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LETTER

Synthesis and Crystal and Molecular Structure of a Technetium–Hydralazino Complex, $[TcCl_2(C_8H_5N_4)(PPh_3)_2]\cdot 0.75C_7H_8$

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The chemistry of technetium has received considerable attention in recent years by virtue of its use in diagnostic nuclear medicine [1]. One approach has focused on the binding of the metastable isotope, Tc-99m, to tumor localizing monoclonal and polyclonal antibodies fór use in tumor imaging [2-4]. In practice, it is essential that the radiolabel does not dissociate from the antibody conjugate over the period of time required for diagnosis. A number of methods for attaching technetium to macromolecules has been described. The reduction of disulfide groups in the macromolecule to thiols and the subsequent use of these groups to bind reduced technetium is one common procedure. However, reduction of disulfide units can lead to protein denaturation and subsequent loss of biological specificity. Furthermore, the method cannot be used to label macromolecules lacking disulfide moieties.

Alternatively, Tc-99m can be linked to macromolecules via bifunctional chelates such as thiosemicarbazides, diamide-dithiol ligands and other chelates [5–9]. Problems associated with these methods include significant non-specific binding of technetium and slow kinetics of Tc-labelling.

We have recently described a simple, efficient and general method for labelling proteins with Tc-99m based on bifunctional hydrazine reagents. The hydrazine–protein conjugates react with Tc-99m glucoheptonate under mild conditions to give stable Tc-99m labelled proteins in >90% radiometric yield [10].

Since the fundamental coordination chemistry of technetium with organohydrazine ligands is largely unexplored [11], we have initiated extensive studies of the chemistry of various hydrazines with this element using macroscopic quantities of the long-lived radionuclide Tc-99. This work has focused on the chemistry of metal precursors with the Tc(V)–oxo core, similar to that present in the radiopharmaceutical preparations. In this paper, we report the synthesis and structural characterization of $[TcCl_2(C_8H_5N_4)(PPh_3)_2]$, a complex synthesized from $[TcOCl_4]^{1-}$ in the presence of hydrazinophthalazine (hydralazine) and excess triphenylphosphine.

Experimental

Synthesis of $[TcCl_2(C_8H_5N_4)(PPh_3)_2]\cdot 0.75C_7H_8$

To a solution of $(C_4H_9)_4N[TcOCl_4]$ (100 mg) in anhydrous methanol (2 ml) was added a suspension of hydralazine·HCl (81 mg) in methanol (2 ml) yielding a homogeneous red–brown solution. To this solution, PPh_3 (324 mg) in methanol (15 ml) was added, resulting in no observable color change. This solution was refluxed for 2 min, cooled to room temperature and chilled in an ice bath for 30 min. The dark brown microcrystalline precipitate was collected by vacuum filtration, redissolved in a minimum amount of CH_2Cl_2 and filtered through a silica gel column using CH_2Cl_2 as eluant. Pure crystalline complex was obtained in 25% yield upon addition of toluene. *Anal.* Calc. for $C_{44}H_{35}N_4P_2Cl_2Tc\cdot 0.75C_7H_8$: C, 64.2; H, 4.46; N, 6.09. Found: C, 63.5; H, 4.52; N, 5.95%. Upon standing in air, the toluene of crystallization is gradually lost, resulting in crystal pitting and loss of luster. IR (KBr pellet, cm^{-1}): 3056(m), 2959(w), 1961(w), 1890(w), 1818(w), 1618(w), 1586(w), 1542(m), 1482(s), 1435(s), 1354(s), 1275(s), 1248(s), 1231(w), 1189(m), 1152(m), 1094(s), 1029(m), 999(m), 906(w), 855(w), 802(w), 786(w), 744(s), 693(s).

X-ray Crystallographic Study of $[TcCl_2(C_8H_5N_4)(PPh_3)_2]\cdot 0.75C_7H_8$

The crystal was mounted on a glass fiber directly from the mother liquor and placed in a stream of N_2 gas at 233 K. Crystal data for $[TcCl_2(C_8H_5N_4)(PPh_3)_2]\cdot 0.75C_7H_8$ are: triclinic space group $P\bar{1}$, $a = 11.592(3)$, $b = 12.205(3)$, $c = 17.884(4)$ Å, $\alpha = 107.76(1)$, $\beta = 99.03(1)$, $\gamma = 106.11(1)°$, $V = 2232.4(12)$ Å^3, $D_{calc} = 1.37$ g cm^{-3}, $Z = 2$. Structure solution and refinement based on 2775 reflections with $F_o \geq 6\sigma(F_o)$ (Mo Kα, $\lambda = 0.71073$ Å; 6238 collected converged at a conventional discrepancy value (R) of 0.0623.

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Discussion

Reactions of metal–oxo species with hydrazine ligands often proceed by condensation-type reactions, resulting in the displacement of the oxo group as H_2O and the formation of the chemically robust metal–hydrazido, $M{=}NNR_2$, or metal–diazenido, $M{=}NNR$, unit [12–14]. In this regard, the hydrazine chemistry of the Tc–oxo group appears to parallel that described for Mo=O and Re=O moieties. The reaction of $[TcOCl_4]^{1-}$ with hydralazine initially yields a red–brown solution from which analytically pure products could not be isolated, presumably as a consequence of the tendency of the coordinated hydrazine to undergo N–N bond cleavage to give nitrido products [15]. However, upon addition of PPh_3 a stable crystalline material, analyzing for $[TcCl_2(C_8H_5N_4)(PPh_3)_2]\cdot 0.75C_7H_8$, is isolated. The infrared spectrum exhibits strong bands at 1482, 1435, 744 and 693 cm^{-1} consistent with the presence of coordinated PPh_3. The prominent features at 1354, 1275 and 1248 cm^{-1} are characteristic of the hydralazino ligand, while the bands at 1618 and 1542 cm^{-1} are assigned to $\nu(N{=}N)$ and $\nu(C{=}N)$ of the chelating hydralazino moiety, respectively. The absence of any features in the 800–1000 cm^{-1} region confirms the displacement of the oxo group.

The structure of $[TcCl_2(C_8H_5N_4)(PPh_3)_2]$ is illustrated in the Fig. 1. The coordination geometry about the Tc center is distorted octahedral, with the phosphine donors adopting the *trans* axial configuration. The equatorial plane is generated by the two chloride donors and the nitrogen donors of the chelating hydralazino ligand. As indicated by the metrical parameters given in the caption to Fig. 1, there is considerable delocalization throughout the Tc–N(1)–N(2) unit. The short Tc–N(1) distance of 1.77(1) Å suggests significant multiple bonding, in contrast to the Tc–N(3) distance of 2.151(9) Å, which approaches the limit for a Tc–sp^2-nitrogen single bond. Similarly, the N(1)–N(2) distance of 1.27(2) Å is significantly shorter than the N(3)–N(4) distance (1.38(1) Å), suggesting a bond order approaching 2 for N(1)–N(2) in contrast to a bond order of 1.5 for N(3)–N(4). Since the N(2)–C(40) bond distance is consistent with negligible multiple bond character, the delocalization seems to be restricted to the Tc–N(1)–N(2) region. The geometry of the Tc–N(1)–N(2) fragment may be compared to that observed for $[TcCl(PPh_3)_2(NNC_6H_4Br)_2]$ [11], where distances of 1.783(7) and 1.229(9) Å were observed for Tc–N(1) and N(1)–N(2), respectively, with an angle of 170.7(7)° for Tc–N(1)–N(2).

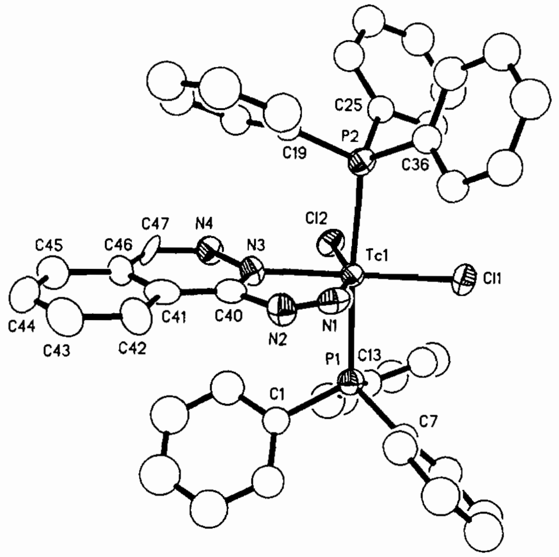

Fig. 1. ORTEP view of the structure of $[TcCl_2(C_8H_5N_4)(PPh_3)_2]$, showing the atom-labelling scheme. Selected bond lengths (Å) and angles (°): Tc–Cl(1), 2.397(3); Tc–Cl(2), 2.371(3); Tc–P(1), 2.490(4); Tc–P(2), 2.477(4); Tc–N(1), 1.77(1); Tc–N(3), 2.151(9); N(1)–N(2), 1.27(2); N(2)–C(40), 1.40(2); N(3)–N(4), 1.38(1); N(3)–C(40), 1.36(2); N(4)–C(47), 1.31(2); C(40)–C(41), 1.43(2); C(41)–C(46), 1.40(2); C(46)–C(47), 1.41(2); P(1)–Tc–P(2), 174.2(1); Cl(1)–Tc–N(3), 176.3(3); Cl(2)–Tc–N(1), 155.7(3); N(1)–Tc–N(3), 69.8(4); Tc–N(1)–N(2), 138.6(7).

Since the hydralazino ligand is present in the triply depronated form, the complex may be formally considered a Tc(V)–hydralazino(3–) complex. The metal–ligand bond lengths conform to this formalism. The major distortions from octahedral symmetry are consequences of chelate ring formation, resulting in a severely acute N(1)–Tc–N(3) angle of 69.8(4)°, and of the strong Tc–N(1) π interaction, inducing the short Tc–N(1) bond distance. The structure is analogous to the previously described $[ReCl_2(C_8H_5N_4)(PPh_3)_2]$ [14].

The isolation of $[TcCl_2(C_8H_5N_4)(PPh_3)_2]$ demonstrates that the Tc–oxo moiety can react with organohydrazine ligands by the conventional condensation-type reaction. Although oxo-atom abstraction by PPh_3 is also possible, the infrared spectrum of the red–brown material produced prior to addition of PPh_3 indicates the absence of bands associated with $\nu(Tc{=}O)$ and confirms that PPh_3 is not the agent responsible for oxo abstraction. This observation suggests that on the tracer level the uptake of Tc-99m from solutions of Tc(V)–oxo compounds may involve the formation of the robust Tc–hydrazido or Tc–diazenido linkage as a consequence of oxo group substitution.

Supplementary Material

Tables of fractional coordinates, thermal parameters, interatomic bond distances and angles, and calculated and observed structure factors are available from J.Z.

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References

1 M. Nicolini, G. Bandoli and U. Mazzi (eds.), *Technetium in Chemistry and Nuclear Medicine,* Raven, New York, 1986.
2 J. Franz, G. M. Freeman, E. K. Barefield, W. A. Volkert, G. J. Ehrhardt and R. A. Holmes, *Nucl. Med. Biol., 14* (1987) 479.
3 C. F. Meares and T. G. Wensel, *Acc. Chem. Res., 17* (1984) 202.
4 G. J. Huber, R. A. Alberto, P. Bläuenstein and G. Anderegg, *J. Chem. Soc., Chem. Commun.,* (1989) 879.
5 D. Lanteigne and D. J. Hnatowich, *Int. J. Appl. Radiat. Isot., 35* (1984) 617.
6 Y. Arano, A. Yokoyama, T. Furukawa, K. Horiuchi, T. Yahata, H. Saji, H. Sakahara, T. Nakashima, M. Koizumi, K. Endo and K. Torizuka, *J. Nucl. Chem., 28* (1987) 1027.
7 A. Fritzberg, *Eur. Patent Appl. EP 188 256 2A.*
8 F. A. Liang, F. Virzi and D. J. Hnatowich, *Nucl. Med. Biol., 14* (1987) 63.
9 S. Z. Lever, K. E. Baidov, A. V. Kramer, H. D. Burns, *Tetrahedron Lett., 29* (1988) 3219.
10 M. J. Abrams, D. A. Schwartz, M. M. Hauser, F. E. Gaul, J. A. Zubieta, S. K. Larsen, A. J. Fuccello, D. J. Riexinger and D. W. Jester, *Abstr., Society of Nuclear Medicine, 37th Meet., Washington, DC, June 19–22, 1990.*
11 T. Nicholson, N. deVries, A. Davison and A. G. Jones, *Inorg. Chem., 28* (1989) 3813.
12 D. Sutton, *Chem. Soc. Rev., 4* (1975) 443.
13 J. R. Dilworth, *Coord. Chem. Rev., 21* (1976) 29.
14 T. Nicholson and J. Zubieta, *Polyhedron, 7* (1988) 171, and refs. therein.
15 M. J. Abrams, S. K. Larsen, S. N. Shaikh and J. Zubieta, unpublished results.