Geometrically Controlled Selective Formation of Nitrido Technetium(V) Asymmetrical Heterocomplexes with Bidentate Ligands

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The search for stable coordination arrangements including technetium in various oxidation states continues to be an active field of research, particularly because of the prominent role still played by the γ-emitting radionuclide technetium-99m in diagnostic nuclear medicine.[1,2] This effort has recently received further impulse owing to the current needs to develop Tc-99m radiopharmaceuticals for monitoring receptor distributions in the central nervous system and in various tissues.[3,4] We report here an efficient procedure for the high-yield preparation of asymmetrical nitrido Tc(V) complexes comprising two different bidentate ligands that may be potentially relevant for the production of new Tc-99m radiopharmaceuticals with improved biological properties.

A common strategy for the design of receptor-specific Tc-99m agents is known as "bifunctional approach".[3,4] It consists of tethering a stable inorganic molecular fragment, containing the metal ion, to a biologically active molecule exhibiting a strong affinity for a specific receptor. A few years ago, we reported an improved procedure for preparing Tc-99m radiopharmaceuticals containing the terminal Tc≡N multiple bond, at tracer level (usually at μM concentrations) and in sterile and pyrogen-free conditions.[5−7] It was found that the resulting $[Tc^{V}{\equiv}N]^{2+}$ core could be viewed as a true inorganic functional group exhibiting a very high stability over a wide range of experimental conditions. Thus, it would be of interest to investigate the possibility of employing the chemistry of nitrido Tc(V) complexes for labeling bioactive molecules.

Generally, complexes containing the Tc≡N triple bond are characterized by a five-coordination arrangement of ligands determined by the strong trans-weakening exerted by the nitrido nitrogen group (N^{3-}).[8] Therefore, a plain strategy for linking a bioactive molecule to a $[Tc{\equiv}N]^{2+}$ core would require the design of a bifunctional ligand combining a tetradentate chelating system with the biological substrate. The metal ion could be, then, coordinated to the tetradentate chelating framework to afford the final conjugated complex. Though the outlined approach has been successfully applied to the isoelectronic $[Tc^{V}{=}O]^{3+}$ core,[1−4] previous studies demonstrated that coordination of a tetradentate ligand to a Tc≡N group is less favored than that of two separate bidentate ligands, presumably as a result of heavy sterical constrains imparted by the more demanding nitrido group.[9] Hence, a further possibility to include a biologically active molecule into a nitrido Tc(V) complex is offered by the formation of a disubstituted complex with two bidentate ligands. However, based on the *biological* requirement that only a *single* bioactive group has to be retained into the structure of the final complex to avoid strong alterations of the properties of the original biomolecule, it comes out that these two bidentate ligands should be necessarily *different*. In particular, this approach requires that the final *heterocomplex* must be composed of a $[Tc{\equiv}N]^{2+}$ core bound to a single *bifunctional* bidentate ligand carrying the bioactive group, and another *ancillary* ligand spanning the remaining two coordination positions of a five-coordination arrangement. Yet, the possibility of obtaining pure asymmetrical heterocomplexes when two different bidentate ligands are reacted with a Tc≡N group is not commonplace. For instance, when the size of the biomolecule is sufficiently small, it is obvious that coordination of two identical bifunctional ligands to the same Tc(V) center has to be expected. Previous attempts to obtain analogous disubstituted heterocomplexes with the isoelectronic $[Tc^{V}{=}O)]^{3+}$ core gave only poor results with production of unstable species in dynamic equilibrium with the corresponding symmetrical compounds composed of two identical bidentate ligands.[10,11]

A detailed investigation of the relationships occurring between the various geometries of five-coordinated nitrido Tc(V) complexes and the nature of the set of donor atoms bound to the metal center allowed an efficient procedure to be devised for the selective preparation of stable asymmetrical heterocomplexes. In a previous paper, we reported the synthesis of disubstituted nitrido Tc(V) complexes with phosphinethiol ligands (PSH) of the type $[Tc(N)(PS)_2]$.[12] The structural characterization of these complexes showed that they possess a trigonal-bipyramidal geometry where the two phosphorus atoms occupy the two apical sites, and the two sulfur atoms and the nitrido nitrogen atom are located on the equatorial plane. This type of geometry is uncommon for nitrido Tc(V) complexes, and never occurs with ligands having π-donors as coordinating atoms. In this latter situation, square-pyramidal geometry is preferred. We attributed these structural features to the strong preference of π-acceptor phosphorus atoms to achieve a reciprocal trans position as opposed to π-donor atoms which tend to assume a cis arrangement. PSH ligands were found to be very powerful coordinating agents toward the $[Tc^{V}{\equiv}N]^{2+}$ core. In square-pyramidal complexes, π-donor substituents were quantitatively removed by these ligands to yield the same $[Tc(N)(PS)_2]$ complexes. Thus, it may be concluded that a P_2S_2 arrangement of atoms, coordinated to a Tc≡N group in a trigonal-bipyramidal geometry, should be highly stable. Even though a nitrido Tc(V) complex with two bidentate ligands hardly would achieve a full trigonal-bipyramidal structure, this conclusion can be generalized to include all sets of two π-acceptor and two π-donor atoms.

In $[Tc(N)(PS)_2]$ complexes, the P and S atoms of the phosphinethiol ligands are joined together through an alkyl bridge. Thus, based on our above arguments, we speculated that by changing the connectivity between P and S atoms as illustrated in Scheme 1, it would be possible to produce asymmetrical complexes having

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Scheme 1

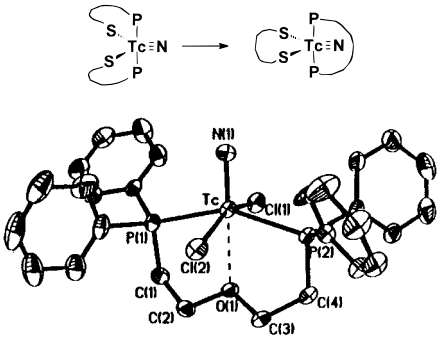

Figure 1. Molecular structure of the trans isomer of **1**. Selected distances (Å) and angles (deg): Tc−Cl1, 2.397(2); Tc−Cl2, 2.402(2); Tc−P(1), 2.424(2); Tc−P(2), 2.447(2); Tc−N(1), 1.665(5); Tc−O(1), 2.500(4); Cl(1)−Tc−Cl(2), 157.8(1); P(1)−Tc−P(2), 152.1(1); N(1)−Tc−O(1), 179.4(2).

a stability similar to that of the precursor compounds. Specifically, by linking separately the two P atoms and the two S atoms, the resulting heterocomplex [Tc(N)(P-P)(S-S)] would be composed by a diphosphine ligand (P-P) and a bidentate dithiol ligand (S-S) coordinated to a Tc≡N group. A far-reaching consequence of this conjecture implies that a highly acidic molecular fragment of the type $[Tc(N)(P\text{-}P)]^{2+}$, formed by a $[Tc{\equiv}N]^{2+}$ core bound to a diphosphine ligand, should exhibit a selective reactivity toward nucleophilic bidentate ligands (YZ) having π-donors as coordinating atoms. This leads to the prediction that there should exist a synthetic route to the selective preparation of the heterocomplexes [Tc(N)(P-P)(YZ)] through the reaction of the ligands P-P and YZ with a nitrido Tc(V) precursor, without the concomitant formation of the corresponding symmetrical species.

All our experimental results confirmed the proposed interpretation. A strong evidence of the tendency of π-acceptor atoms to achieve a trans position in nitrido Tc(V) complexes was obtained from the study of the complex $[Tc(N)(POP)Cl_2]$ (**1**) containing the diphosphine ligand $Ph_2\text{-}(CH_2)_2\text{-}O\text{-}(CH_2)_2\text{-}PPh_2$ (POP). This ligand was selected because of the backbone of five atoms connecting the two terminal phosphorus atoms, which was expected to have a length sufficiently long to avoid steric hindrance in attaining a final trans configuration. It was found that **1** occurs in two distinct isomeric forms differing in the relative cis or trans positions of the two phosphorus atoms of the POP ligand. The yellow cis isomer was isolated from the reaction of the ligand POP with the precursor complex $[Tc(N)Cl_2(PPh_3)_2]$. When dissolved in acetonitrile, this isomer irreversibly converted into the corresponding red-orange trans isomer.[13] These results were confirmed by the crystal structure determination of **1** (Figure 1), which definitely revealed the trans arrangement of the two phosphorus atoms.[14] A weak, nonbonding interaction occurring between the metal center and the oxygen atom of the POP ligand in the position trans to the Tc≡N group was responsible of the final geometry, which could be depicted as octahedrally distorted. The existence of this latter interaction cannot be considered to provide the main driving force for the transition from cis to trans configuration. This fact becomes more evident when the behavior of the complex $[Tc(N)(POP)Cl_2]$ is compared to that of the analogous complex $[Tc(N)(PNP)Cl_2]$ [PNP = $Ph_2P\text{-}(CH_2)_2\text{-}N(CH_2CH_2OCH_3)\text{-}(CH_2)_2\text{-}PPh_2$] (**2**). Indeed, characterization of this compound[13] showed that it remains blocked in the cis arrangement presumably as a consequence of the stronger trans interaction between the nitrogen atom of the PNP ligand and the Tc≡N group. Thus, conversion to the trans isomer is much more hampered than that for **1** and did not occur in solution. These results are consistent with a previously reported determination of the crystal structures of similar compounds[15] and were confirmed by quantum mechanical calculations carried out on complexes **1** and **2**.[16] It should be emphasized that previous structural data on nitrido Tc(V) complexes containing other phosphine ligands may be easily accounted for when viewed into the context of the interpretation proposed here. In particular, the crystal structures of the complexes $[Tc(N)Cl_2(PPh_3)_2]$,[17] $[Tc(N)(NCS)_2(CH_3CN)(PPh_3)_2]$,[18] and $[Tc(N)(P\text{-}P)Cl_2]$ {P-P = $Ph_2P\text{-}(CH_2)_2\text{-}O\text{-}(CH_2)_2\text{-}O\text{-}(CH_2)_2\text{-}PPh_2$, [1,8-bis(diphenylphosphino)-3,6-dioxaoctane]}[15] all revealed the trans arrangement of the two P atoms.

The reactivity of the cis and trans isomers of **1** and that of **2** toward bidentate π-donor ligands were investigated by conducting reactions with the species (OSH_2) 2-mercaptoethanol, mercaptoacetic acid, and 2-mercaptobenzoic acid having $[O^-, S^-]$ as a set of π-donor atoms. The trans isomer was found to be almost inert toward substitution of the two chloride atoms. This result may be attributed to the sterical shielding imparted on the incoming ligand by the specific configuration of the POP ligand as revealed by its crystal structure (Figure 1). In contrast, after mixing the cis isomer of **1** and complex **2** with OSH_2 ligands, the neutral asymmetrical heterocomplexes [Tc(N)(PXP)(OS)] (X = O, N) were isolated. The same products were also obtained by simple mixing of the ligands PXP and YZ in the presence of a nitrido Tc(V) precursor. Reactions were carried out both at the macroscopic level starting from $[Tc(N)Cl_2(PPh_3)_2]$ and at tracer level starting from $[^{99m}TcO_4]^-$ and using a well-established procedure for the preparation of the Tc≡N group in aqueous physiological solution.[5,7] In these experiments, it was not necessary to form separately the fragment $[Tc(N)(PXP)]^{2+}$ and then let it further react with a π-donating ligand. It appears, therefore, that the most salient feature of these procedures was that no production of the corresponding symmetrical complexes $[Tc(N)(OS)_2]^{2-}$ was detected under a very broad range of experimental conditions. With $[^{99m}TcO_4]^-$, it was possible to decrease the concentration of the reacting ligands from the mM to the μM range, thus giving rise to Tc-99m complexes in very high specific activity. Moreover, the use of different solvents and of a physiological solution did not affect the outcome of the reactions. It should be noted that similar heterocomplexes were also obtained using bidentate ligands having different pairs of coordinating atoms. These results will be described in a subsequent paper.

In conclusion, we outlined here an efficient route for introducing two different bidentate chelating ligands into a nitrido Tc(V) complex. This synthetic approach appears to be regulated by the strong tendency of the metal-containing fragment $[Tc(N)(P\text{-}P)]^{2+}$ to undergo a geometrical switching between the cis and trans arrangements of the two π-acceptor P atoms. This makes the cis isomer selectively activated *only* toward incoming bidentate π-donor ligands. The new procedure was also successfully applied, at tracer level, with the γ-emitting nuclide Tc-99m, and may be, therefore, potentially useful for the development of Tc-99m radiopharmaceuticals incorporating biologically active molecules.

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Supporting Information Available: Experimental details for $[Tc(N)(POP)Cl_2]$, $[Tc(N)(PNP)Cl_2]$, [Tc(N)(POP)(OS)], and [Tc(N)(PNP)(OS)] [OSH_2 = 2-mercaptoethanol ($OS1H_2$), mercaptoacetic acid ($OS2H_2$), and 2-mercaptobenzoic acid ($OS3H_2$)], including preparation at the carrier-free level with Tc-99m (PDF). An X-ray crystallographic file (CIF) for the crystal structure determination of *trans*-$[Tc(N)(POP)Cl_2]$. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) See Supporting Information.

(14) Crystal data: *trans*-$C_{28}H_{28}NOP_2Cl_2Tc$, MW = 625.9, red crystals, orthorombic, *Pbca*, a = 20.049(6) Å, b = 13.635(3) Å, c = 20.125 Å, V = 5502(3) Å^3, T = 293(2) K, Z = 8, $R1$ = 0.045, $wR2$ = 0.097 ($I \geq 2\sigma(I)$), and GOF = 1.036.

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