Formation of the Tc≡N Multiple Bond from the Reaction of Ammonium Pertechnetate with *S*-Methyl Dithiocarbazate and its Application to the Preparation of Technetium-99m Radiopharmaceuticals†

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The reaction of pertechnetate with the *S*-methyl ester of dithiocarbazic acid, $H_2N–NR–C(=S)SCH_3$ (R = H or CH_3), in the presence of HCl and triphenylphosphine, affords the technetium(v) nitrido complex $[TcNCl_2(PPh_3)_2]$ in high yield. Derivatives of *S*-methyl dithiocarbazate of the type $R^1(R^2)C=N–NR^3–C(=S)SCH_3$, where R^1 = *o*-C_6H_4OH, C_6H_5, or CH_3, R^2 = H or CH_3, and R^3 = H or CH_3, behave as sources of N^{3-} groups, giving rise to a variety of technetium complexes containing the Tc≡N multiple bond. These reactions apply equally well to the preparation of technetium-99m radiopharmaceuticals containing the Tc≡N group, at the non-carrier-added level of nuclear medicine.

We recently described the synthesis of technetium(v) nitrido[1] and oxo[2] complexes with Schiff bases derived from the *S*-methyl ester of dithiocarbazic acid, $H_2N–NR–C(=S)SCH_3$ (R = H or CH_3). These two classes of compounds were prepared, respectively, by reaction of the complexes $[TcNCl_2(PPh_3)_2]$ and $[TcOCl_4]^-$ with the appropriate Schiff base, and are characterized by a square-pyramidal structure with the TcX (X = N or O) group in an apical position.

In our first studies the two classes of complexes appeared well separated, and we did not identify any feasible chemical route to their interconversion. However, in attempting to transfer this chemistry to the preparation of new ^{99m}Tc radiopharmaceuticals, we carried out the reactions with the derivatives of dithiocarbazic acid starting from ammonium pertechnetate in the presence of HCl and PPh_3. The results of this investigation revealed that the technetium(v) nitrido complexes were the final products of a stepwise reaction, transforming $[TcO_4]^-$ primarily into a mono-oxotechnetium(v) complex which, afterwards, changed into the corresponding nitrido species. Hence, we attributed these results to the property of the derivatives of dithiocarbazic acid to behave both as co-ordinating ligands and as sources of nitride-nitrogen atoms, a fact never observed before.

We report here the description of this new synthetic route for the preparation of the Tc≡N multiple bond, and compare it with the previously reported methods;[3–5] we will also describe how this new synthetic approach can be applied very efficiently to the production of ^{99m}Tc radiopharmaceuticals containing the Tc≡N group at the non-carrier-added (n.c.a.) level of nuclear medicine, a result that had not yet been completely achieved in ^{99m}Tc radiopharmaceutical chemistry.

Results and Discussion

All the complexes have been characterized by elemental analyses of C, H, N, S, and Tc (Table 1), and by comparison of their i.r. spectra with those reported in the literature for the same compounds (Table 2).[1–4]

The ligands (L) derived from the *S*-methyl ester of dithiocarbazic acid, were utilized in the general reaction (1). For the purpose of discussion, it is convenient to classify these ligands into three categories resulting from the possible existence of an equilibrium between the thione and thiol forms

$$[TcO_4]^- + L + HCl + PPh_3 \longrightarrow TcN\ complexes \quad (1)$$

Table 1. Elemental analyses (%) for the complexes (calculated values in parentheses)

Complex	C	H	N	S	Tc
$[TcO(L^{3a})Cl]$	29.1	2.4	7.8	16.5	25.9
	(28.8)	(2.1)	(7.4)	(17.0)	(26.4)
$[TcO(L^{3b})Cl]$	31.4	2.8	7.6	16.2	25.1
	(30.9)	(2.6)	(7.2)	(16.5)	(25.5)
$[TcN(L^{3a})(PPh_3)]$	53.9	3.6	7.1	11.0	16.8
	(54.1)	(3.9)	(7.0)	(10.5)	(16.5)
$[TcN(L^{3b})(PPh_3)]$	54.4	4.8	6.8	10.8	16.3
	(54.8)	(4.1)	(6.8)	(10.5)	(16.1)
$[TcN(L^{2a})_2]$	41.1	3.2	13.7	23.6	18.2
	(40.7)	(3.4)	(13.2)	(24.1)	(18.6)
$[TcN(L^{2b})_2]$	27.3	4.9	16.2	28.7	23.2
	(27.6)	(4.1)	(16.1)	(29.4)	(22.7)
$[TcNCl_2(PPh_3)_2]$	61.3	4.3	1.9		14.5
	(61.0)	(4.3)	(2.0)		(14.0)
$[ReNCl_2(PPh_3)_2]$	54.7	3.6	1.8		
	(54.3)	(3.8)	(1.8)		

Table 2. I.r. (cm^{-1}) data for the complexes

Complex	ν(C=N)	ν(Tc=N)	ν(Tc=O)
$[TcO(L^{3a})Cl]$	1 600		985
$[TcO(L^{3b})Cl]$	1 595		980
$[TcN(L^{3a})(PPh_3)]$	1 600	1 060	
$[TcN(L^{3b})(PPh_3)]$	1 590	1 065	
$[TcN(L^{2a})_2]$	1 580	1 075	
$[TcN(L^{2b})_2]$	1 590	1 070	

† A preliminary account of this work has been presented to the 3rd Symposium on Technetium in Chemistry and in Nuclear Medicine, Montegrotto, September 1989.

$R^1(R^2)C{=}N{-}NH{-}C(=S)SCH_3$

H_2L^{3a} $R^1 = o\text{-}C_6H_4OH$, $R^2 = H$
H_2L^{3b} $R^1 = o\text{-}C_6H_4OH$, $R^2 = CH_3$

$R^3(R^4)C{=}N{-}N(R^5){-}C(=S)SCH_3$

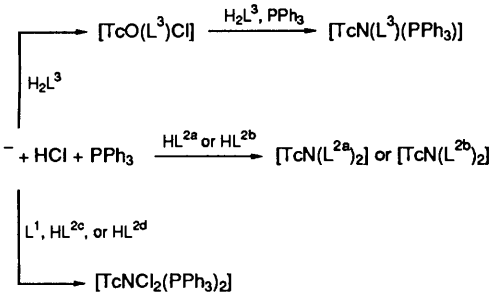
HL^{2a} $R^3 = C_6H_5$, $R^4 = H$, $R^5 = H$
HL^{2b} $R^3 = CH_3$, $R^4 = CH_3$, $R^5 = H$
HL^{2c} $R^3 = o\text{-}C_6H_4OH$, $R^4 = H$, $R^5 = CH_3$
HL^{2d} $NH_2{-}NH{-}C(=S)SCH_3$

$R^6(R^7)C{=}N{-}N(CH_3){-}C(=S)SCH_3$

L^{1a} $R^6 = C_6H_5$, $R^7 = H$
L^{1b} $NH_2{-}N(CH_3){-}C(=S)SCH_3$

$$R(R')C{=}N{-}NH{-}C(=S)SCH_3 \rightleftharpoons R(R')C{=}N{-}N{=}C(SH)SCH_3$$

in solution: (*a*) tridentate dianionic ligands (H_2L^3); (*b*) bidentate monoanionic ligands (HL^2); and (*c*) monodentate neutral ligands (L^1). In participating in reaction (1), each class of ligands gives rise to its own type of final complexes which, in all cases, contain the $[Tc{\equiv}N]^{2+}$ core. These reactions are summarized in the Scheme.



Scheme.

Two steps in reaction (1) were observed when the tridentate H_2L^3 ligands reacted with pertechnetate, depending on the $H_2L^3/[TcO_4]^- = A$ and $PPh_3/[TcO_4]^- = B$ stoicheiometric ratios, and setting constant the $HCl/[TcO_4]^- = C$ stoicheiometric ratio (see Experimental section). Using a value of $A = 2$ and of $B = 4$, the square-pyramidal mono-oxo-complexes $[TcO(L^3)Cl]$ were obtained in 70% yield. These compounds have been already prepared through a different synthetic route, and are characterized by a square-pyramidal structure with the Tc=O group in an apical position; the tridentate dianionic L^3 ligand spans three positions in the plane normal to the Tc=O through the charged phenolic oxygen atom, the neutral β-nitrogen atom, and the charged thiol sulphur atom, the fourth site on that plane being occupied by a chlorine atom.[2] Lowering the values of A and B greatly decreased the yield in mono-oxo complexes. However, a similar reduction in the yield of $[TcO(L^3)Cl]$ was observed by increasing the values of both A and B, a fact that was quickly found to be due to the formation, in the same reaction, of the technetium(v) nitrido species $[TcN(L^3)(PPh_3)]$. Also these latter complexes have been previously reported, and the determination of their molecular structure showed that they are square pyramidal with the Tc≡N group in an apical position; the L^3 ligand is co-ordinated in the plane normal to the Tc≡N in the same way as in the corresponding mono-oxo complexes, the fourth basal position being occupied by a PPh_3 group.[1] These results could easily be accounted for by admitting that the nitrido complexes were the final products of a stepwise reaction, leading first to the square-pyramidal mono-oxo species $[TcO(L^3)Cl]$, which, successively, turned into the square-pyramidal nitrido complexes $[TcN(L^3)(PPh_3)]$ by substitution of the oxo and chlorine atoms by the N^{3-} and PPh_3 groups, respectively (see Scheme). This conjecture was further supported by the observation that the complexes $[TcO(L^3)Cl]$ reacted, in ethanol, with excess of H_2L^3, in the presence of PPh_3, to give the corresponding nitrido complexes $[TcN(L^3)(PPh_3)]$ (see Experimental section). Evidently, the H_2L^3 derivatives play, in reaction (1), both the role of co-ordinating ligands and of N^{3-} donors, while the presence of triphenylphosphine appears to be fundamental for obtaining the reduced $[Tc^V{\equiv}N]^{2+}$ group starting from pertechnetate.

Using the bidentate HL^{2a} and HL^{2b} ligands, no mono-oxo complexes have been isolated through reaction (1), whatever the values of A and B (different from zero), C being constant. The final products were invariably the disubstituted nitrido complexes $[TcN(L)_2]$ (L = L^{2a} or L^{2b}), which we have already described to possess a square-pyramidal structure with the Tc≡N group in an apical position, and the two bidentate ligands occupying the four basal positions through the neutral β-nitrogen atom and the charged thiol sulphur atom.[1] When $B \geqslant 4$ the yields of the final compounds were found to depend strongly upon the ligand excess.

The monodentate L^1 ligands and the ligands HL^{2c} and HL^{2d} gave rise, through reaction (1), to the well characterized technetium(v) nitrido complex $[TcNCl_2(PPh_3)_2]$.[3] These ligands, therefore, behaved only as sources of N^{3-} groups, without producing any substituted compound. The same results were obtained by carrying out reaction (1) with L^1 and HL^{2c} or HL^{2d} ligands using perrhenate, $[ReO_4]^-$, as starting material: we found that the final product was, in all cases, the analogous rhenium(v) nitrido complex $[ReNCl_2(PPh_3)_2]$.[4]

The spectroscopic properties (Table 2) of the compounds prepared in this study are in close agreement with those reported in the literature for the same type of complexes,[1-4] and will not be discussed further here.

The formation of the M≡N (M = Tc or Re) multiple bond in reaction (1) appears somewhat unexpected. Reactions of complexes of Cr, Mo, Mn, Re, Fe, Co, Ni, Pd, Pt, Cu, Zn, Cd, and Pb with ligands similar to those utilized in this study have been previously investigated.[6] Both metal chelates or mono- and dinuclear complexes with linear diazenido and N,S-chelating hydrazido-(1−) or -(3−) ligands derived from *S*-methyl dithiocarbazate were obtained, but the formation of nitrido species was not detected. The present work, therefore, reports the first observation of the N^{3-}-donor behaviour of these ligands with transition metals, and points out reaction (1) as a new alternative method for the synthesis of the M≡N multiple bond for technetium and rhenium.

Only two methods for the preparation of the M≡N (M = Tc or Re) bond have been proposed before, which uses sodium azide and hydrazine as sources of N^{3-} groups.[3-5] The alternative method described here appears more efficient, considering that the formation of the metal–nitrogen multiple bond takes place in high yield, at room temperature and under mild conditions (see Experimental section). This has to be compared with the relatively more drastic conditions required by the two methods cited above, and is probably due to the presence of very suitable leaving groups on the hydrazine-like >N–N< functional moiety, which permit easy generation of the nitride ion. However, the role played by the metal in the reaction is not completely understood; in particular, it has not been definitively established whether the ability of the derivatives of dithiocarbazic acid to generate N^{3-} ions is limited to reactions involving technetium and rhenium complexes, or might be observed also with other metals.

Table 3. Chromatography

Complex	R_f (reversed phase)
$[^{99/99m}TcO(L^{3a})Cl]$	0.60
$[^{99/99m}TcO(L^{3b})Cl]$	0.67
$[^{99/99m}TcN(L^{3a})(PPh_3)]$	0.23, 0.53,[a] 0.81[b]
$[^{99/99m}TcN(L^{3b})(PPh_3)]$	0.28
$[^{99/99m}TcN(L^{2a})_2]$	0.38
$[^{99/99m}TcN(L^{2b})_2]$	0.36
$[^{99/99m}TcNCl_2(PPh_3)_2]$	0.63—0.80[c]
$[^{99/99m}TcN(L^4)_2]$	0.95[d]
$[^{99/99m}TcN(L^5)Cl]^+$	0.20

[a] Silica gel (eluant toluene). [b] Cellulose [eluant EtOH–water–0.5 mol dm^{-3} ammonium acetate (4:2:1)]. [c] Tailed. [d] Silica gel [eluant EtOH–$CHCl_3$–toluene–0.5 mol dm^{-3} ammonium acetate (6:3:3:1)].

Radiopharmaceutical Development.—The most important application of the synthesis of the Tc≡N group reported here would be in the field of nuclear medicine, as a consequence of the widespread use of compounds of the γ-emitting metastable isomer ^{99m}Tc as imaging agents.[7] Recently, Baldas and Bonnyman[8] proposed a method for preparing the Tc≡N group at the non-carrier-added (n.c.a.) level, based on the reaction scheme (2). This method requires the evaporation, at reduced

$$[^{99m}TcO_4]^- + HCl + NaN_3 \xrightarrow{heat} [^{99m}TcNCl_4]^- \xrightarrow{ligand} {}^{99m}TcN \text{ complexes} \quad (2)$$

pressure, of both the starting aqueous solution of pertechnetate before the addition of HCl and NaN_3, and then the solution containing the intermediate species $[^{99m}TcNCl_4]^-$ before the addition of the ligand; such a procedure, however, does not appear to be completely applicable to diagnostic nuclear medicine because it does not permit careful control of the sterility and apyrogenicity of the radiopharmaceutical preparation.

The new synthetic approach for preparing the Tc≡N group discussed here is perfectly transferable to the n.c.a. level, and avoids all problems associated with the Baldas procedure. This was demonstrated by comparing the chromatographic behaviour of the products, prepared in milligram amount at the carrier added (c.a.) level through reaction (1), and whose characterization and molecular structure we have discussed above, with that of the products obtained through the same reaction at the n.c.a. level (Table 3).

The first comparison was made to verify, at the n.c.a. level, the course of the reactions illustrated in the Scheme. The chromatographic R_f values (Table 3) showed that, using H_2L^3 ligands, no intermediate mono-oxo complexes of the type $[^{99m}TcO(L^3)Cl]$ could be obtained, the only products being the technetium(v) nitrido complexes $[^{99m}TcN(L^3)(PPh_3)]$. This is likely due to the very large excess of the ligand and PPh_3 used in the radiopharmaceutical preparation. The nitrido complexes, instead, are easily obtained by adding to a physiological solution containing $[^{99m}TcO_4]^-$, taken from the $^{99}Mo/^{99m}Tc$ generator, an excess of H_2L^3 and PPh_3 in ethanol (see Experimental section). Similar results were observed using the bidentate ligands HL^{2a} and HL^{2b}: the n.c.a. preparation produced the complexes $[^{99m}TcN(L)_2]$ (L = L^{2a} or L^{2b}), the identity of which was confirmed by comparing their R_f values with those of the corresponding complexes prepared at the c.a. level (Table 3).

A more complicated situation arises when the monodentate L^1 ligands and the ligands HL^{2c} and HL^{2d} are used; while at the c.a. level the isolated product was always the complex $[TcNCl_2(PPh_3)_2]$ (see above), the chromatographic characterization showed that the n.c.a. preparation led to a mixture of products, as indicated by the tailed distribution of the R_f values. However, we found that, by adding to the same reaction vial containing such a mixture an excess of a tridentate H_2L^3 ligand, only one product was finally obtained in 98% yield, corresponding to the complex $[^{99m}TcN(L^3)(PPh_3)]$. This suggested that the mixture is composed of a number of complexes all possessing the Tc≡N group, which react in a similar manner with the tridentate H_2L^3 ligands, giving rise to the same final TcN complex.

In order to give further support to this hypothesis, we performed a second series of n.c.a. preparations based on the reaction scheme (3). In reaction (3), by $[^{99m}TcN]_{int}$ we mean the

$$[^{99m}TcO_4]^- + L^1(HL^{2c} \text{ or } HL^{2d}) + HCl + PPh_3 \longrightarrow [^{99m}TcN]_{int} \xrightarrow{ligand} {}^{99m}TcN \text{ complex} \quad (3)$$

supposed mixture of the intermediate TcN complexes produced using L^1 and HL^{2c} or HL^{2d} ligands. By further addition of an appropriate ligand to the same reaction solution containing the $[^{99m}TcN]_{int}$ species the final ^{99m}TcN complex can be obtained. The ligands HL^4 = 8-quinolinethiol (C_9H_7NS) and L^5 = 4,7,diazadecane-1,10-diamine $[H_2N(CH_2)_3NH(CH_2)_2NH(CH_2)_3NH_2]$ were used, in reaction (3), as exchanging ligands because they give rise, at the macroscopic c.a. level, to the well characterized technetium(v) nitrido complexes $[TcN(L^4)_2]$[9] and $[TcN(L^5)Cl]^+$,[10] respectively. We found that, in these two cases, the chromatographic R_f values of the products, prepared in high yields (98% for L^4, 70% for L^5) at the n.c.a. level through reaction (3), were identical to those corresponding to the complexes $[TcN(L^4)_2]$ and $[TcN(L^5)Cl]^+$ prepared at the c.a. level, These results both indicate that the two ^{99m}Tc compounds, obtained at the n.c.a. level with the ligands L^4 and L^5, are identical to those prepared in macroscopic amount, and give strong support to the conjecture that the $[^{99m}TcN]_{int}$ mixture is formed by complexes all having the Tc≡N group.

Conclusion

While the new method for producing the M≡N (M = Tc or Re) group presented here may constitute an alternative route to the previously reported methods generally used for the development of this chemistry in macroscopic amounts, presently it appears as the only efficient procedure for preparing, in microscopic amounts, ^{99m}Tc radiocompounds containing the Tc≡N multiple bond. In particular, this procedure meets all the requirements of sterility and apyrogenicity, which must be satisfied for a radiopharmaceutical preparation to be utilized in humans, a result that may permit an approach to a completely new class of ^{99m}Tc-based diagnostic agents.

Experimental

Materials.—Technetium-99 is a weak β emitter (0.292 MeV, *ca.* 4.67×10^{-17} J, $t_{\frac{1}{2}} = 2.12 \times 10^5$ years). All manipulations should be carried out in a laboratory equipped with monitored fumehoods and glove-boxes. Normal laboratory glassware is sufficient to stop virtually all the β emission from the sample; however, concentrated samples of over 0.7 mCi cm^{-3} can produce small amounts of Bremsstrahlung from the action of β particles on the glass. Technetium-99m is a γ emitter (142 keV, $t_{\frac{1}{2}} = 6.02$ h). All preparations carried out with this nuclide were conducted in a sealed vial successively stored in a lead container, while all manipulations were performed using a lead shield.

All common laboratory chemicals were reagent grade. Technetium-99, as $[NH_4][^{99}TcO_4]$ in 0.1 mol dm^{-3} ammonia solutions, was supplied by the Radiochemical Centre, Amersham. Solid samples of this salt were obtained by taking to dryness, under reduced pressure, small portions (4—10 cm^3) of its ammonia solutions. Technetium-99m, as $Na[^{99m}TcO_4]$, was obtained from a $^{99}Mo/^{99m}Tc$ Elumatic isotopic generator purchased from ORIS Industrie S.A. The salt $[NBu^n_4][ReO_4]$ was purchased from Aldrich-Chemie. The ligands illustrated were prepared by literature methods.[1,2,6] 8-Quinolinethiol hydrochloride and 4,7-diazadecane-1,10-diamine were obtained from Fluka Chemie.

Instrumentation and Methods.—I.r. spectra were recorded on a Perkin-Elmer 599 grating spectrometer using KBr pellets. Elemental analyses were performed on a model 1106 Carlo Erba elemental analyzer; the elemental analyses for radioactive technetium were carried out on a Packard liquid-scintillation instrument, model TRICARB 300C, with Insta-gel as scintillator, after dissolution of the samples in hydrogen peroxide–nitric acid solutions.

To establish the equivalence of the chemistry occurring at ^{99}Tc (*ca.* 10^{-4} mol dm^{-3}) and at non-carrier added (n.c.a.) ^{99m}Tc ($\leqslant 10^{-8}$ mol dm^{-3}) concentrations, $[^{99m}TcO_4]^-$ was added as a tracer in order to follow the course of the reaction radiometrically. A typical carrier-added (c.a.) synthesis involved combining solid $[NH_4][^{99}TcO_4]$ and $Na[^{99m}TcO_4]$ in saline followed by the addition of the reagents as described below. The radiochemical purity and yields of the products prepared at the n.c.a. level were determined by reversed-phase thin-layer chromatography (t.l.c.) using Whatman RP-18 plates developed with CH_3OH–CH_3CN–thf–0.5 mol dm^{-3} ammonium acetate (pH 7.0) (3:3:2:2). Radioactivity profiles were quantitated using a linear scanner fitted with a sodium iodide detector.[11] The R_f values obtained in this way were then compared with those determined for c.a. preparations through the same chromatographic procedure.

Synthesis of the Complexes.—$[TcO(L^3)Cl]$ (L^3 = *tridentate ligand*). To a stirred solution of $[NH_4][TcO_4]$ (4.0 cm^3, 0.34 mol dm^{-3}, 1.36 mmol), the appropriate ligand (2.72 mmol), dissolved in ethanol (5 cm^3), was added at room temperature, followed by 12 mol dm^{-3} hydrochloric acid (32 cm^3) and triphenylphosphine (1.4 g, 5.44 mmol) dissolved in hot ethanol (10 cm^3). After 15 min a red precipitate began to form, and the precipitation was favoured by adding isopropyl alcohol (10 cm^3). The stirring was continued for 30 min, and then the solid was filtered off and washed with hot ethanol and diethyl ether. Recrystallization was from methylene chloride and ethanol. The yields were about 70%; however, they were found to be dependent upon the $H_2L^3/[TcO_4]^- = A$ and $PPh_3/[TcO_4]^- = B$ stoicheiometric ratios. When $A < 2$ and $B < 4$, variable amounts of the complexes $[TcCl_6]^{2-}$ and $[TcCl_4(PPh_3)_2]$ were isolated, together with $[TcO(L^3)Cl]$; when $A > 2$ and $B > 4$, it was possible to recover, from the mother-liquors of the reaction solution, increasing amounts of the nitrido complex $[TcN(L^3)(PPh_3)]$, whose preparation is described below.

$[TcN(L^3)(PPh_3)]$, $[TcN(L^2)_2]$ [L^3 = *tridentate ligand* (L^{3a} *or* L^{3b}), L^2 = *bidentate ligand* (L^{2a} *or* L^{2b})]. To a stirred solution of $[NH_4][TcO_4]$ (4.0 cm^3, 0.34 mol dm^{-3}, 1.36 mmol), the appropriate ligand (5.44 mmol), dissolved in ethanol (10 cm^3), was added at room temperature, followed by 12 mol dm^{-3} hydrochloric acid (32 cm^3). The resulting solution was heated to 70 °C, and triphenylphosphine (2.1 g, 8.01 mmol), dissolved in hot ethanol (10 cm^3), was added. The solution was refluxed for 30 min and its colour became yellow. Evaporation under reduced pressure gave a light yellow residue, which was washed with hot ethanol and diethyl ether. Recrystallization was from methylene chloride–ethanol to yield yellow crystals of the final product. Yield > 90%.

The complexes $[TcN(L^3)(PPh_3)]$ were also obtained by mixing, in refluxing ethanol for 15 min, the corresponding mono-oxo complexes $[TcO(L^3)Cl]$ with excess of H_2L^3 and triphenylphosphine. The resulting yellow solution was treated as described above to isolate the final products in 95% yield. The same procedure was not applied to the synthesis of the complexes $[TcN(L)_2]$ ($L = L^{2a}$ or L^{2b}), owing to the failure to obtain the corresponding mono-oxo species.

$[MNCl_2(PPh_3)_2]$ (M = Tc *or* Re). To a stirred solution of $[NH_4][TcO_4]$ (4.0 cm^3, 0.34 mol dm^{-3}, 1.36 mmol), or $[NBu^n_4][ReO_4]$ (20 cm^3, 0.67 g, 1.36 mmol) in ethanol, the appropriate L^1, HL^{2c}, or HL^{2d} ligand (4.08 mmol), dissolved in ethanol (10 cm^3), was added at room temperature, followed by 12 mol dm^{-3} hydrochloric acid (32 cm^3). The solution became deep red, and triphenylphosphine (2.1 g, 8.01 mmol), dissolved in hot ethanol (10 cm^3), was added. After 15 min of stirring, at room temperature for Tc and at 40 °C for Re, the precipitate was filtered off and washed with hot ethanol, acetone and diethyl ether. Yield > 95%.

Radiopharmaceutical Preparations.—A typical n.c.a. synthesis was carried out as follows: an ethanolic solution (0.4 cm^3, 2.0×10^{-2} mol dm^{-3}) of the appropriate ligand ($L = H_2L^3$, HL^2, or L^1), 1.0 mol dm^{-3} HCl (0.10 cm^3), and an ethanolic solution (0.20 cm^3, 2.0×10^{-2} mol dm^{-3}) of triphenylphosphine were added to a reaction vial. To this mixture $Na[^{99m}TcO_4]$ (0.50—1.0 cm^3, 10^{-9}—10^{-11} mol of ^{99m}Tc corresponding to an activity ranging between 18 MBq and 3.7 GBq), taken from the generator, was added. The vial was then sealed and the temperature raised to 80 °C for 30 min in a water-bath. After cooling the reaction solution, small portions (*ca.* 10^{-5} dm^3) of it were taken away for chromatographic analysis. The yields were always up to 98% based on the total activity.[12]

Exchange Reactions.—After completion of the procedure outlined above for preparing the intermediate ^{99m}TcN complexes, the exchange of the ligands co-ordinated to the Tc≡N group was carried out as follows: a 0.5 mol dm^{-3} HCO_3^-–CO_3^{2-} buffer (0.5 cm^3) was added to the same reaction vial containing the ^{99m}TcN species to adjust the pH to 9.5, followed by an ethanolic solution (0.4 cm^3, 6.0×10^{-2} mol dm^{-3}) of the ligand L^4 or L^5. The temperature was raised to 80 °C for 10 min in a water-bath to obtain the final product. The yield was 95% for L^4 and 70% for L^5. The chromatographic analysis showed that the two products prepared with the ligands L^4 and L^5 could be formulated as $[TcN(L^4)_2]$ and $[TcN(L^5)Cl]^+$, respectively.

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