# Development of $^{99m}Tc$ Heart Imaging Agents

Mark A. Massa Literature Seminar October 26, 1989

The first artificially produced element, technetium, was identified by Perrier and Segré in 1937 [1]. None of its 21 known isotopes is stable on a geological time scale, and this is in part due to the stability of neighboring Mo and Ru isotopes in the same mass range [2]. Only the low radiation β emitting isotope $^{99}Tc$, which must be handled with special precautions [3], can be isolated on a weighable scale. Relatively little is known about the chemistry of Tc, but within the last decade, interest has grown dramatically due to the element's increased availability and more importantly its use in nuclear medicine [4]. The isotope $^{99m}Tc$ has ideal properties for imaging internal organs and now accounts for approximately 80 % of diagnostic radioimaging procedures [5]. As a consequence, a major focus of Tc chemistry is to develop complexes that localize in various organs which then can be imaged by scintillation cameras. Of the major organs, only the heart does not have a clinically useful $^{99m}Tc$ radiopharmaceutical agent. This seminar reviews research aimed at developing $^{99m}Tc$ reagents to replace the current agent of choice, $^{201}Tl^+$ [3a].

In comparison to the other Group VIIA elements, Tc most closely resembles Re with $TcO_4^-$ being a much milder oxidant than $MnO_4^-$ and only slightly stronger than $ReO_4^-$ [2]. Medically useful Tc complexes must be soluble in water and are known in oxidation states ranging from +1 to +7 [3a].

One of the first cationic Tc complexes examined for heart imaging was $[Tc(o\text{-}C_6H_4(AsMe_2)_2)_2Cl_2]^+$, (Figure 1). While this agent does localize in the heart, it is of limited use clinically due to its insolubility in water [6]. A similar complex, $[Tc(DMPE)_2Cl_2]^+$, was the first heart imaging agent evaluated in man. This complex is synthesized by the reaction of $TcO_4^-$ with HCl followed by the addition of 1,2-bis(dimethylphosphino)ethane (DMPE). Unforunately, this complex is reduced in vivo to the neutral Tc(II) complex, which does not accumulate in the heart [8]. Schiff base complexes of Tc(III) have been prepared which are not reduced in the redox range of biological systems, and these complexes have been evaluated on humans with some success [9]. Recently developed complexes of the formula, $[Tc(DMPE)_2(SR)_2]^+$, (Figure 2), with both alkyl and aryl substituents have been investigated electrochemically in order to elucidate those factors which influence the complex's redox properties [10].

A second class of heart imaging agents are Tc(I) homoleptic cationic complexes. Complexes of stoichiometry $[Tc(CNR)_6]^+$, prepared by a reduction/substitution reaction of $TcO_4^-$ with the isonitrile, show promise as heart imaging agents [11]. Similar complexes with the stoichiometry $[Tc(PR_3)_6]^+$ have been characterized by several methods including $^{99}Tc$ NMR spectroscopy [12]. In a subsequent study, treatment of $[Tc(SC(NH_2)_2)_6]^{3+}$ with a mixture of isonitriles gives complexes of the stoichiometry $[Tc(CNR)_k(CNR')_{6-k}]^+$ (k = 0 - 6) [13]. New synthetic procedures have been developed for diarene complexes, first synthesized in 1962 [14], which are also well suited for radiopharmaceutical applications [15].

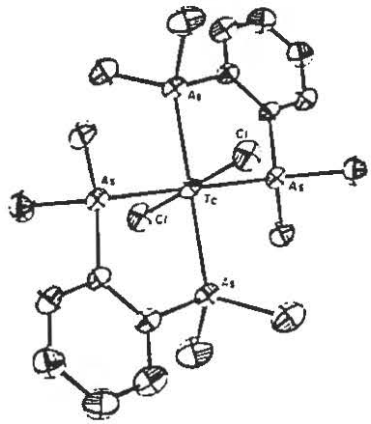

Figure 1. Perspective View of $[Tc(diars)_2Cl_2]^+$

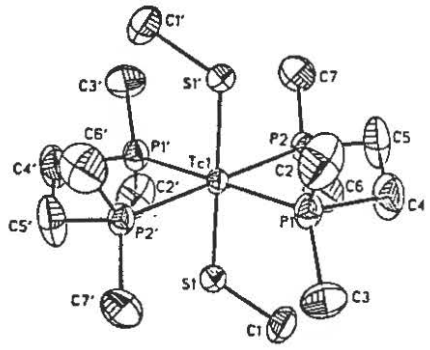

Figure 2. Perspective View of $[Tc(DMPE)_2(SMe)_2]^+$

Although technetium complexes have been developed which localize in the heart, complications such as concurrent uptake by the liver or slow clearance from the blood stream make imaging of certain regions of the heart difficult [16]. Improvements will come with better understanding of the biological mechanisms by which the complex binds to the desired organ, and with new advances in the chemistry of technetium.

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