Synthesis and Characterization of the New Neutral Myocardial Imaging Agent [^{99m}TcN(noet)$_2$] (noet = *N*-Ethyl-*N*-ethoxydithiocarbamato)

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The synthesis, characterization and electrochemical behaviour of neutral [TcN(noet)$_2$] [noet = Et(EtO)N–CS_2^-], the first technetium(v) nitrido complex currently under preliminary clinical evaluation for myocardial perfusion, are reported.

A number of complexes of the γ-emitting nuclear isomer ^{99m}Tc (E_γ = 142 keV, $t_{\frac{1}{2}}$ = 6.02 h) containing the $[Tc{=}O]^{3+}$ core have proved useful in diagnostic nuclear medicine as perfusion imaging agents.[1] Presently, no technetium-99m complexes containing the isoelectronic $[Tc{\equiv}N]^{2+}$ core and having useful imaging properties have been reported, probably owing to the lack of a convenient synthesis of the Tc≡N multiple bond at tracer level. Recently, we described a new, efficient method for preparing the Tc≡N group, at tracer level, in sterile and apyrogen conditions.[2] We applied this method to the preparation of technetium(v) nitrido complexes with dithiocarbamato ligands of general formula $R^1(R^2)N{-}CS_2^-$, and we discovered that the resulting products [^{99m}TcN{$R^1(R^2)N{-}CS_2$}$_2$] showed high myocardial uptakes in various animal models and in humans.[3] In particular, the derivative [^{99m}TcN{Et(EtO)N–CS_2}$_2$] [^{99m}TcN(noet)$_2$] exhibited more favourable imaging properties for its application to nuclear medicine. This complex therefore constitutes the first reported example of a technetium-99m myocardial imaging agent containing the Tc≡N group. We report here the synthesis and characterization of this new ^{99m}Tc radiopharmaceutical on a millimolar level, and its electrochemical behaviour in solution. These data are of primary importance in order to understand the structure–biodistribution relationship of this type of complexes.

The complex [TcN(noet)$_2$] was prepared at tracer level (10^{-9}–10^{-11} mol dm^{-3} of ^{99m}Tc) and at a millimolar level (10^{-3} mol dm^{-3} of ^{99}Tc) using the procedure in eqns. (1) and (2).† The synthesis was carried out in H_2O–EtOH (8:1). At tracer level, the nature of the intermediate species [^{99m}TcN]$_{int}$ was not identified, while at a millimolar level this was found to be the complex [$TcNCl_2(PPh_3)_2$]. However, after neutralization, addition of the ligand to the same reaction solution containing the technetium nitrido intermediate led to the formation of the same final complex [TcN{Et(EtO)N–CS_2}$_2$] in both cases. This synthesis is probably a rare example of a reaction producing the same technetium complex at two very different concentration scales. At a millimolar level, the complex [TcN{Et(EtO)N–CS_2}$_2$] was obtained as a yellow powder, which was recrystallized from CH_2Cl_2–EtOH to give pale yellow crystals (yield 82% based on ^{99}Tc). A crystal of the compound suitable for X-ray crystallography was obtained.[4] Its crystal structure is similar to that reported for the complex [$TcN(Et_2N{-}CS_2)_2$][5] and details will be reported elsewhere. The compound has a square-pyramidal geometry with an apical TC≡N bond and two monoanionic dithiocarbamate ligands spanning the four positions in the basal plane through the four sulfur atoms. The equivalence between the isolated

† ^{99}Tc is a low β-emitter (0.292 MeV) with half-life of 2.12×10^5 years. When this material is handled in milligrams amounts, it does not present a serious health hazard since common laboratory materials provide adequate shielding. However, all manipulations must be carried out in a laboratory approved for low level radioactivity, with monitored hoods and glove boxes.

complex [^{99}TcN{Et(EtO)N–CS_2}$_2$] and that prepared at tracer level was established by TLC and reverse phase HPLC using EtOH–MeCN–tetrahydrofuran–$AcONH_4$ (pH 7.0; 0.5 mol dm^{-3}) (3 : 3 : 2 : 2) as mobile phase.

$$[TcO_4]^- + HCl + PPh_3 + H_2N\text{–}N(Me)\text{–}C(=S)SMe \rightarrow [TcN]_{int} \quad (1)$$

$$[TcN]_{int} + [Et(EtO)N\text{–}CS_2]Na \rightarrow [TcN\{Et(EtO)N\text{–}CS_2\}_2] \quad (2)$$

The neutral compound [TcN(noet)$_2$] showed high myocardial uptake in humans (*ca.* 3.5% of injected dose) and slow heart clearance. This behaviour contrasts with that predicted by Deutsch, who suggested that only technetium complexes carrying a positive net charge could localize in myocardium tissue for a prolonged time.[6] This conjecture was supported by the finding that various monocationic complexes became fixed in myocardium cells,[7] and that, although neutral seven-coordinate ^{99m}Tc–bato complexes (boronic acid adducts of technetium dioxime complexes)[8] were efficiently extracted by the heart, they were, however, rapidly eliminated from that region within few minutes. In order to investigate the possibility that some oxidation of [TcN(noet)$_2$] may occur under physiological conditions so as to impart a positive net charge to the complex, we carried out cyclic voltammetric measurements of MeCN solutions of this complex. The results revealed that no oxidation or reduction took place in the interval +1.225 to −1.75 V (*vs.* saturated sodium calomel electrode). An irreversible two-electron oxidation occurred at −1.225 V. This value is far from the accessible range of biological potentials, a fact which seems to indicate that, under physiological conditions [TcN(noet)$_2$] should behave as a neutral species.

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