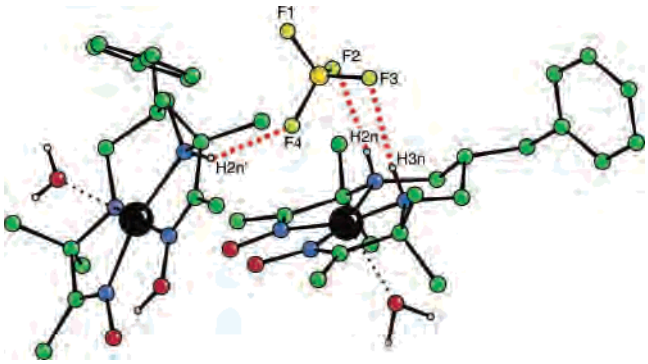


Figure 6. Intermolecular close contacts within the asymmetric unit of **10**.

permits one ligand to loosely hydrogen bond to the amine hydrogens on one face of the PnAO while the other is aligned to minimize steric clash with the methyl substituents at C3 and C9. Steric clash is further reduced by this nitrite group leaning away from the methyl groups on C3 and C9 by approximately 5° from its ideal octahedral position.

The copper complexes **10** and **11** (Figure 5) both exhibit square-based pyramidal geometry comprising the PnAO nitrogen donors and a capping water molecule. In each case the water molecule lies *anti* to the amine hydrogens. The unit cell of **10** contains two similar complexes in the asymmetric unit which are associated via multiple hydrogen bonds to one of the noncoordinating BF_4^- anions (Figure 6), the remaining anion being loosely hydrogen bonded to a coordinating water molecule.

Since complexes **9**−**11** do not require a high formal charge to be neutralized at the core, the amine donors remain protonated, giving rise to charged species, 2+ overall for the Co(III) complex and 1+ for the Cu(II) complexes. Further, the cobalt and copper atoms also lie within the plane of the PnAO donor ring and adopt a pseudochair conformation of the C6 chelate ring. This contradicts a previous study[4] which reported that the chair conformation of **13** was the only example of a metal−PnAO complex exhibiting this conformation. Our review of the metal complexes of PnAO derivatives reported in the Cambridge Crystallographic Database[12] indicates that all non-technetium complexes exist exclusively in pseudochair conformations.

The cobalt and copper complexes discussed here behave in a typical and predictable fashion. When compared to the corresponding complex with simple PnAO **1**, monoalkylation at the 6-position has effectively substituted the existing pseudoequatorial hydrogen, leaving the ligand−metal conformation unchanged. The cobalt and copper complexes share the expected preference for a pseudoequatorial C6-substituent as seen in the Tc complexes, and its presence did not affect the established binding motif.

Interestingly our searches did not reveal any instance of the use of rhenium as a model for technetium in the context of PnAO ligands. Being a congener of technetium and similar in size due to lanthanide contraction, it might be expected to be the perfect, nonradioactive analogue of technetium. However, it is present in the form of perrhenate (ReO_4^-) as a Cu(II)−PnAO complex counterion,[15] suggesting that unsuccessful attempts may have been made to prepare an oxorhenium(V) [ReO^{3+}]−PnAO complex. Further attempts to utilize rhenium in this way may be beneficial in permitting the wider study of TcO−PnAO complex behavior.

Conclusions

We have shown that the attachment of a single substituent in the C6-position does not significantly perturb the complexation behavior of PnAO ligands with technetium. It is likely therefore that oxotechnetium(V) complexes of 6-substituted PnAO ligands will retain similar overall in vivo stability. This result is of particular relevance to the use of PnAO ligands as technetium binding units attached to large functional pendant groups.

We have also shown that typical, easily accessible metal complexes remain similarly unperturbed upon substitution at the C6-position, further evidence of the suitability of this site for elaboration.

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Supporting Information Available: Details of the X-ray structure determinations, in CIF format, of the structures of **6**−**11** and Ortep figures of structures **6**, **7**, and **10** including the numbering schemes used for crystallographic data in PDF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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