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Characterization of technetium radiopharmaceuticals by thin-layer spectroelectrochemistry*

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Abstract: Optically transparent thin-layer electrode (OTTLE) techniques have been used to characterize technetium complexes of biomedical importance. Different Tc oxidation states have been generated at the electrodes and absorption spectra determined. Small cell volumes allow the study of materials available in small quantities, and a flow cell configuration has also been used. Heart and bone imaging agents have been studied.

Keywords: *Spectroelectrochemistry; optically transparent thin-layer electrodes; technetium complexes; radiopharmaceuticals; heart imaging agents; bone imaging agents; chromatographic detection.*

Introduction

In the field of diagnostic nuclear medicine, a gamma-ray emitting radiopharmaceutical is administered to a patient in order to provide a functional and/or structural image of the organ(s) in which the radiopharmaceutical localizes. This organ visualization, obtained by either two- or three-dimensional detection of the gamma emission, can yield diagnostic and prognostic information. Thus, radiopharmaceuticals offer a unique means of assessing disease states.

In order to prepare a useful radiopharmaceutical it is necessary to utilize a radioisotope that possesses exceptional nuclear and chemical properties. One element that has been exploited with great success is technetium, Tc. The metastable isotope, ^{99m}Tc, is remarkably well suited for use in diagnostic nuclear medicine. Technetium-99m has a physical half-life of only 6 h and decays by emission of a monoenergetic gamma-ray, which has an emission energy of 141 keV. In addition, the decay product, ^{99}Tc, is long-lived with a half-life of 2.1×10^5 years and emits only a weak beta particle. The combination of these properties along with the fact that ^{99m}Tc does not exhibit accompanying alpha or beta particle emission minimizes the radiation burden to a

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patient. Thus, relatively large doses of technetium (20–30 mCi) can be used to produce acceptable organ images without inflicting damage to healthy tissue.

A significant number of technetium radiopharmaceuticals are nothing more than classical coordination complexes prepared by the coordination of various inorganic and organic ligands to the isotopic metal centre, ^{99m}Tc. Since technetium can exist in oxidation states from (−1) to (+7), with coordination numbers from 4 to 9, a wide variety of complexes are possible. Each complex exhibits a unique set of chemical and physical properties which determine the mechanism and specificity of organ localization. Slight modifications of a complex through changes either in the ligand environment or oxidation state can drastically alter its thermodynamic and kinetic stability and consequently its *in vivo* distribution. It is evident that an understanding of the biological behaviour of a technetium-99m radiopharmaceutical depends upon a knowledge of the chemical and structural properties of the technetium complex. Thus, defining the scope and limitations of such technetium-based radiopharmaceuticals is a large task, which requires characterization of many chemical systems.

Radiopharmaceutical preparations generally utilize concentrations of technetium on the order of 10^{-8}–10^{-6} M [1], which makes characterization of these agents by conventional physical methods quite difficult or impossible. However, the nuclear properties and availability of the ^{99}Tc isotope allow for the development of synthetic procedures on milligram amounts of material. Technetium complexes can then be studied using macroscopic amounts of ^{99}Tc prior to translating their preparation and chemistry to the microscopic concentrations encountered with the ^{99m}Tc agents [2]. Electrochemistry has proven to be an extremely useful and informative method for investigating potential technetium radiopharmaceuticals [3–7]. Not only is it possible to characterize the redox properties of a complex, but also one can often establish the purity of a complex as well as monitor the course of a preparative reaction.

One electrochemical technique which we have utilized extensively for the characterization of ^{99}Tc-complexes has been thin-layer spectroelectrochemistry. Spectroelectrochemistry combines two characterization techniques, electrochemistry and spectroscopy, to give an effective approach for studying the redox chemistry of inorganic, organic and biological molecules. Oxidation states are changed electrochemically and spectral measurements on the solution adjacent to the electrode are made simultaneously with the electrogeneration process. Such spectroelectrochemical techniques are a convenient means for obtaining spectra and redox potentials and observing subsequent chemical reactions of electrogenerated species.

A number of spectroelectrochemical techniques based on optically transparent electrodes (OTE) have been developed [8–12]. One such technique involves spectral observation of a thin layer of solution confined next to an OTE [13]. Electrodes of this type have been termed optically transparent thin-layer electrodes (OTTLE). By taking advantage of the rapid electrolysis rates and small cell volumes inherent in thin-layer electrochemistry, simultaneous determination of formal redox potentials ($E^{0'}$), electron stoichiometries (n), and spectra of electrogenerated species is possible, while using only very small quantities of materials [10, 11, 14–18]. These aspects of OTTLE spectroelectrochemistry are particularly useful in characterizing new technetium complexes, which, because of the radioactivity of ^{99}Tc, are often available in only very limited amounts. This article reviews the methodology and applications of this technique to the characterization of some technetium complexes which have been investigated for use as heart and skeletal imaging agents.

Thin-layer Spectroelectrochemistry

Optically transparent thin-layer electrodes

An OTTLE confines a thin layer of solution adjacent to an electrode that is transparent to light, a condition which has been achieved with numerous cell designs. For example, OTTLE cell designs have been reported for various purposes such as the study of biological and molten salt systems; use with nonaqueous solvents; maintenance of strictly anaerobic conditions; fluorescence, infrared, and EXAFS measurements; and increased optical pathlength [19–45]. One easily constructed OTTLE cell consists of a gold minigrid electrode sandwiched between two microscope slides with Teflon tape spacers as shown in Fig. 1 [13–15]. Solution is drawn from the reservoir cup into the thin layer by suction at the top of the cell. The thin solution layer is maintained within the OTTLE by capillary action and is typically 0.2–0.3 mm thick. In such a cell only about 40 μL is electrolysed in the volume defined by the area of the minigrid. Exhaustive electrolysis can be achieved in times as short as 30 s. The optical beam is passed through the centre of the minigrid to avoid problems with edge effects [14]. Oxygen can be excluded when necessary by placing the cell in a plastic box, fitted with optical windows, and filled with inert gas.

Although the gold minigrid, either 100 or 500 wires per inch, is the most widely used transparent electrode material, other materials have been utilized. Mercury can be deposited on the gold minigrid to extend the negative potential range [46]. Other transparent electrodes such as platinum mesh [23, 28], reticulated vitreous carbon [47], platinum film [19] and tin oxide [48] have also been used.

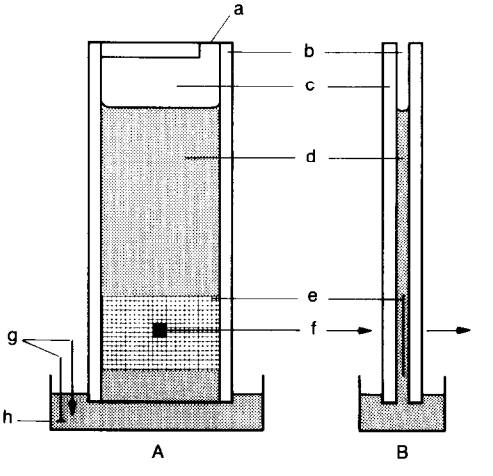

Figure 1
Optically transparent thin-layer electrochemical cell. (A) front view and (B) side view. (a) point of suction application to change solution; (b) Teflon tape spacers; (c) microscope slides (1 × 3 in.); (d) solution; (e) transparent gold minigrid electrode; (f) optical path of spectrometer; (g) reference and auxiliary electrodes; (h) solution cup. Epoxy holds the cell together. (Reprinted with permission from [ref. 15]. Copyright (1976) American Chemical Society.)

Spectropotentiostatic technique

Most thin-layer spectroelectrochemical studies have used potential as the excitation signal. Potential control provides a facile means of precisely adjusting the redox potential of the thin solution layer as determined by the Nernst equation for reversible systems:

$$E = E^{0'}_{O,R} + \frac{RT}{nF} \ln \frac{[O]}{[R]}. \quad (1)$$

Nernstian equilibrium can usually be achieved by electrolysis in a few minutes or less. Thin-layer electrochemistry thus offers a simple way of quickly and precisely controlling the oxidation state of species in a very small volume of solution for simultaneous spectral observation.

The spectropotentiostatic technique developed for obtaining spectra $E^{0'}$ and n-values of redox couples is based on control of the ratio [O]/[R] of the redox couple in the thin solution layer by the potential applied to the cell [14, 15]. The redox couple is incrementally converted from one oxidation state to the other by a series of applied potentials for which each corresponding value of [O]/[R] is determined from spectra. Each potential is maintained until electrolysis ceases so that the equilibrium value of [O]/[R] is established as defined by the Nernst equation. A Nernst plot can then be made from the values of E and the corresponding ratios of [O]/[R] determined spectrally. $E^{0'}$ and n values are evaluated from the y-intercept and slope of the Nernst plot, respectively.

Application to Technetium Systems

Scope

Technetium-99m has been used extensively in clinical settings to produce images of the lung, blood pool, bone, liver, kidneys and thyroid. In this discussion however, we will focus on recent research aimed at the preparation and characterization of technetium complexes for utilization as heart and bone imaging agents, and in particular, how electrochemistry and thin-layer spectroelectrochemistry have been used to investigate the chemical properties of these complexes. The importance of these electrochemical studies cannot be underscored enough since redox processes can play key roles in determining not only the synthetic preparation and stability of a complex, but also the biological activity of the radiopharmaceutical. Discussions of other relevant aspects of technetium radiopharmaceuticals and their chemistry can be found in several recent reviews [2, 49–52].

Heart imaging agents

The development of technetium heart imaging agents is based on work that demonstrated the affinity of monopositive metal cations, such as K^+, Rb^+, Cs^+ and Tl^+, for myocardial tissue [53–54]. $[^{201}Tl(aq)]^+$ is currently used in clinical settings as the agent of choice, but it suffers from poor radionuclide properties. Thus, it was proposed that by combining the exceptional nuclear properties of technetium within the framework of a cationic coordination complex, sufficient localization in the heart might produce a clinically useful image [55, 56].

The initial series of complexes investigated as potential heart agents was composed of discrete cationic technetium(III) complexes with the general formula *trans*-$[TcD_2X_2]^+$, where D is a chelating tertiary phosphine or arsine ligand and X is a halogen. For example, the ^{99m}Tc complexes *trans*-$[Tc(diars)_2Cl_2]^+$, *trans*-$[Tc(diars)_2Br_2]^+$ and *trans*-$[Tc(dmpe)_2Cl_2]^+$, where diars represents 1,2-bis(dimethylarsino)benzene and dmpe represents 1,2-bis(dimethylphosphino)ethane, all produced heart images in mongrel dogs [55–57]. In comparison to $[^{201}Tl(aq)]^+$, $[Tc(dmpe)_2Cl_2]^+$ exhibited superior imaging properties in animal studies [58, 59]; however, similar results were not observed in human images and thus the results of clinical evaluation of $[Tc(dmpe)_2Cl_2]^+$ as a heart imaging agent were disappointing [60].

Phosphine and arsine ligands are good at stabilizing the lower oxidation states of technetium [Tc(III), Tc(II) and Tc(I)]. Members of several classes of compounds which incorporate these ligands exhibit rich electrochemistry and intense charge-transfer absorption bands in the ultraviolet–visible region. The combination of these properties permits characterization by OTTLE spectroelectrochemistry.

A typical thin-layer spectroelectrochemical study is illustrated with the complex $[Tc(dmpe)_2Cl_2]^+$ [5]. Figure 2 depicts the thin-layer cyclic voltammogram of $[Tc(dmpe)_2Cl_2]^+$ with 0.5 M TEAP in DMF, where TEAP is tetraethylammonium perchlorate and DMF is *N,N*-dimethylformamide. As can be seen in Fig. 2, thin-layer cyclic voltammetry can be used to identify the Tc(III)/Tc(II) couple. During a cyclic voltammetry experiment, the potential applied to the working electrode is scanned and the current is measured. A negative potential scan initiated at +0.1 V for $[Tc(dmpe)_2Cl_2]^+$, with a scan rate of 2 mV s^{-1}, results in the reduction of Tc(III) to Tc(II) as indicated by the cathodic current. The rapid drop in current after the peak signifies complete conversion to the Tc(II) oxidation state within the thin solution layer.

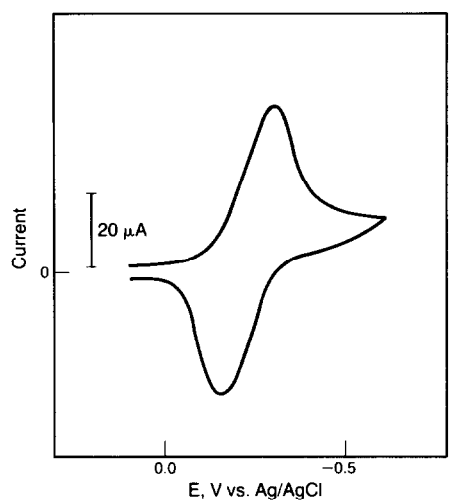

Figure 2
Thin-layer cyclic voltammogram of 1.54 mM $[Tc(dmpe)_2Cl_2]^+$ in 0.5 M TEAP/DMF at an OTTLE with a scan rate of 2 mV s^{-1}.

Upon reversal of the scan at −0.6 V, reoxidation of $[Tc(dmpe)_2Cl_2]^0$ to the original $[Tc(dmpe)_2Cl_2]^+$ complex is observed. Repetitive cycles between +0.1 and −0.6 V yield identical cyclic voltammograms, which indicate the stability of the electrogenerated Tc(II) complex. The $E_{1/2}$ for this process, equation (2), is −0.231 V versus Ag/AgCl:

$$[Tc(dmpe)_2Cl_2]^+ + e^- \rightleftharpoons [Tc(dmpe)_2Cl_2]^0. \quad (2)$$

Spectra recorded for the Tc(III)/Tc(II) couple during a spectropotentiostatic experiment are shown in Fig. 3. The Tc(III) and Tc(II) complexes exhibit absorption maxima at 469 and 414 nm, respectively. The shift of the Tc(II) band to higher energy allows assignment of this absorption to a ligand-to-metal charge-transfer band with the charge-transfer originating from the *trans*-halogen atoms [5]. This is consistent with the fact that the Tc(II) is harder to reduce than is the Tc(III) complex. An isosbestic point is observed at 434 nm, which indicates that there is a clean interconversion between the Tc(III) and Tc(II) complexes without concomitant ligand loss. Each spectrum was recorded five min

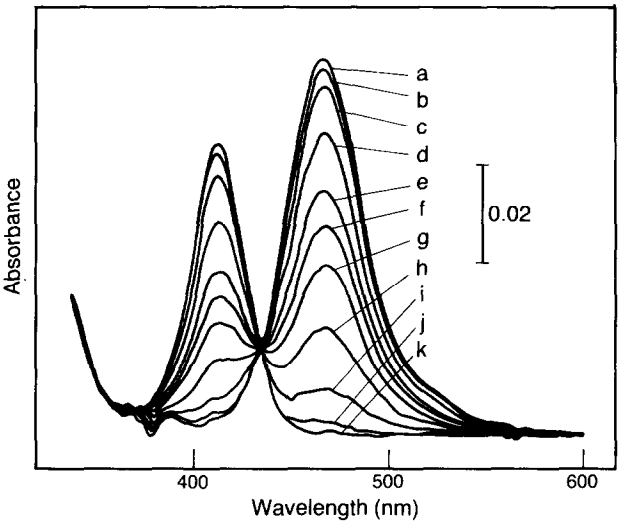

Figure 3
Spectra recorded during an OTTLE spectropotentiostatic experiment on 1.54 mM $[Tc(dmpe)_2Cl_2]^+$ in 0.5 M TEAP/DMF. Applied potentials in V versus Ag/AgCl are as follows: (a) 0.000, (b) −0.130, (c) −0.170, (d) −0.200, (e) −0.220, (f) −0.230, (g) −0.240, (h) −0.260, (i) −0.290, (j) −0.330 and (k) −0.450. (Reprinted with permission from [ref. 5]. Copyright (1984) American Chemical Society).

after potential application to ensure the solution was in equilibrium with the electrode potential. A Nernst plot (Fig. 4) of the data in Fig. 3 at 414 or 469 nm yields $E^{0'} = -0.232$ V versus Ag/AgCl and $n = 0.95$.

Analogous complexes of the radioactive isotope of rhenium, ^{186}Re, have also been investigated for their myocardial diagnostic capabilities [61, 62]. While the periodic relationship of technetium and rhenium results in complexes that exhibit similar physical properties, subtle chemical differences can result in distinctly different biological behaviour. A major difference is the relative redox properties of complexes of both elements. Table 1 compares the results from thin-layer electrochemical studies on $[MD_2X_2]^+$ complexes of technetium and rhenium [63]. As can be seen from the data in Table 1, the complexes of rhenium are about 200 mV more difficult to reduce than the corresponding technetium complexes. This difference in redox potentials for the $[MD_2X_2]^+$ analogues of technetium and rhenium is large enough to shift one complex or the other out of the range of potentials readily accessible to biological systems. This possibility was examined by a comparative biodistribution study of $[^{99m}Tc(dmpe)_2Cl_2]^+$ and $[^{186}Re(dmpe)_2Cl_2]^+$ [61]. The biodistribution data reveal that *in vivo* reduction of the former complex to $[^{99m}Tc(dmpe)_2Cl_2]^0$ hinders the myocardial uptake of the technetium radiopharmaceutical. Since many of the technetium complexes investigated in this series have redox potentials that are biologically accessible, their reduction to the more lipophilic neutral complex may strongly influence the uptake and subsequently enhance the rate of myocardial clearance. Support for this conclusion comes from the fact that although both $[^{99m}Tc(dmpe)_2Cl_2]^+$ and $[^{186}Re(dmpe)_2Cl_2]^+$ accumulate in the heart, $[^{99m}Tc(dmpe)_2Cl_2]^+$ clears more rapidly via the liver and spleen. This behaviour is consistent with the clearance of a complex with lipophilic properties such as $[^{99m}Tc(dmpe)_2Cl_2]^0$. In comparison, the Re(III) analogue demonstrates prolonged heart

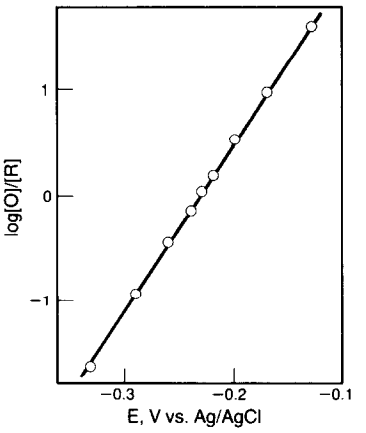

Figure 4
Nernst plot of data at 469 nm from Fig. 3. (Reprinted with permission from [ref. 5]. Copyright (1984) American Chemical Society).

Table 1
$E_{1/2}$ for M(III)/(II) couple from thin-layer cyclic voltammetry*

	Tc†	Re‡	ΔE
$M(dmpe)_2Cl_2^+$	−0.231	−0.423	192
$M(dmpe)_2Br_2^+$	−0.098	−0.297	199
$M(depe)_2Cl_2^+$	−0.260	−0.451	191
$M(diars)_2Cl_2^+$	−0.061	−0.321	260
$M(dppe)_2Cl_2^+$	−0.010	−0.205	195

*Potentials in V versus Ag/AgCl. dmpe, 1,2-bis(dimethylphosphino)ethane; depe, 1,2-bis(diethylphosphino)ethane; diars, 1,2-bis(dimethylarsino)benzene; dppe, 1,2-bis(diphenylphosphino) ethane.
†Taken from [refs 5 and 7].
‡Taken from [ref. 63].

uptake which can be attributed to the redox stability of this complex. Further evidence that the Re(III) complex is incapable of being reduced to Re(II) *in vivo* is that the Tc(I) complex, $Tc(dmpe)_3^+$, does not show an enhanced clearance from the heart [64, 65] and is also incapable of being reduced to a neutral form [5].

The studies involving the *trans*-$[MD_2X_2]^+$ complexes indicate that an effective technetium(III) cationic heart imaging agent may result if the reduction potential is not biologically accessible. Another series of cationic Tc(III) complexes, which have the general formula of *trans*-$[Tc(PR_3)_2L]^+$ [66], where PR_3 is a monodentate tertiary phosphine and L is a tetradentate Schiff base ligand were investigated to assess this possibility. Thin-layer spectroelectrochemical studies [3] reveal a wide range of potentials for the Tc(III)/Tc(II) couple (−0.69 to −1.11 V versus Ag/AgCl). In comparison to the data presented in Table 1, all members of this series of complexes are even more difficult to reduce than $[Re(dmpe)_2Cl_2]^+$, which has already been shown not to undergo significant *in vivo* reduction. Thus, the $[^{99}Tc(PR_3)_2L]^+$ complexes represent a class of biologically nonreducible Tc(III) complexes. Complimentary animal studies result in excellent heart images and suggest that *in vivo* reduction does not occur for the $[^{99m}Tc(PR_3)_2L]^+$ complexes. This added redox stability is a consequence of the presence

of only two coordinating phosphorus atoms instead of the four phosphorus atoms present in $[^{99}Tc(dmpe)_2Cl_2]^+$. Further variation in the redox properties can be accomplished by utilizing PR_3 and L ligands with different donor properties. In essence, the redox properties of a complex can be varied by controlling the coordination environment of technetium. Tuning of the technetium redox properties in this manner forms the basis for the development of more effective myocardial radiopharmaceuticals.

Bone imaging agents

The ^{99m}Tc-radiopharmaceuticals utilized for skeletal imaging are complexes of technetium with diphosphonate ligands, which themselves have a strong affinity for bone. These ligands are structurally similar to pyrophosphate and have the general formula $O_3P{-}CRR'{-}PO_3^{4-}$. A typical preparation involves the reduction of pertechnetate (TcO_4^-), either chemically or electrochemically, in the presence of excess diphosphonate ligand. The resulting solution consists of a complex mixture of technetium complexes in a variety of polymeric forms and oxidation states [67, 68]. This preparation requires chromatographic separation of the individual components before they can be characterized.

In order to study individual components by thin-layer spectroelectrochemistry, an OTTLE cell has been adapted to a flow-through configuration for use in conjunction with chromatography [69]. The chromatographic eluent flows directly into the OTTLE cell (Fig. 5), thereby enabling individual components to be examined by spectroelectrochemistry. On-line experimentation has the distinct advantage of immediate sample

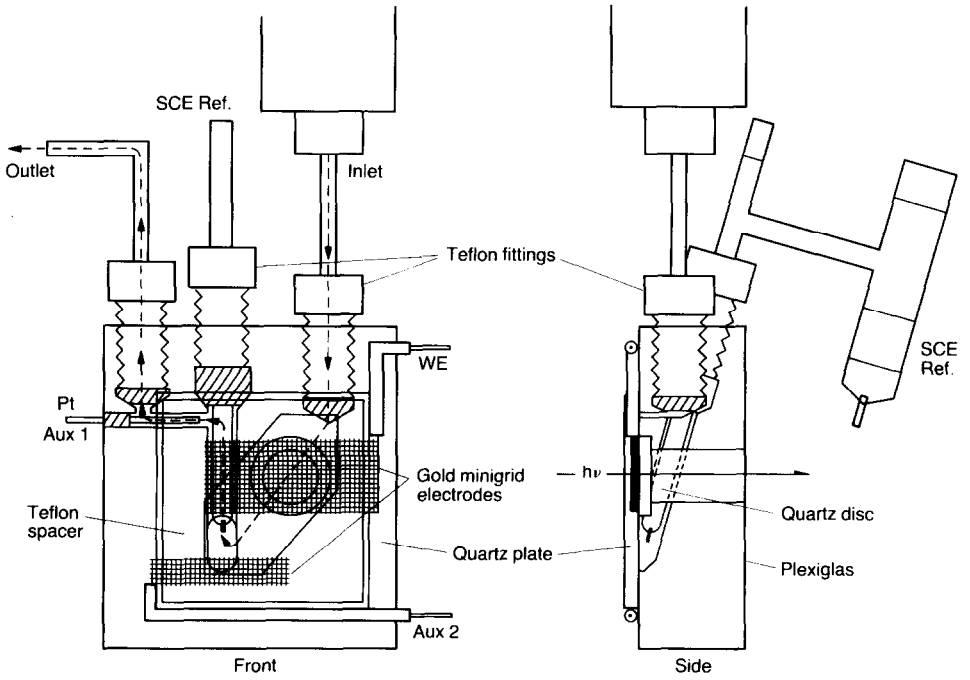

Figure 5
Diagram of the OTTLE flow cell. WE represents the working electrode. (Reprinted with permission from [ref. 69]. Copyright (1980) American Chemical Society.)

evaluation after chromatographic purification. This combination of methods minimizes sample handling and interferences from possible chemical reactions that occur with time. Furthermore, the cell has a volume of about 10 μl, which makes it suitable for use in conjunction with high-performance liquid chromatography.

The usefulness of the OTTLE flow cell has been demonstrated with a radiopharmaceutical analogue consisting of a technetium-99-hydroxyethylidene diphosphonate ($HEDP;O_3P-C(OH)CH_3-PO_3^{4-}$) complex mixture (heretofore referred to as $Tc(NH_2OH)$–HEDP, where NH_2OH is hydroxylamine hydrochloride, the reductant). The complex reaction mixture was eluted on an anion-exchange column. The mixture separated into three component fractions that were yellow, green and red. The yellow component, which eluted first, was trapped in the OTTLE flow cell for spectroelectrochemical characterization. The cyclic voltammogram in Fig. 6 is characteristic of a redox couple which is uncomplicated by chemical reactions. Spectra recorded during the spectropotentiostatic experiment are shown in Fig. 7. A potential of −0.60 V versus NaSCE was first applied to remove any dissolved oxygen by reduction to water. This potential also reduced the Tc–HEDP complex. Spectrum A in Fig. 7 was then recorded. Subsequently, the electrode was stepped to more positive potentials until the redox couple was entirely in the oxidized form. Each spectrum was recorded 20 min after

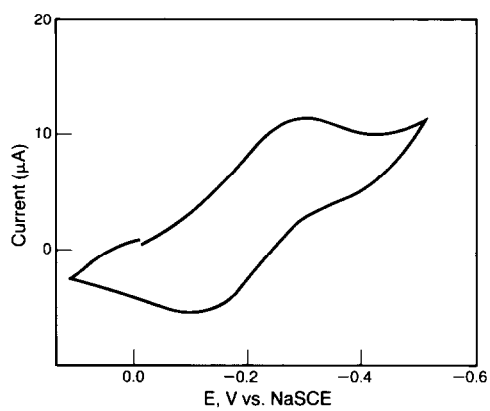

Figure 6
Thin-layer cyclic voltammogram of the $Tc(NH_2OH)$–HEDP yellow component in the OTTLE flow cell.

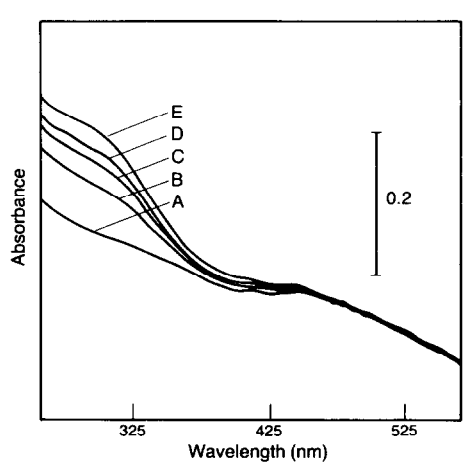

Figure 7
Spectra recorded during the OTTLE spectropotentiostatic experiment on the $Tc(NH_2OH)$–HEDP yellow component. Applied potentials in V versus NaSCE are as follows: (A) −0.60, (B) −0.21, (C) −0.19, (D) −0.17 and (E) +0.25.

potential application to ensure that the thin-layer solution had equilibrated to the new ratio of [O]/[R]. A Nernst plot indicates the existence of a one-electron (n = 0.99) reversible couple with an $E^{0'}$ of −0.207 V versus NaSCE.

Summary

OTTLE spectroelectrochemistry is an extremely useful technique for studying the redox and spectral properties of technetium radiopharmaceuticals. The small volume and rapid electrolysis features are ideally suited for these complexes due to synthetic limitations caused by their radioactive properties.

OTTLE spectroelectrochemistry has been especially valuable for the redox characterization of cationic heart imaging agents wherein the electrochemical properties of the technetium complex may directly influence its biological specificity and clearance. In addition, the OTTLE cell has been adapted in a flow-through configuration to be used in tandem with the chromatographic separation of technetium bone imaging agents.

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