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Speciation of Pentavalent Technetium Complexes with Aniline and Thiobenzene Derivatives

Kyle E. Childs
University of Nevada, Las Vegas, childsk@unlv.nevada.edu

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SPECIATION OF PENTAVALENT TECHNETIUM COMPLEXES WITH ANILINE

AND THIOBENZENE DERIVATIVES

By

Kyle Edward Childs

Bachelor of Science – Chemistry/Radiochemistry
South Carolina State University
2012

A thesis submitted in partial fulfillment

of the requirements for the

Master of Science – Chemistry

Department of Chemistry

College of Sciences

The Graduate College

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Kyle Edward Childs

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Speciation of Pentavalent Technetium Complexes with Aniline and Thiobenzene Derivatives

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Kenneth Czerwinski, Ph.D., Committee Chair

Frederic Poineau, Ph.D., Committee Member

Paul Forster, Ph.D., Committee Member

David Hatchett, Ph.D., Committee Member

Thomas Hartmann, Ph.D., Graduate College Representative

Kathryn Hausbeck Korgan, Ph.D., Interim Dean of the Graduate College

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ABSTRACT
Speciation of Pentavalent Technetium Complexes with Aniline and Thiobenzene Derivatives

By

Kyle Edward Childs

Dr. Kenneth Czerwinski, Advisory Committee Chair
Professor of Radiochemistry
University of Nevada, Las Vegas

The reaction of bidentate aniline oligomers with pentavalent technetium has been investigated previously through the reaction of $(n\text{-}Bu_4N)TcOCl_4$ with o-phenylenediamine (PDA). The initial studies found that PDA reacted in a 1 to 2 molar ratio with pentavalent technetium in in ethanol. This study was expanded by the examination of a second aniline derivatives, 2-aminophenol (AMP)) and two thiobenzene derivatives (2-mercaptophenol (MP) and thiosalicylic acid (TSA)) to evaluate the kinetic formation of these complexes with pentavalent technetium. The pentavalent technetium complexes all showed reactivity with technetium having a coordination numbers of 5 with all ligands reacting in a 1 to 2 metal to ligand ratio, which was confirmed by the use of electrospray ionization mass spectrometry (ESI- MS). Kinetic measurements were performed by UV-visible spectroscopy in a 24 hours period. Separate spectra were also obtained of the metal ligand complex at varying ratios of metal to ligand concentration to determine extinction coefficients for each metal-ligand complex based on Beer-Lambert's equation. While most of the reactions took about 24 hours to reach

completion, the complex of $TcO(TSA)_2^-$ has the fastest formation rate while the

$TcO(PDA)_2^-$ had that fastest reaction rate for the analine derivatives

Acknowledgements

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Chapter 1: Introduction

1.1.   Technetium background

Technetium, element 43, is the lowest atomic number radioelement. In 1869, Mendeleev predicted the existence of an element (M = 100) that would occupy the vacant block between molybdenum and ruthenium.[1] This element was called "ekamanganese." In 1934, Mattauch's rule predicted that element 43 would have no stable isotopes.[1] In 1937, Perrier and Segre discovered technetium from a molybdenum plate that was irradiated at the Berkeley cyclotron. The molybdenum plate was shipped to Italy and technetium was isolated in Palermo. Technetium has 31 isotopes with half-lives ranging from 0.82 seconds (^{110}Tc) to 4.2×10^6 y (^{98}Tc).[2] The long-lived isotopes of technetium are ^{97}Tc, ^{98}Tc and ^{99}Tc, the most common isotopes are ^{99m}Tc (E_γ = 142 keV, $T_{1/2}$ = 6 h) and ^{99}Tc (E_β = 292 keV, $T_{1/2}$ = 2.12 x 10^5 y).

The isotope ^{99}Tc is a major fission product; it is produced in a ca. 6.13% yield from the fission of ^{235}U. Every year, approximately 2 tons of ^{99}Tc are produced by the nuclear industry the United States. The isotope ^{99}Tc is also used in laboratories to study the chemistry of technetium.[1]

The isotope ^{99m}Tc is used in the radiopharmaceutical industry as an imaging agent. The isotope ^{99m}Tc is the daughter of ^{99}Mo and decays to ^{99}Tc (Figure 1.1). The isotope ^{99}Mo is produced from the fission of ^{235}U in reactors. Technetium has a biological half-life of about 24 hours, making it ideal for radiopharmaceuticals as it readily is excreted from the body in a very short amount of time.[1]
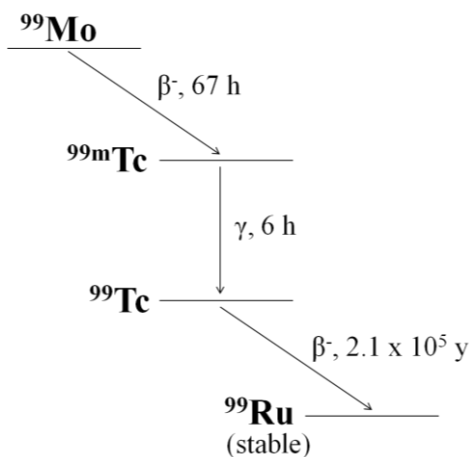
Figure 1.1- Decay diagram of ^{99}Mo

1.2. Chemistry of technetium

Technetium displays a rich coordination chemistry and complexes with coordination numbers from 4 (e.g., TcO_4^-) to 10 (e.g., TcH_{10}^{3-}) having been reported.[2] The electronic configuration of technetium is $[Kr]4d^5 5s^2$ and technetium exhibits 9 oxidation states (from -1 to +7) with the thermodynamically stable oxidation states being +7, +4, and 0. Technetium complexes in the pentavalent and hexavalent oxidation state have been well studied. These complexes can exhibit various core structure: mono-oxo($[TcO]^{3+}$), dioxo $[TcO_2]^+$, $[Tc_2O_3]^{4+}$), amino ($[TcNR]^{3+}$) and nitrido ($[TcN]^{3+}$) cores.[1]

1.2.1. Technetium complexes with the $[TcO]^{3+}$ core

Pentavalent Tc complexes with the $[TcO]^{3+}$ core are well known and more than 100 complexes have been structurally characterized. Because the $[TcO]^{3+}$ group induces a trans-effect, a labile five-coordinated complex forms.[3] The most common structure

observed for oxotechnetium species in the solid state is square pyramidal.[3] In this structure, the metal center is located above the equatorial plane formed by the four basal ligand atoms and the oxo group oriented directly above the metal center (Figure 1.2). In complexes with the $[TcO]^{3+}$ core, the oxygen is chemically inert while the more electronegative ligands atoms can be easily replaced with multidentate ligands.

Bond lengths (average, [Å])		
Tc=O		1.65
Tc–L	L = Cl	2.30
	L = O	1.95
	L = S	2.33
Tc – basal plane		0.65 - 0.80
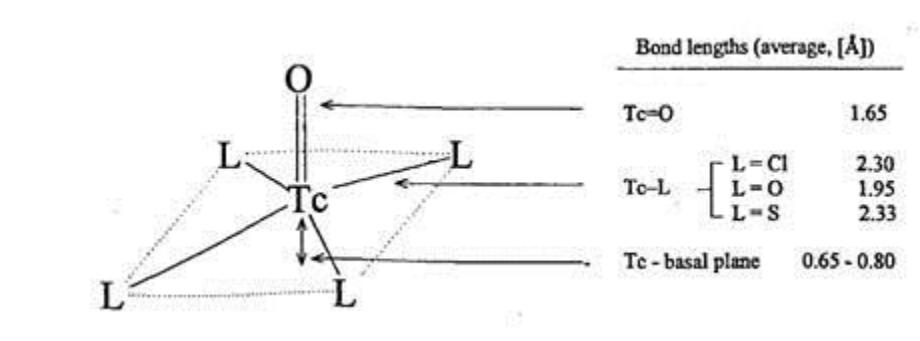
Figure 1.2 - Structure of TcO(L)$_4$ complexes[3]

One of the primary precursors used to study the Tc(+5) chemistry are the oxo-tetrahalotechnetates (i.e., TcOX$_4^-$, X = Cl, Br). Reasons for the extensive use of these complexes are their easy preparation and their high reactivity in solution (i.e., the halogens ligands are chemically labile can be easily replaced). These complexes can be obtained (Equation1.1) as tetrabutylammonium salts from the reaction of tetrabutylammonium pertechnetate (n-Bu$_4$N)TcO$_4$ with cold concentrated acids.[1,4]

$$(\text{n-Bu}_4\text{N})\text{TcO}_4 + 6\text{HX} \rightarrow (\text{n-Bu}_4\text{N})\text{TcOX}_4 + 3\text{H}_2\text{O} + \text{X}_2 \qquad \text{(Equation 1.1)}$$
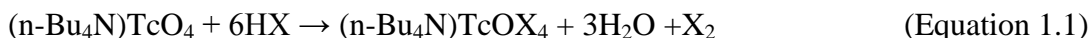
The oxo-tetrahalotechnetates salts are air stable, meaning they can be kept in air without signs of decompsotion. In water, the $TcOX_4^-$ (X = Cl, Br) anions are not stable and disproportionate to Tc(7+) and Tc(4+) species (Equation 1. 2).[1,4]

$$3\ TcOX_4^- + 7H_2O \rightarrow Tc^{7+}O_4^- + 2Tc^{4+}O(OH)_2 + 10HX + 2X^- \qquad \text{(Equation 1.2)}$$
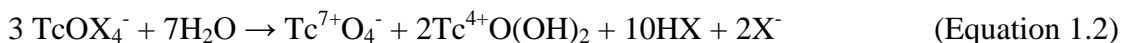
1.2.2. Technetium complexes with the $[TcN]^{3+}$ core

Complexes with $[TcN]^{3+}$ core generally exibits the square pyramidal geoometry and a Tc≡N triple bond is observed. In these complexes, the presence of the nitrogen ligand (isoelectronic to the oxo ligand) stablizes the Tc(6+) oxidation state by acting as a strong π-donor. The Tc≡N is a strong bond and is preserved during ligand substitution reactions and reduction ($[TcN]^{3+}$ + e- → $[TcN]^{2+}$).

One of the main precursors used in the study of the chemistry of Tc(+6) are the nitrido-tetrahalotechnetates (i.e., $TcNX_4^-$, X = Cl, Br). These complexes can be obtained as tetrabutylammonium salts from the reaction of tetrabutylammonium pertechnetate with hot concentrated hydrohalic acid and sodium azide.[5] The nitrido group is preserved during most reduction reactions, as when the $[TcNCl_4]^-$ or $[TcNBr_4]^-$ ions undergo ligand exchange/reduction with "soft" ligands, such as thiols or phosphines, to produce TcN_2C complexes.[5]

1.3. Chemistry of aniline and thiobenzene bidentate aromatic derivatives

Derivatives of aniline ($C_6H_5NH_2$) and thiobenzene (C_6H_5SH) have received attention due to their coordination chemistry and chelating properties.[6] Aniline derivatives are used in the formation of Schiff bases through condensation reactions with aldehydes and ketones.[8] These ligands provide a variety of donor atoms making them ideal for complexing with $[TcO]^{3+}$ and $[TcN]^{3+}$ core in monodenate and multidentates modes.[7] Schiff bases of aniline and their metal complexes also have been shown to be biologically active.[8] Simple aniline and thiobenzene derivatives can easily be manipulated to add reactive functional groups to form bifunctioncal chelators. The addition of reactive functional groups allows for Tc-L complex to covalently bond with a targeting vector. Functional groups such as carboxylic acids or activated esters are used for amide couplings, isothiocyanates for thiourea couplings, and maleimides for thiol couplings (Figure. 1.3).[9] It should be noted that the types of ligands used with Tc can differ from those presented in Figure.1.3.
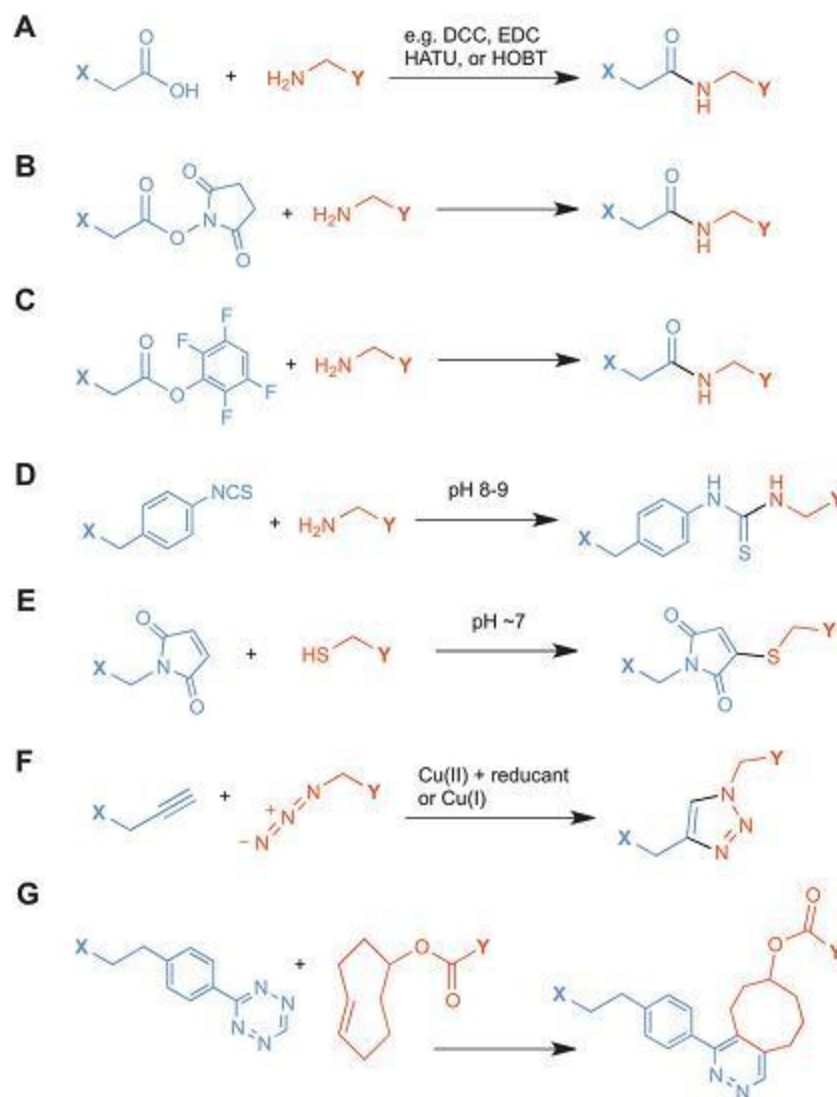
Figure 1.3 - Bioconjugation reactions: (A) standard peptide coupling reaction between a carboxylic acid and a primary amine with a coupling reagent; (B and C) peptide coupling reactions between activated esters of tetrafluorophenyl (TFP) or N-hydroxysuccinimide (NHS) and a primary amine; (D) thiourea bond formation between an isothiocyanate and a primary amine; (E) thioether bond formation between a maleimide and thiol; (F) standard Cu(I) catalyzed Huisgen 1,3-dipolar cycloaddition (''click'' reaction) between an azide and an alkyne; and (G) strain-promoted Diels–Alder ''click'' reaction between a tetrazine and transcyclooctene.[9]

In absence of coordinating ligand, Tc(+5) is unstable in aqueous media and disproportionate to Tc(4+) and Tc(7+).[1] This is an issue for the development of Tc(+5)

radiopharmaceuticals. By exploring the ligation of aniline and thiobenzene derivatives to the technetium core, it may be possible to stabilize technetium at the desired oxidation states as the aromaticity of these ligands provides steric bulk, shielding the metal center. The coordination of aromatic rings also results in the formation of chelate rings, further increasing the stability of the metal complex.

Bidentate aromatic ligands form neutral, monoanionic and dianionic chelate technetium complexes. The results obtained can lead to greater understanding of the coordination abilities associated with the $[TcO]^{3+}$ and $[TcN]^{3+}$ cores. The aniline ligand can be derived to incorporate amine, thio, hydroxyl, and carboxylic acid functional groups. These compounds can be further reacted through condensation reactions to make more complex ligands that can lead to greater stability and improved targeting.[6]

1.4. Purpose of study

Due to optimal nuclear properties and versatile coordination chemistry, the isotope ^{99m}Tc is the most commonly used radionuclide in nuclear imaging. The extensive use of ^{99m}Tc in diagnostic medicine has been accompanied by the development of a large number of ligands that specifically target certain cells and tissues. In this context, the understanding of thermodynamic and kinetic stability as well as the coordination chemistry of ^{99}Tc compounds is essential for the development of ^{99m}Tc radiopharmaceuticals. One class of ligands of interest for radiopharmaceuticals applications are aniline and thiobenzene derivatives.

The goal of this study is to evaluate the use of aniline and thiobenzene derivatives to develop ^{99}Tc complexes for radiopharmaceutical applications. In this study, the reaction between $TcOCl_4^-$ with derivative ligands will be investigated. The speciation of the Tc-aniline and Tc-thiobenzene complexes will be studied in solution by spectroscopic techniques and stoichiometry will be proposed. Kinetic stability of the complexes will be evaluated and their formation mechanism discussed. This information will assist in gaining understanding of the use of aniline and thiobenzene derived complexes for the development of ^{99m}Tc-radiopharmacetucials.

Chapter 2: Experimental

2.1.   Handling of technetium

The isotope ^{99}Tc is a weak β-emitter (E_β = 292 keV, $t_{1/2}$ = 2.12x 10^5 y) and precautions are required for its handling. All manipulations were carried out in laboratories approved for radioactivity using efficient HEPA-filtered fume hoods. Normal radiation safety procedures and protocols have been prepared and were used in accordance with guidelines set by the state of Nevada and the University of Nevada Las Vegas. During handling of solid ^{99}Tc, continuous air monitors as well as dosimeters are used by all personnel handling the material, and quarterly bioassay's taken to monitor internal dose.. Any handling that could form ^{99}Tc-containing aerosols required the use of a breathing zone air monitor.

Solutions of ^{99}Tc were prepared in disposable, glass liquid scintillation vials and centrifuge tubes. During storage and centrifugation, the vials and tubes were capped and sealed with Parafilm and placed in secondary containment to prevent contamination or spills. When working with non-dispersible forms of ^{99}Tc, particularly low activity solutions, synthetic techniques were performed on laboratory benches with absorbent pads.

For spectroscopic measurements, all solutions contained low enough activity that electrospray measurements could be performed without prefilling the syringe in a hood. Samples for UV-visible measurement were prepared in the radiation laboratory, capped and sealed before leaving the laboratory and entering the spectrophotometer.

2.2. Preparation of precursors

2.2.1 Ammonium pertechnetate – NH$_4$TcO$_4$

Ammonium pertechnetate was obtained from Oak Ridge National Laboratory in the form of an impure black compound that needed to be purified. For the purification procedure, the black compound (200 mg) was put in a 50 mL Erlenmeyer flask, then ~2 mL of H$_2$O and 50 µL of concentrated hydrogen peroxide where added in the flask. The suspension was stirred and heated (100 °C) on a hotplate for 15 minutes, then the solution was cooled to room temperature and solid ammonium pertechnetate (white) precipitated to the bottom of the flask. The water was removed with a glass pipette and the solid washed with isopropanol and diethyl ether then dried in open air.

2.2.2 Tetrabutylammonium pertechnetate – (n-Bu$_4$N)TcO$_4$

The (n-Bu$_4$N)TcO$_4$ salt was prepared after treatment of the impure ammonium pertechnetate in H$_2$O at 100 °C with H$_2$O$_2$ followed by precipitation with (n-Bu$_4$N)Cl. In this procedure, impure ammonium pertechnetate (100 mg) was suspended in 5 mL of H$_2$O / 50 µL of concentrated H$_2$O$_2$ solution. The solution was heated to 100 °C until the black compound was dissolved. The solution was then cooled to room temperature. The solution was transferred to a 15 mL glass centrifuge tube, and (n-Bu$_4$N)Cl (280 mg in 3 mL DI H$_2$O) was added into the tube. After centrifugation, the supernatant was removed with a pipette, the solid was washed with H$_2$O (5 mL) then dried at 90 °C for 12 hours.

2.2.3. Tetrabutylammonium tetrachlorooxotechnetate – (n-Bu₄N)TcOCl₄

The (n-Bu₄N)TcOCl₄ salt was prepared from the reaction of (n-Bu₄N)TcO₄ with cold 12 M HCl. The (n-Bu₄N)TcO₄ salt (300 mg) was added to 4 mL of cold (4°C)12 M HCl in a 15 mL glass centrifuge tube and the suspension was stirred for 30 minutes. Initially, the solution turned orange then progressively green along with the evolution of chlorine gas. The supernatant was removed and the solid washed with cold isopropanol (2 x 3 mL) and diethyl ether (2 x 5 mL). The solid was recrystallized twice with 4 mL of acetone and 16 mL of ether. The grey-green solid was washed twice with ether and dried in open air.

2.3.   Aniline and thiophenol derivatives

All compounds used for synthesis were purchased from Sigma-Aldrich either as solids, powders or as concentrated solutions.

2.3.1. o-Phenylenediamine (C₆H₈N₂)

O-phenylenediamine (PDA) (Figure 2.1) was purchased as a powder derived from a peroxidase substrate at 98% purity. For the experiment, a 0.08M stock solution of the compound was prepared by dissolving 0.173 grams of o-phenylenediamine in 20 mL of ethanol. The UV-visible spectra of o-phenylenediamine in ethanol is presented in Figure 2.2
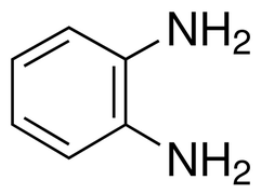
Figure 2.1 - Structure of o-phenylenediamine
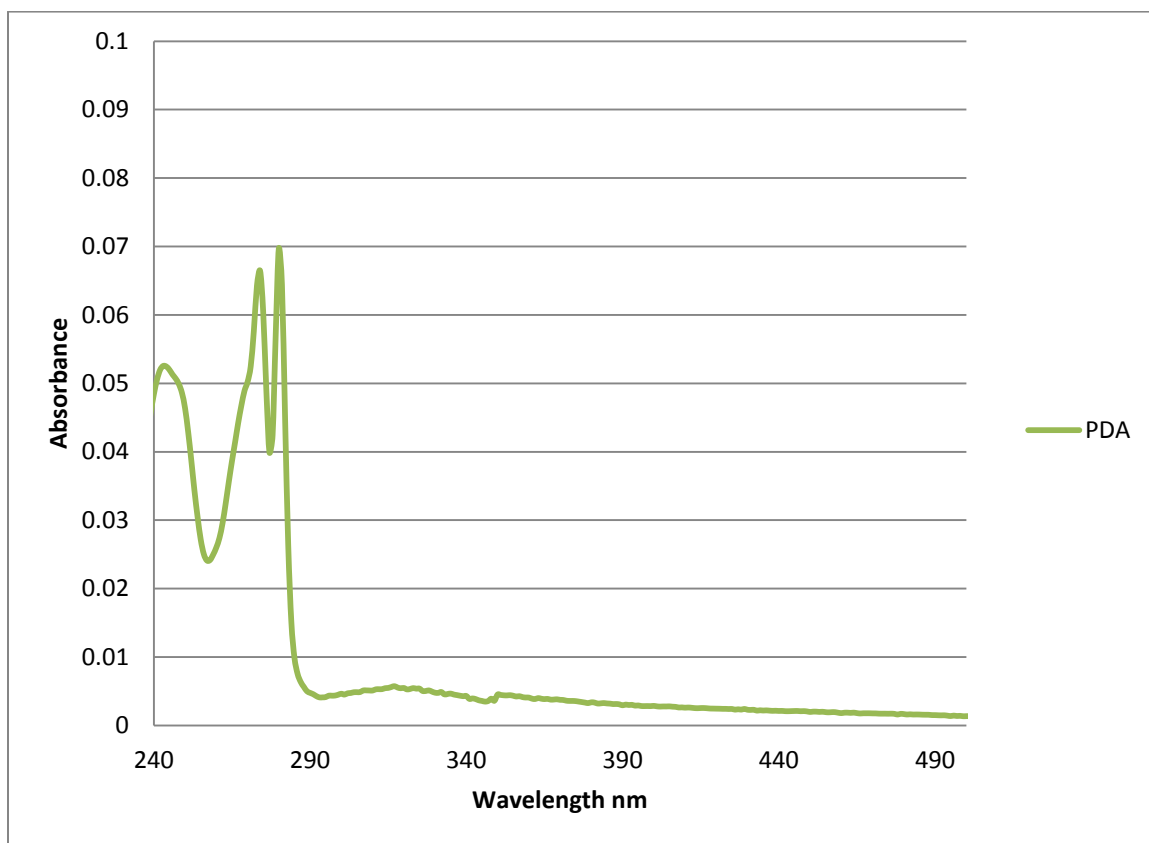
Figure 2.2 – UV-visible spectrum of o-phenylenediamine (1.2×10^{-5} M) in ethanol

2.3.2. 2-Aminophenol ($H_2NC_6H_4OH$)

2-Aminophenol (AMP) (Figure 2.3) was purchased as a powder (99% purity). A 0.08M stock solution was prepared by dissolving 0.175 grams of 2-aminophenol in 20 mL of ethanol. The UV-visible spectra of 2-aminophenol in ethanol is presented in Figure 2.4.
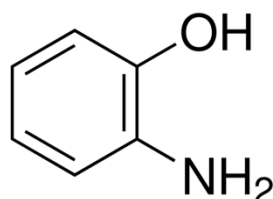
Figure 2.3 - Structure of 2-aminophenol
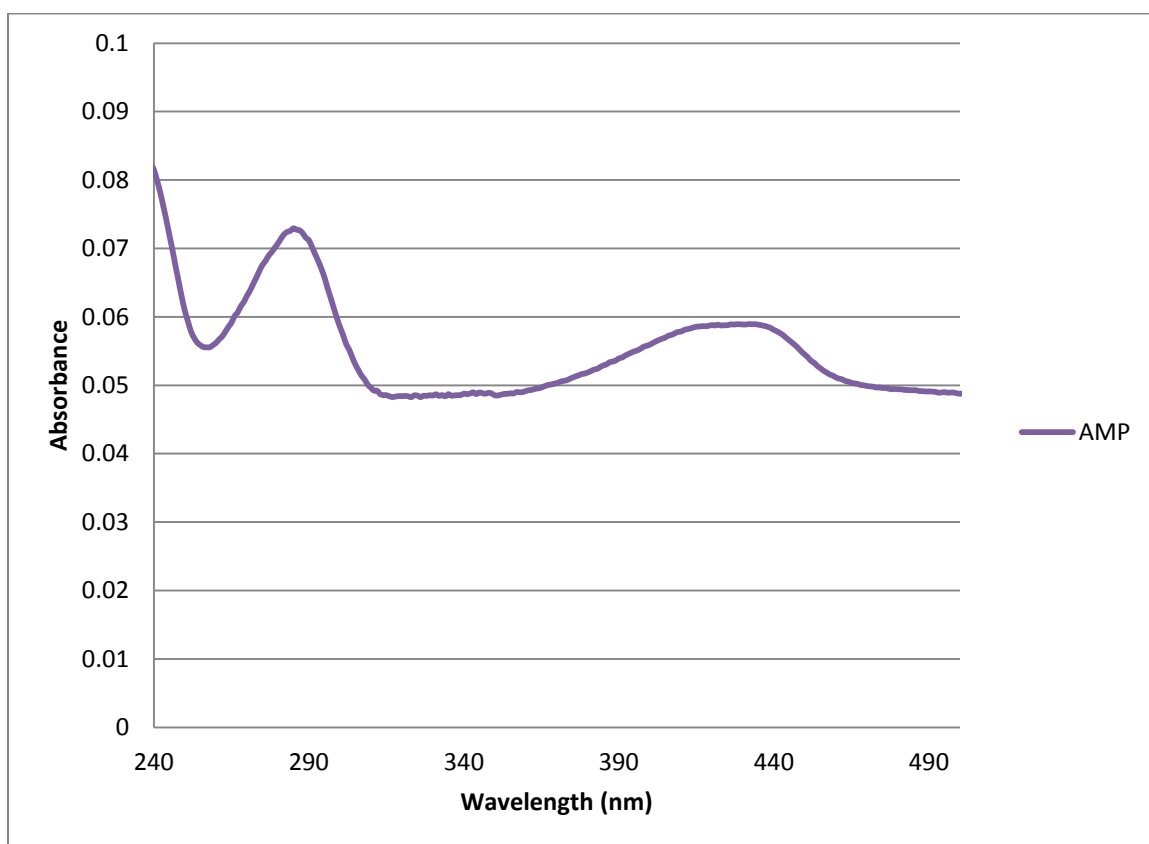
Figure 2.4 – UV-visible spectrum of 2-aminophenol (1.2×10^{-5} M) in ethanol

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2.3.3. 2-Mercaptophenol (HSC$_6$H$_4$OH)

2-Mercaptophenol (MP) (Figure 2.5) was purchased as a 5 mL liquid (ρ = 1.255 g/mL), 95% purity). The 0.08 M stock solution was prepared by combining 0.160 mL of 2-mercaptophenol with 19.84 mL of ethanol. The UV-visible spectra of 2-mercaptophenol in ethanol is presented in Figure 2.6.
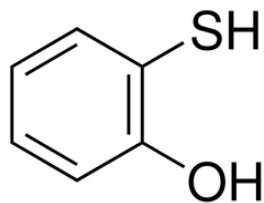
Figure 2.5 - Structure of 2-mercaptophenol
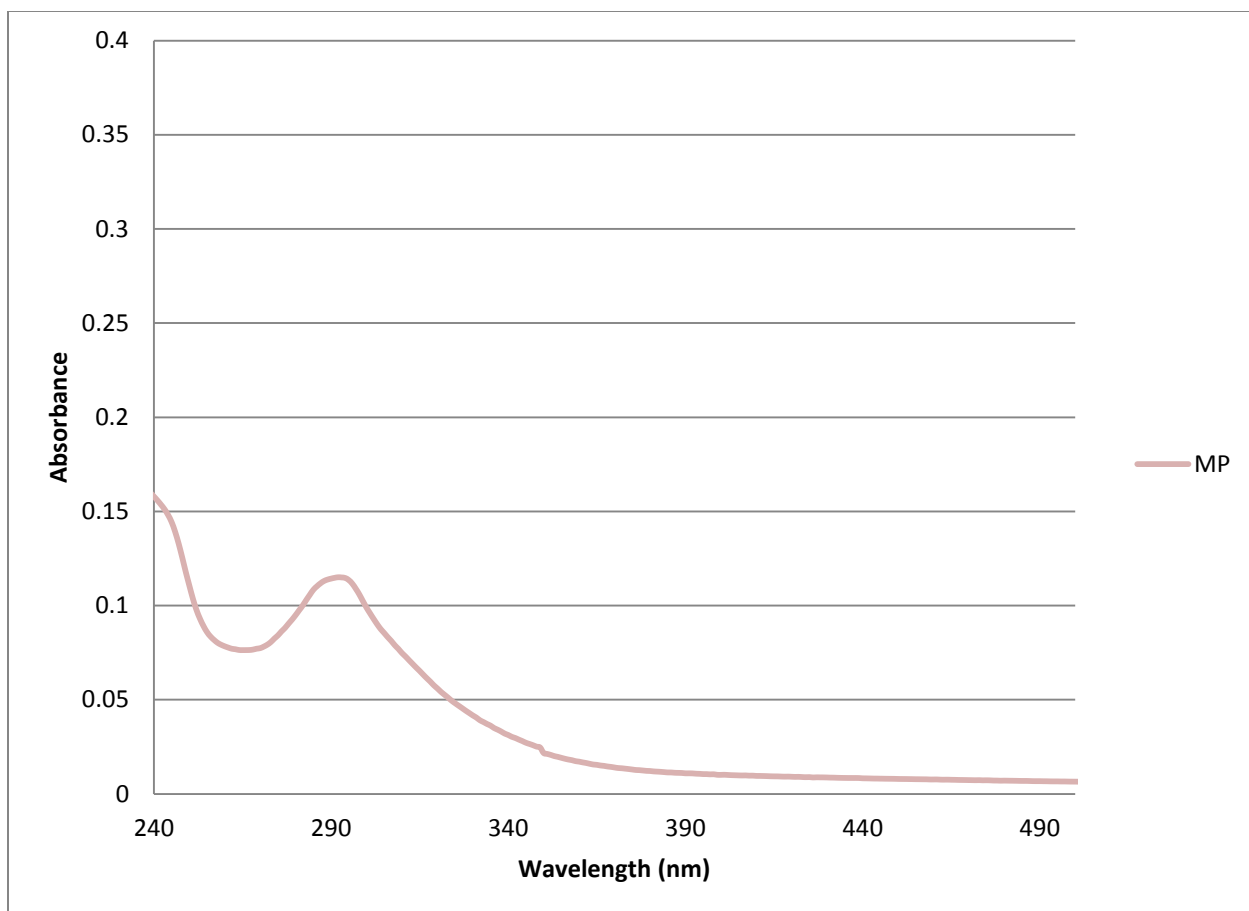
Figure 2.6 – UV-visible spectrum of *2*-mercaptophenol ($1.2\text{x}10^{-5}$ M) in ethanol

2.3.4. Thiosalicylic acid (HSC$_6$H$_4$CO$_2$H)

Thiosalicylic acid (TSA) (Figure 2.7) was purchased as a solid (97% purity). The 0.08 M stock solution was prepared by dissolving 0.247 grams of thiosalicylic acid in 20 mL of ethanol. The UV-visible spectrum of thiosalicylic acid in ethanol is presented in Figure 2.8.
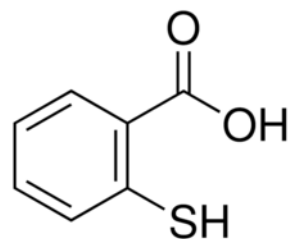
Figure 2.7 - Structure of thiosalicylic acid
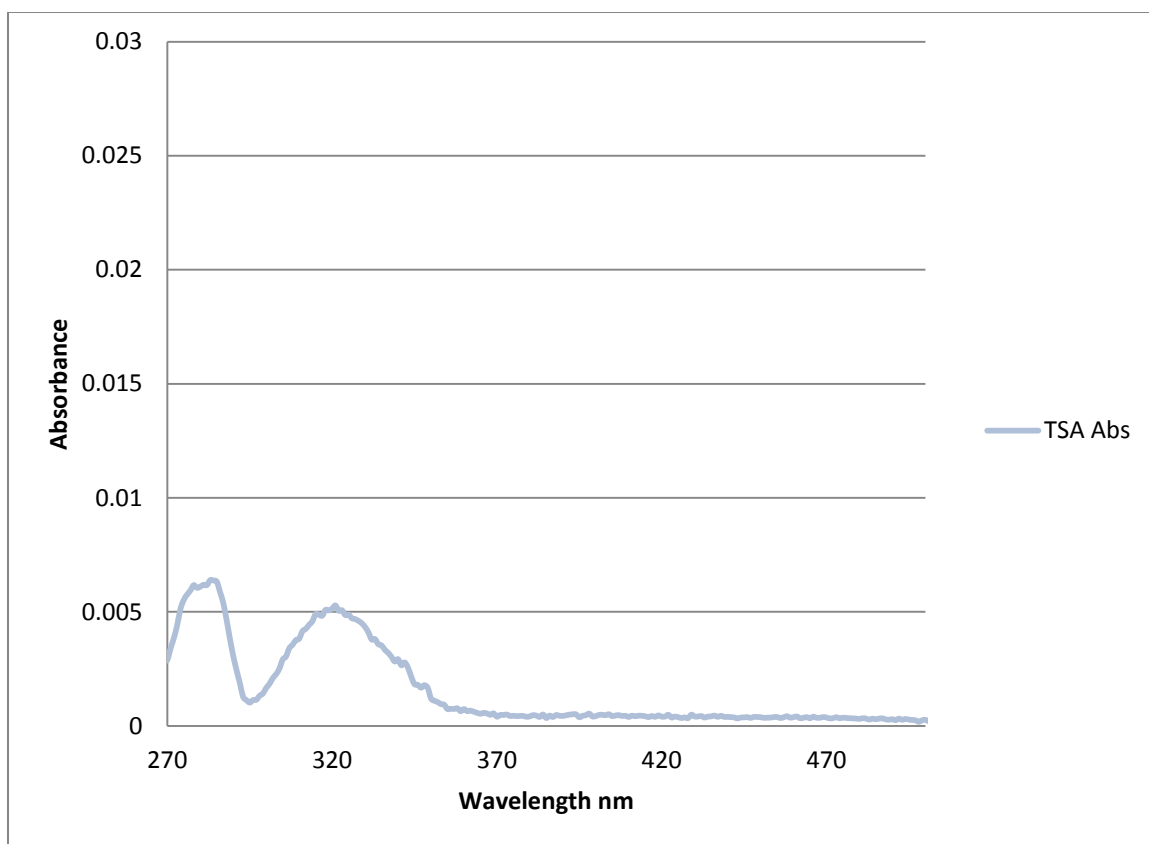
Figure 2.8 – UV-visible spectrum of thiosalicylic acid $(3 \times 10^{-6}\,M)$ in ethanol

2.4. Instrumentation

2.4.1. UV-visible spectrometer

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UV-visible measurements were performed using a Cary 6000i UV-Vis-NIR in 2 mL, (optical path length, L = 1 cm) screw cap quartz cuvettes at room temperature. The spectrophotometer was used in double beam mode with a absolute ethanol blank for baseline correction. Measurements were taken from 200 nm to 800 nm. Concentrations of the species were determined using the Beer-Lambert equation: $O_D = \varepsilon. L. C$, where O_D is the optical density, ε is the extinction coefficient ($M^{-1}.cm^{-1}$), L is the optical path length (cm) and C is the concentration (M).

2.4.2. Electrospray ionization mass spectrometer

Electrospray ionization mass spectrometry (ESI-MS) measurements were performed using a Dionex electrospray-mass spectrometer. All solutions were prepared in ethanol and the eluent used was 50:50 acetonitrile and water at a flow rate of 0.25 mL/min. Flow to the MS was nebulized through an ESI source using nitrogen gas at 450 psi. The electrospray capillary was held at 350 °C with a needle voltage of 3 kV. The entrance cone was held at a voltage of 30 V. Negative ion monitoring was utilized.

2.5. Synthesis, kinetic and structural analysis

Samples used in this study were prepared after dissolution of (n-Bu$_4$N)TcOCl$_4$ in ethanol followed by addition of an ethanol solution containing the ligand. For the determination of the extinction coefficients, ethanol solutions (15 mL, Tc = 3×10^{-6}M) with Tc: ligand molar ratio from 1:1 up to 1:4 were prepared and reacted for 24 hours then measured using UV-visible spectroscopy. Kinetic measurements were performed by

combining Tc at 1×10^{-5} M and ligand at 4×10^{-5} M and measuring the change in absorbance with time for about 24 hours. The ESI-MS samples were produced by combining Tc at 1×10^{-5} M and ligand at 4×10^{-7} M and allowing them to react for 24 hours at which point the ESI-MS measurement would be performed.

Chapter 3: Results and Discussion

3.1 Sample preparation and characterization

A solution of Tc(+5) in the form of $(n\text{-}Bu_4N)TcOCl_4$ in ethanol was prepared by dissolution in ethanol (Tc = 1.0 µM) and a solution of the ligand in ethanol was added to the Tc solution (molar ratio Tc : L = 1: 4) in excess ethanol. The reaction was followed as a function of the time by UV-visible spectroscopy over the course of 24 hours. A previous study showed that the reaction between $TcOCl_4^-$ and aminophenol (PDA) (Tc: PDA ~1 : 2) takes ~18 hours to reach completion. In our studies, it was estimated that a reaction time of 24 hours should lead to the formation of $TcOL_2$ complexes. After 24 hours of reaction, the speciation of the $TcOL_2$ complexes (molar ratio Tc : L = 1:1, 1:2, 1:3, 1:4) was performed by UV-Visible and ESI-MS spectroscopy. Finally, the study of the absorption spectra as a function of the time was used to determined reaction rate and mechanism of formation of the $TcOL_2$ complexes. In the following section, the speciation, reaction rate and mechanism of formation for the Tc-L system (L = O-phenylenediamine, 2-Aminophenol, 2-Mercaptophenol and Thiosalicylic Acid) is presented.

3.2 Study of the reaction between $TcOCl_4^-$ and o-phenylenediamine

The reaction between $TcOCl_4^-$ and o-phenylenediamine in ethanol (Tc = $1x10^{-7}$ M, Tc: L =1:4) was studied for a 24 hours period. After 24 hours, the solution was analyzed by ESI-MS. Separately; Tc ($3x10^{-6}$ M) was reacted with PDA in a metal to ligand ratio ranging from 1:1 to 1:4 for a 24 hours period and analyzed by UV-visible

spectroscopy. The ESI-MS spectra (Figure 3.1) shows a peak at m/z = 325.06 which is consistent with the presence of $TcO(PDA)_2^-$ (m/z = 323).
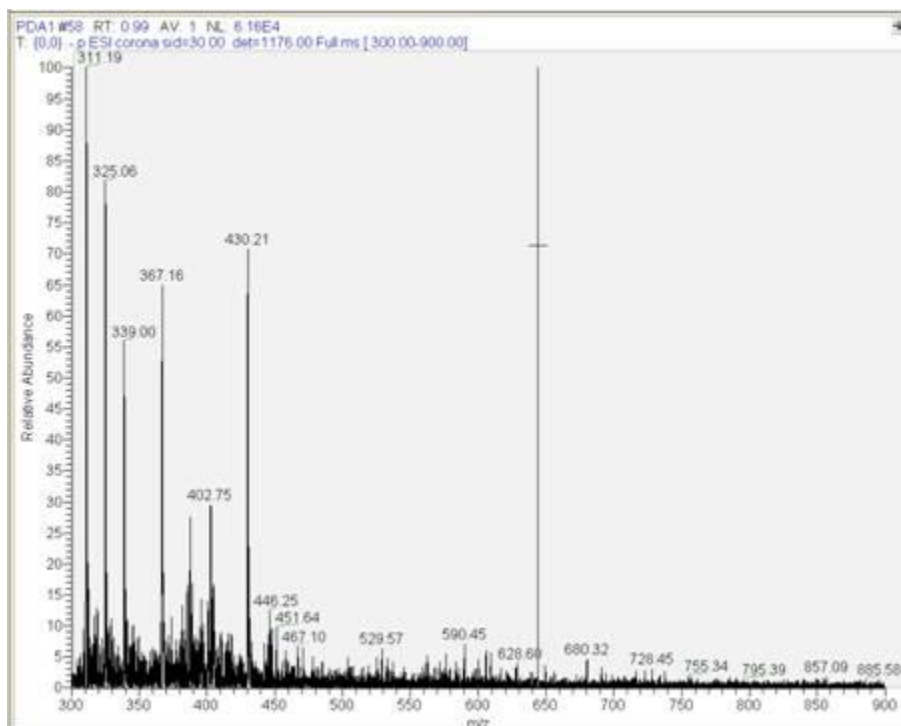
Figure 3.1 – ESI-MS spectrum of the solution obtained after reaction (24 hours) between $TcOCl_4^-$ and o-phenylenediamine ([Tc] = $1x10^{-5}$ M, Tc:L = 1:4)

The UV-visible spectra of the $TcO(PDA)_2^-$ species recorded after 24 hours is presented in Figure 3.2. The UV-visible spectra of $TcO(PDA)_2^-$ exhibit a peak at 280 nm for which the extinction coefficient ($1.96x10^4$ $M^{-1}.cm^{-1}$) was determined using the Beer-Lambert's equation(see table A.1.)
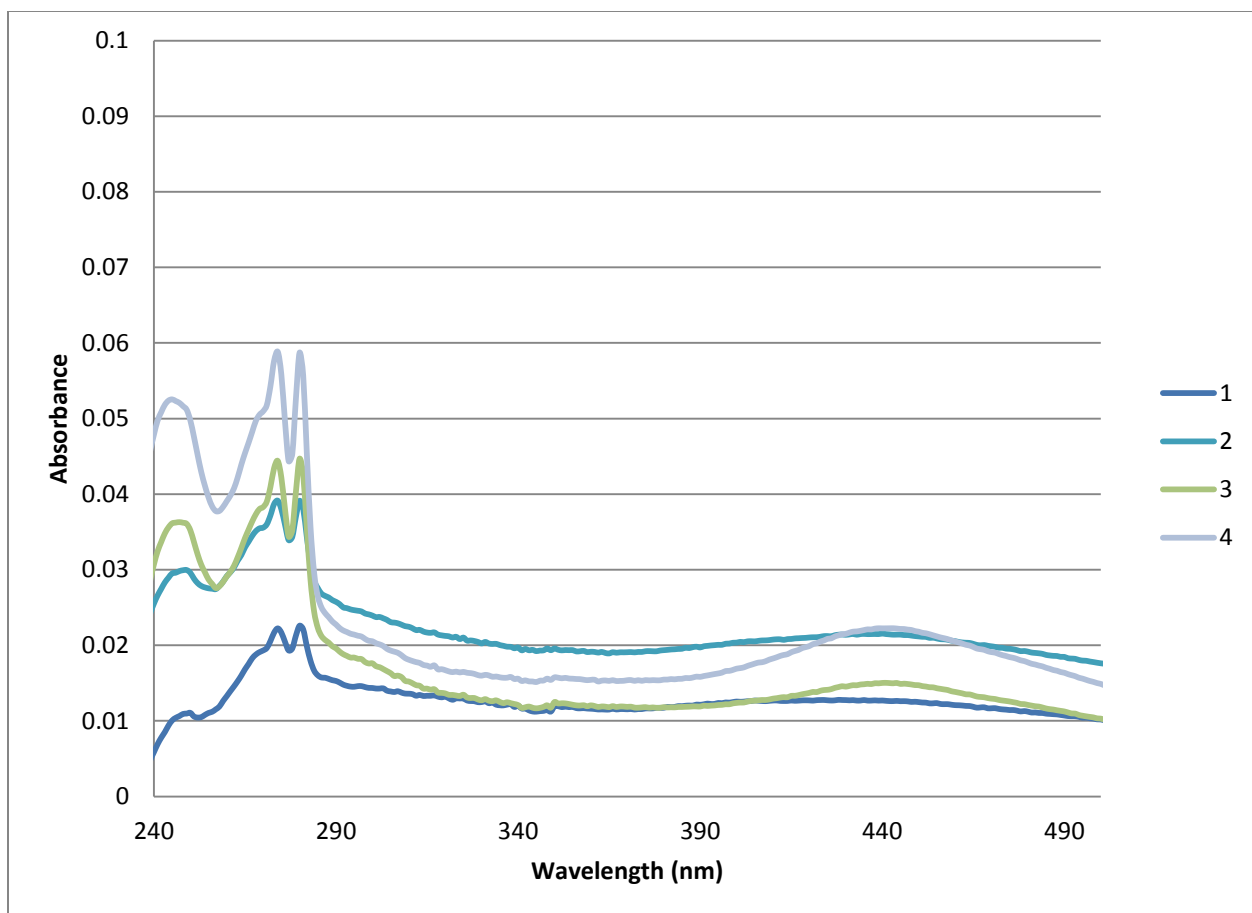
Figure 3.2 UV-visible spectra of the TcO(PDA)$_2^-$ complex obtained after reaction (24 hours) between TcOCl$_4^-$ and o-phenylenediamine at varying molar ratios ([Tc] = 3x10^{-6} M, Tc:L = 1:1, 1:2, 1:3, 1:4)

The formation of the TcO(PDA)$_2^-$ complex after 24 hours is consistent with the previous results. It has been shown that the TcO(PDA)$_2^-$ complex was formed after the reaction of TcOCl$_4^-$ with PDA (Tc: L = 1 : 2 molar ratio). The structure of TcO(PDA)$_2^-$ determined by single crystal X-ray diffraction is presented in Figure 3.3. Authors concluded that further experimentation into the speciation of Tc(+5) with PDA and similar aniline and thiobenzene derivatives would be useful to establish which is the most ideal for radiopharmaceutical development.

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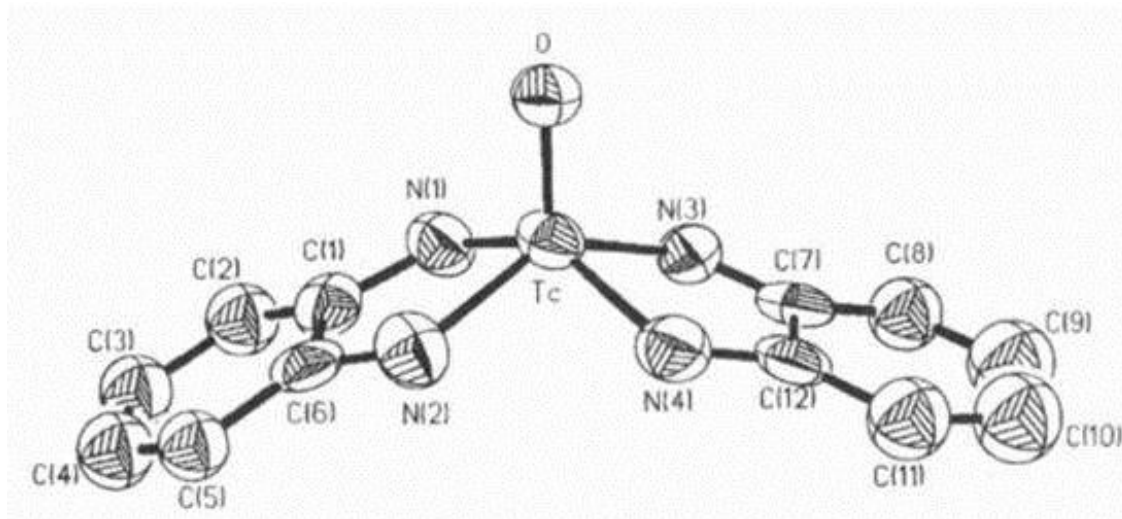
Figure 3.3 – Molecular structure of TcO(PDA)$_2^-$ [8]

The kinetic of formation of the TcO(PDA)$_2^-$ complex was studied and the initial reaction rate (r_0) determined. The reaction between TcOCl$_4^-$ and PDA was followed over 24 hours and spectra were regularly recorded (Figure 3.4) The representation of concentration of the TcO(PDA)$_2^-$ as a function of the time (Figure 3.5) was determined using the band at 280 nm.

$$TcOCl_4^- + 2\,PDA^{2-} \rightarrow TcO(PDA)_2^- + 4Cl^- \hspace{2cm} \text{(Equation 3.1)}$$

The initial reaction rate (r_0) was determined as $d(TcO(PDA)_2^-)/dt$ (for t= 0). The relation between the initial reaction rate and the initial rate constant k_0 is:

$r_0 = k_0[TcOCl_4]_{(t=0)}[PDA]^2$

The initial reaction rate was respectively determined to be 2.26×10^{-9} $M^{-1} \cdot min^{-1}$ (see table A.2.)   The rate constant cannot be established with clear certainty as the reaction does not fit a specific reaction order, and this was true for all reactions performed in this study.
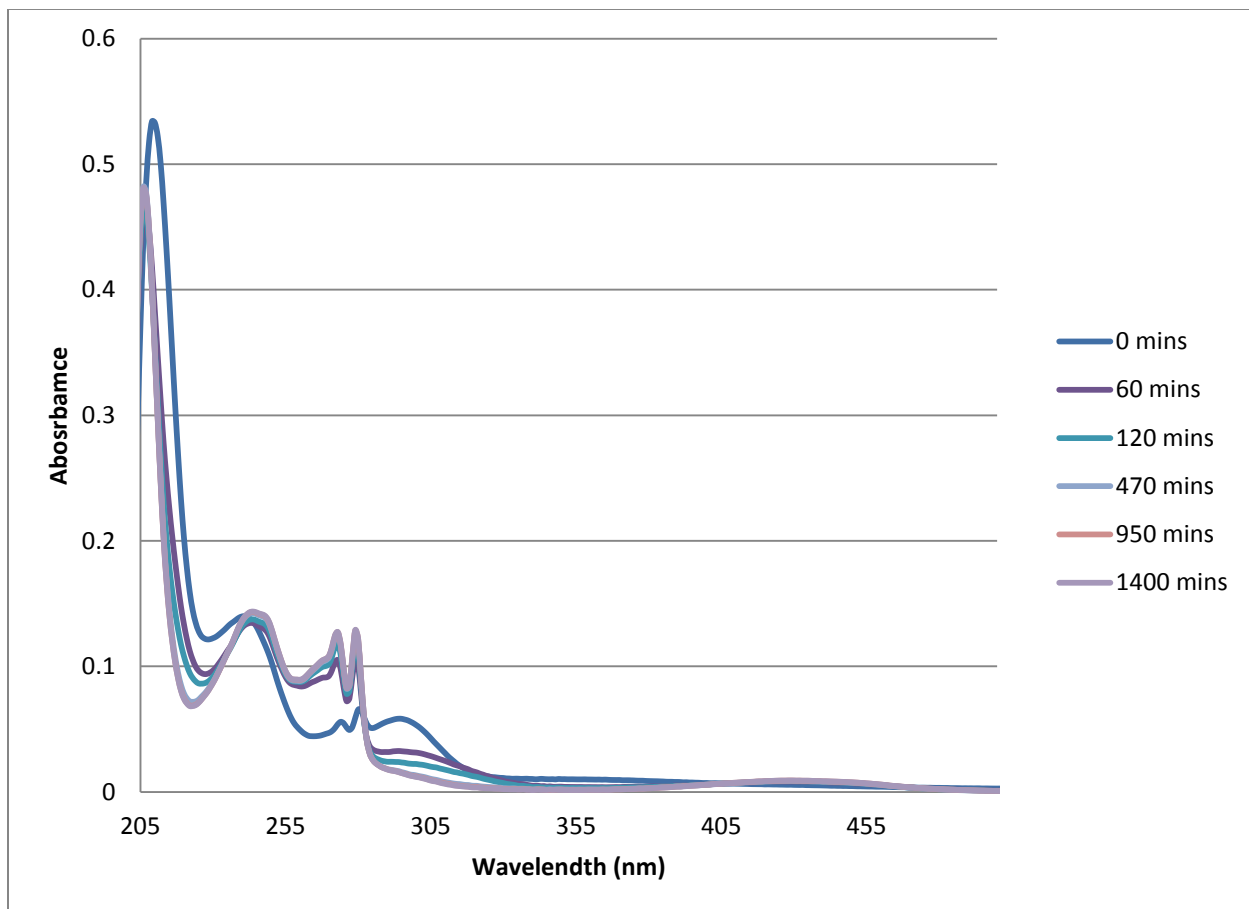
Figure 3.4- UV-visible spectrum as a function of time for the reaction of (n-Bu$_4$N)TcOCl$_4$ with o-phenylenediamine in ethanol. ([Tc] = 1×10^{-5} M, Tc:L = 1:4)
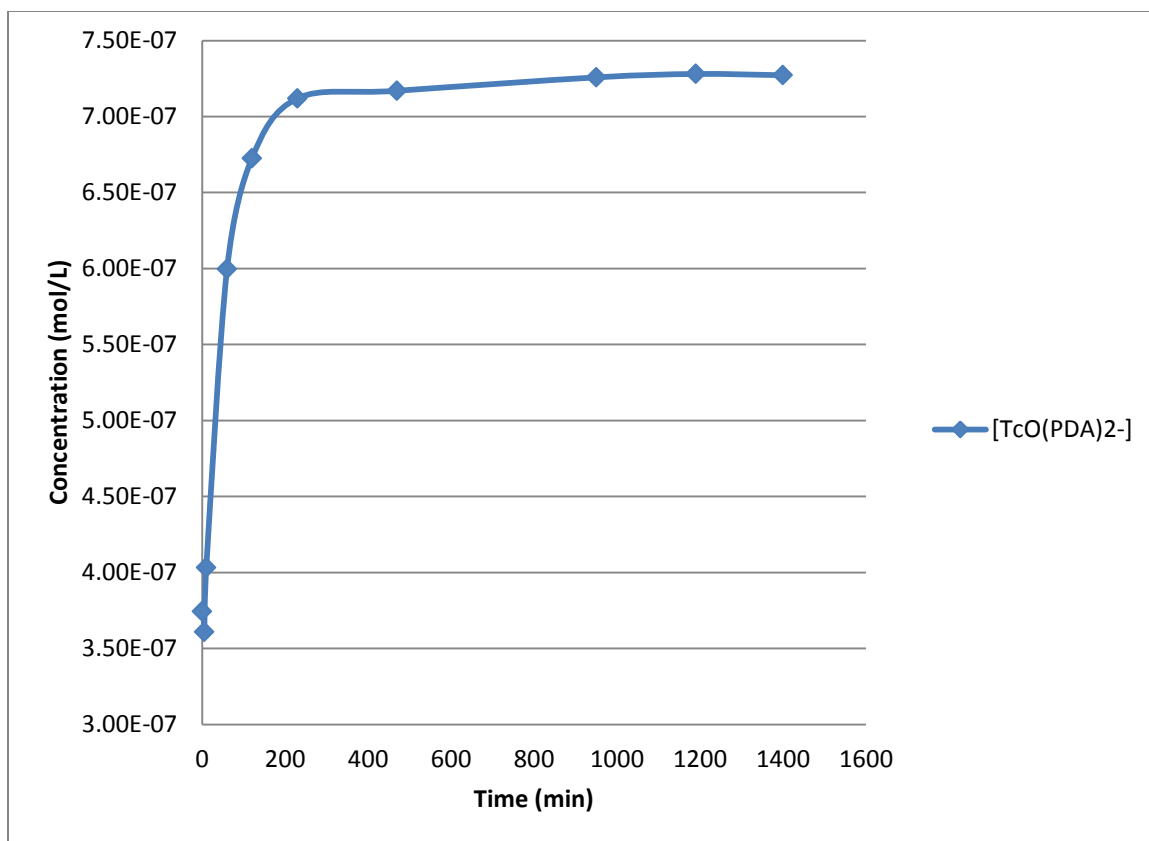
Figure 3.5 – Change of Tc)(PDA)$_2$ concentration (Mol·L^{-1}) as a function of time after the reaction of (n-Bu$_4$N)TcOCl$_4$ with o-phenylenediamine in ethanol. ([Tc]=1x10^{-5} M, Tc:L = 1:4)

3.3   Study of the reaction between TcOCl$_4^-$ - and 2-aminophenol

The reaction between TcOCl$_4^-$ and 2-aminophenol in ethanol ([Tc] = 1x10^{-5} M, Tc: L =1:4) was studied for 24 hours and analyzed by ESI-MS at completion. Separately, TcOCl$_4^-$ (3x10^{-6} M) was reacted with AMP in a ratio ranging from 1:1 to 1:4 for a 24 hour period and analyzed by UV-visible spectroscopy. The ESI-MS spectrum (Figure 3.6) exhibits a peak at m/z = 325.03 which is mostly consistent with the presence of TcO(AMP)$_2^-$ (m/z = 327).
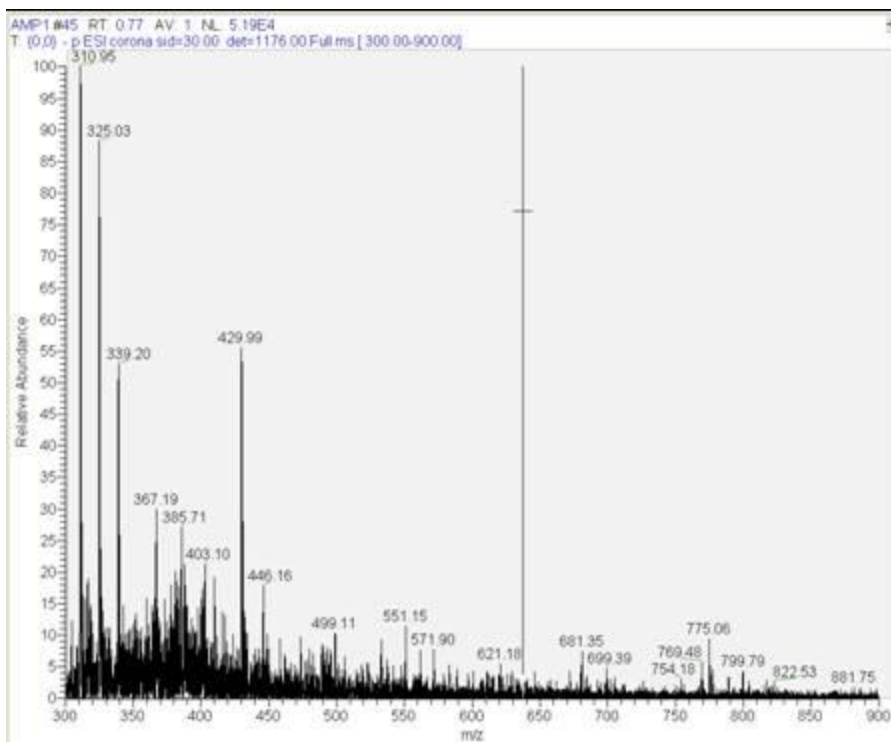
Figure 3.6 – ESI-MS spectrum of the reaction (24 hours) between $TcOCl_4^-$ and AMP ([Tc] = $1x10^{-5}$ M, Tc:L = 1:4)

The UV-visible spectra of the $TcO(AMP)_2^-$ species recorded after 24 hours is presented in Figure 3.7. The UV-visible spectra of $TcO(AMP)_2^-$ exhibits band at 236 nm. The extinction coefficient determined using the Beer-Lambert's equation, was $4.47x10^5$ M^{-1}. cm^{-1} (See table A.3).
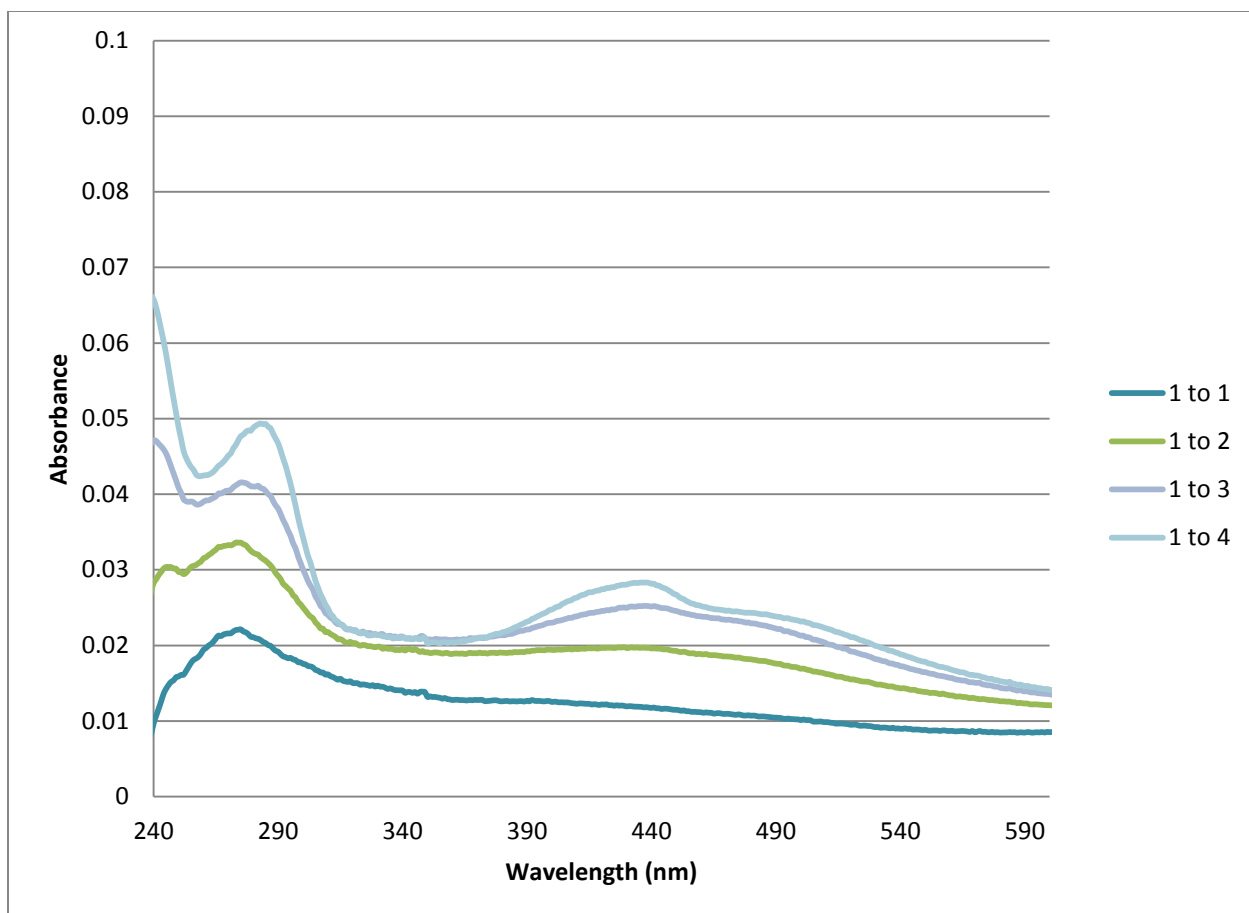
Figure 3.7 UV-visible spectra of the $TcO(AMP)_2^-$ complex obtained after reaction (24 hours) between $TcOCl_4^-$ and AMP ([Tc] = $3x10^{-6}$ M, Tc:L = 1:1, 1:2, 1:3, 1:4)

The time required for the formation of $TcO(AMP)_2^-$ is similar to that for the formation of the $TcO(PDA)_2^-$ (24 hours). The kinetic formation of the $TcO(AMP)_2^-$ complex was further studied and the initial reaction rate (r_0) Equation 2.2 was determined. The initial reaction rate was respectively $8.99x10^{-12}M^{-1}\cdot min^{-1}$ (See table A.4).

Figure 3.8 - UV-visible spectrum as a function of the time for the reaction of (n-Bu$_4$N)TcOCl$_4$ with AMP in ethanol. ([Tc] =1x10^{-5} M, Tc:L = 1:4)

The reaction between TcOCl$_4^-$ and AMP was studied for a 24 hours period. The representation of the absorbance at 236 nm for the TcO(AMP)$_2$ complex (Figure 3.9) is represented as a function of the time. Analysis of Figure 3.9 show three distinct regions:

Region A (0 - 240 min): the absorbance increases linearly from 0 to 0.251

Region B (240 – 480 min): the absorbance decreases from 0.251 to 0.246

Region C (t > 480 min): the absorbance increases linearly.

The opposite trend is observed for the free ligand (peak at 208 nm, Figure 3.10). The absorbance peaks for the free ligand rises dramatically and the peak associated with the metal-ligand complex decreases. A gradual decrease in free ligand presence and the continuous increase in the concentration of $TcO(AMP)_2^-$ is also observed.

This trend suggests that the formation of $TcO(AMP)_2^-$ from $TcOCl_4^-$ occurs in two steps. The first step involves the replacement of two chlorine ligands by one AMP ligand (Equation 2.1), the second step is the replacement of the remaining two chlorine ligand by one AMP (Equation 2.2).

$$TcOCl_4^- + AMP \rightarrow TcOCl_2(AMP)^- \hspace{3cm} \text{(Equation 3.2)}$$

$$TcOCl_2(AMP)^- + AMP \rightarrow TcO(AMP)_2^- \hspace{3cm} \text{(Equation 3.3)}$$
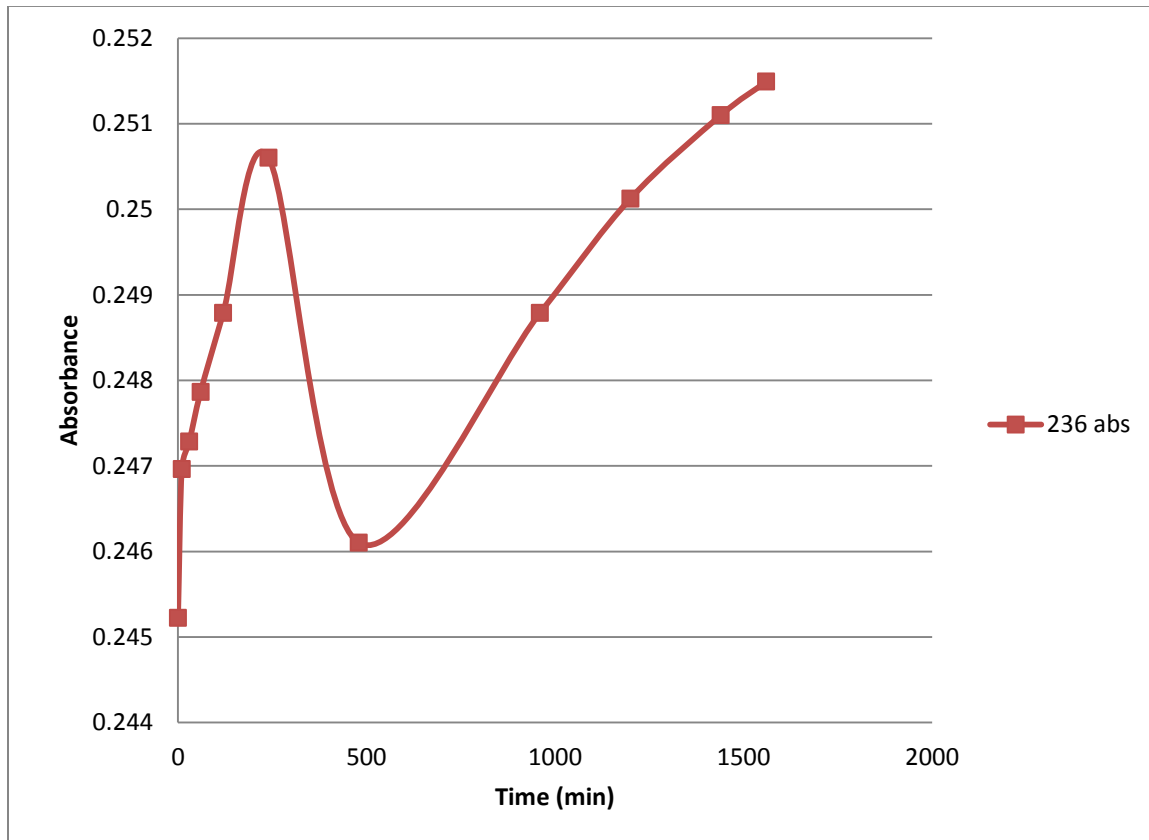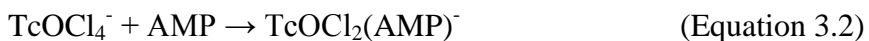
Figure 3.9 – Change in absorbance at 236 nm as a function of time for the solution

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obtained after the reaction of (n-Bu$_4$N)TcOCl$_4$ with AMP in ethanol. ([Tc] = 1x10^{-5} M, Tc:L =1:4)
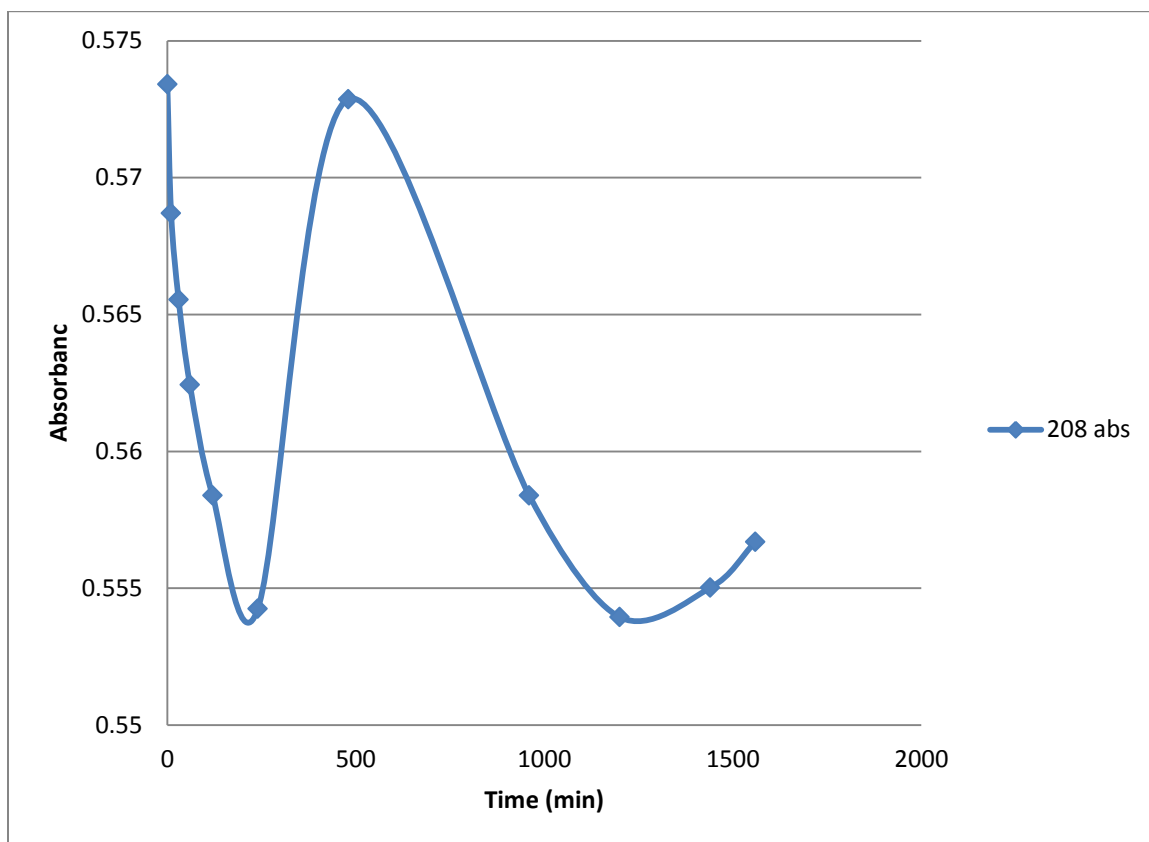
Figure 3.10 Change in absorbance at 208 nm as a function of time for the solution obtained after the reaction of (n-Bu$_4$N)TcOCl$_4$ with AMP in ethanol. ([Tc] =1x10^{-5} M, Tc:L =1:4)

3.4   Study of the reaction between TcOCl$_4^-$ and 2-mercaptophenol

The reaction between TcOCl$_4^-$ and 2-mercaptophenol in ethanol ([Tc]= 1x10^{-5} M, Tc: L =1:4) was studied for 24 hours. After 24 hours, the solution was analyzed by ESI-MS. In parallel, TcOCl$_4^-$ (3x10^{-6} M) was reacted with MP in a ratio ranging from 1:1 to 1:4 for a 24 hours period and analyzed by UV-visible spectroscopy. The ESI-MS spectra

(Figure 3.11) shows a peak at m/z = 362.69 which is consistent with the presence of TcO(MP)$_2^-$ (m/z = 363).
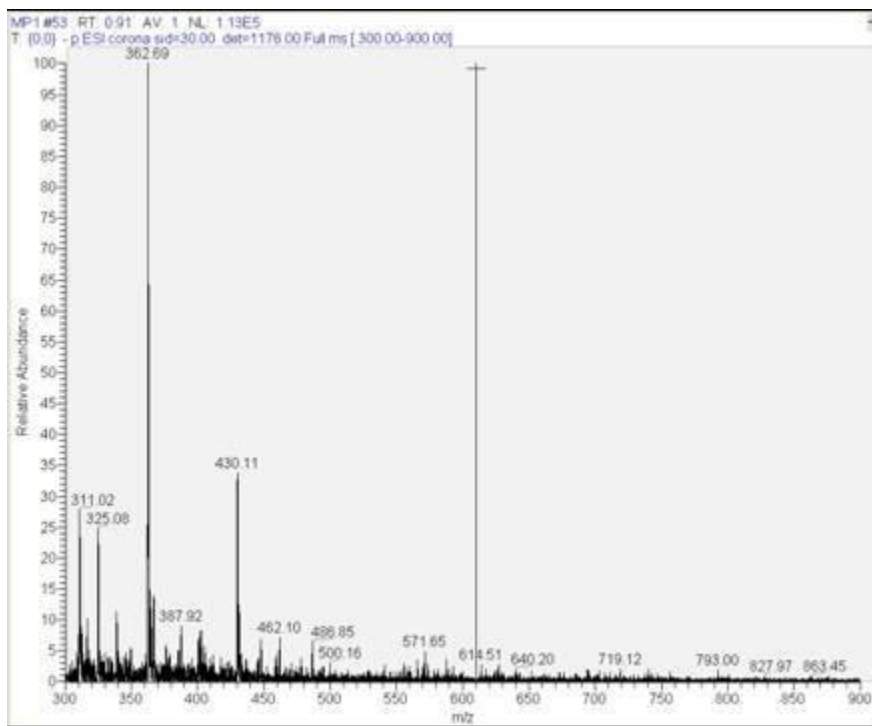
Figure 3.11 – ESI-MS spectrum of the reaction (24 hours) between TcOCl$_4^-$ and MP ([Tc] = 1x10^{-5} M, Tc:L = 1:4)

The UV-visible spectra of the TcO(MP)$_2^-$ species recorded after 24 hours is presented in Figure 3.12. The UV-visible spectra for the reaction of TcOCl4- with MP exhibits a band at 285 nm associated with free ligand , for which the extinction coefficient (1.87x10^{4}M^{-1}·cm^{-1}) was determined using the Beer-Lambert's law (See tabe A.5).
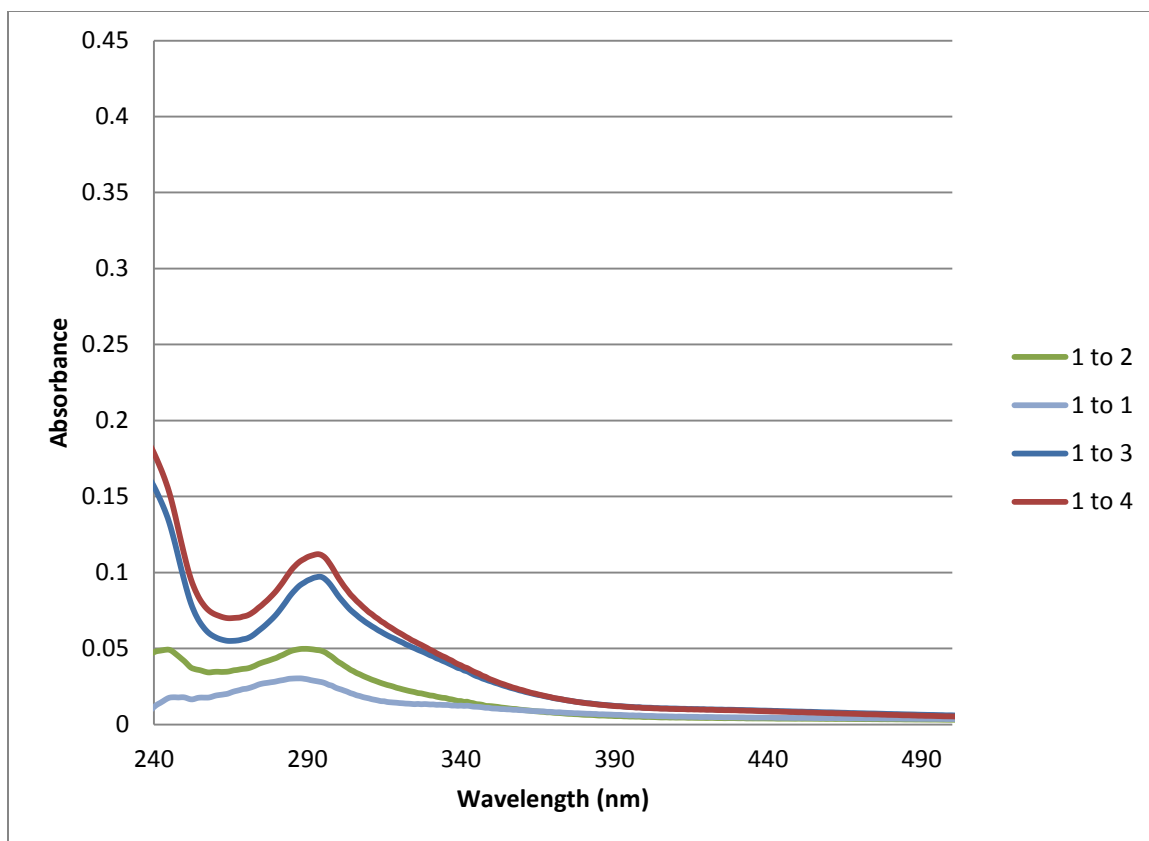
Figure 3.12 - UV-visible spectra of the TcO(MP)$_2^-$ complex obtained after reaction (24 hours) between TcOCl$_4^-$ and o- phenylenediamine ([Tc] = 3x10^{-6} M, Tc:L = 1:1, 1:2, 1:3, 1:4)

The kinetic formation of the TcO(MP)$_2^-$ complex was studied and the initial reaction rate (r$_0$) determined. The reaction between TcOCl$_4^-$ and MP was followed over a 24 hours and spectra were regularly recorded (Figure 3.13). UV-visible measurements show a steady increase in absorbance for TcO(MP)$_2^-$ while the free ligand absorbance steadily decreases. The representation of the TcO(MP)$_2^-$ concentration as a function of the time (Figure 3.14) was determined using the band at 285 nm and taking the difference of initial ligand concentration to find the concentration of the complex. The initial reaction rate was respectively 5.31x10^{-10} M^{-1}·min^{-11}(See table A.6).
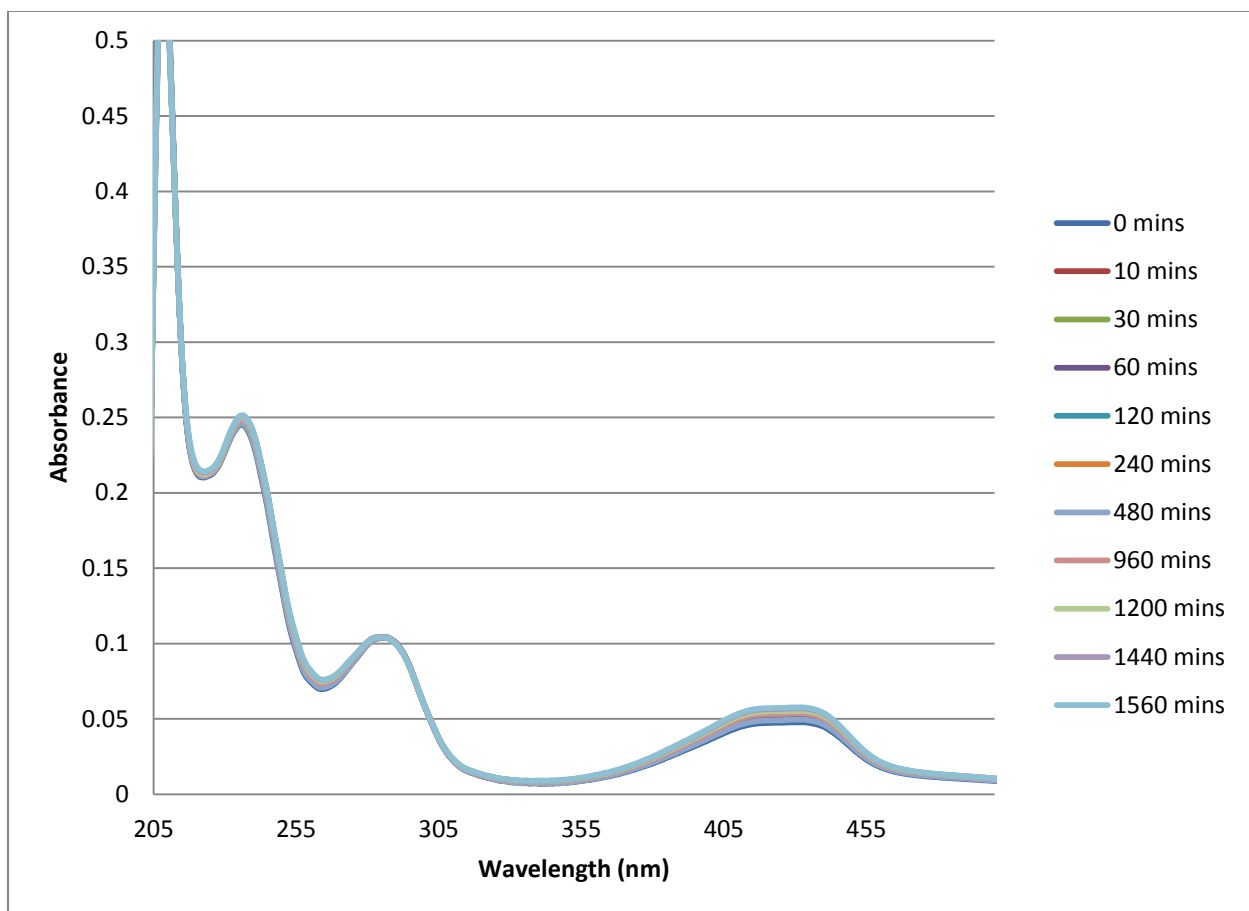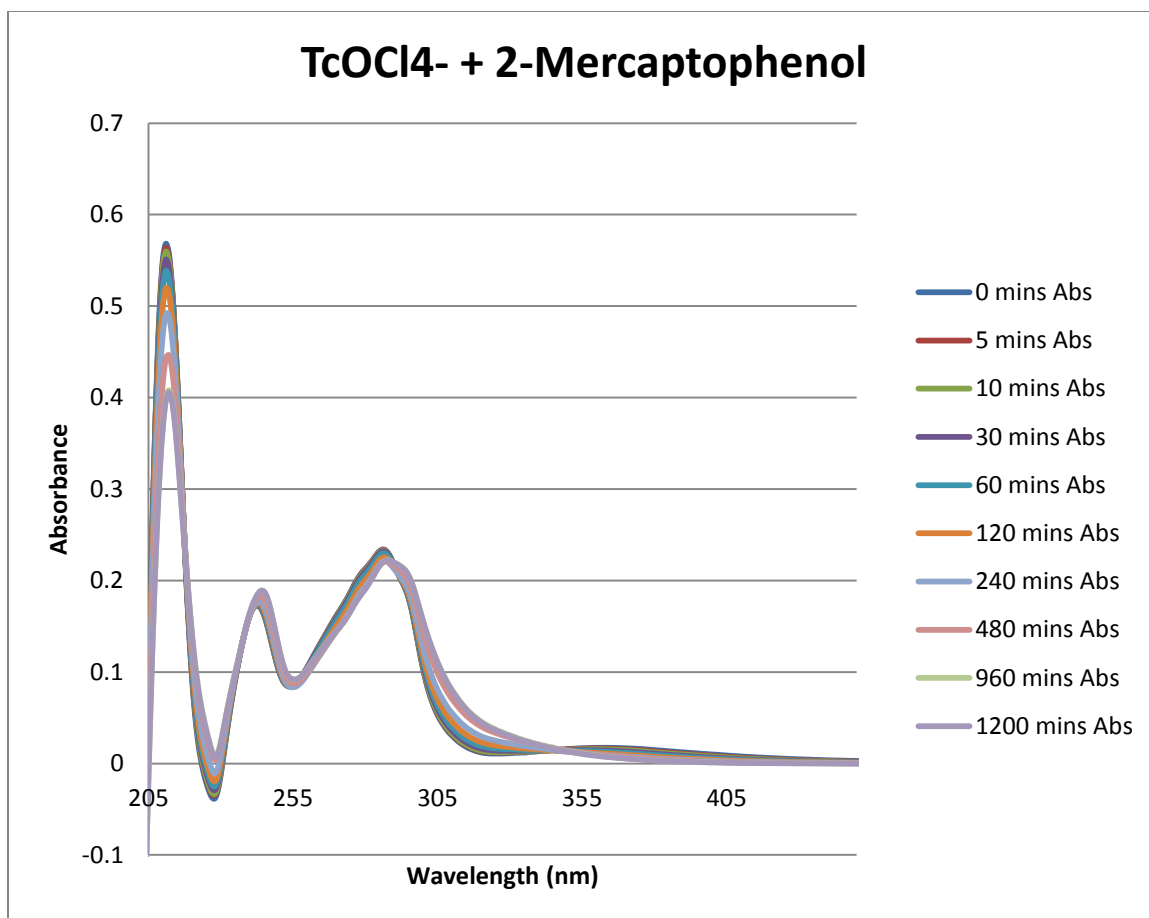
Figure 3.13 - UV-visible spectrum as a function of time of the reaction of (n-Bu$_4$N)TcOCl$_4$ with MP in ethanol. ([Tc] =1x10^{-5} M, Tc:L =1:4)
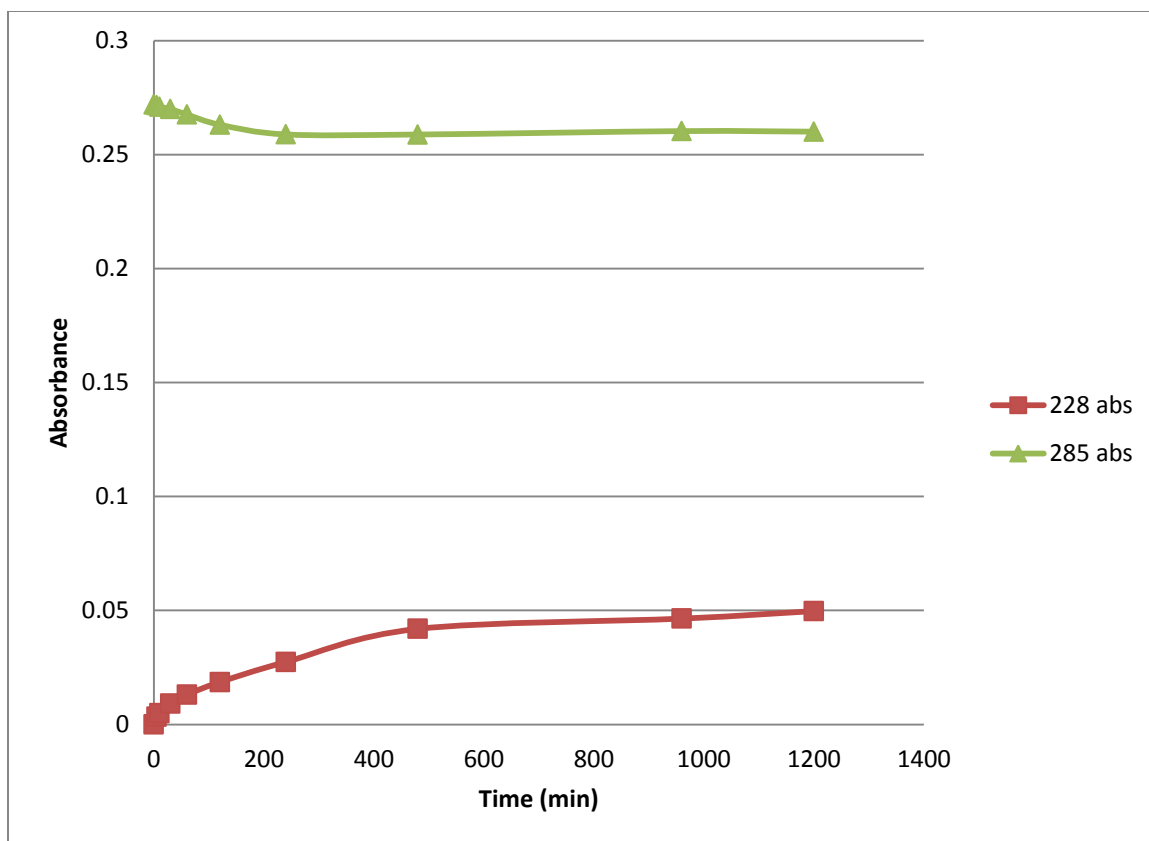
Figure 3.14 – Changes in absorbance at 228 nm (in red, TcO(MP)$_2^-$) and 285 nm (in green, free MP ligand) as a function of the time in the solution obtained after the reaction of (n-Bu$_4$N)TcOCl$_4$ with MP in ethanol. ([Tc] = 1x10^{-5} mol·L^{-1}, Tc:L =1:4)

3.5   Study of the reaction between TcOCl$_4^-$ and thiosalicylic acid

The reaction between TcOCl$_4^-$ and thiosalicylic acid in ethanol ([Tc] = 1x10^{-5} M, Tc: L =1:4) was studied for a 24 hours period. After 24 hours, the solution was analyzed by ESI-MS. A solution of TcOCl$_4^-$ (3x10^{-6} M) was reacted with TSA in a ratio ranging from 1:1 to 1:4 for a 24 hours period and analyzed by UV-visible spectroscopy. The ESI-MS spectrum (Figure 3.15) shows a peak at   m/z = 418.78 which is consistent with the presence of TcO(TSA)$_2^-$ (m/z = 419). The UV-visible spectra recorded after 24 hours is

presented in Figure 3.15. The UV-visible spectra exhibits an intense band at 310 nm for which the extinction coefficient was $3.51 \times 10^4 M^{-1} . cm^{-1}$ (See table A.7).
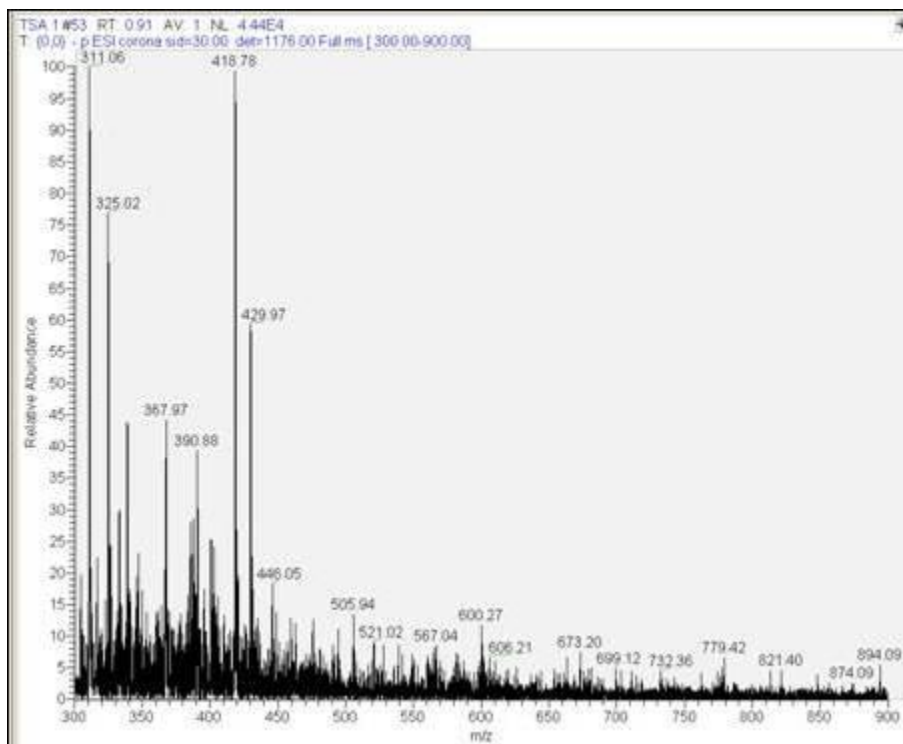
Figure 3.15 – ESI-MS spectrum of the reaction (24 hours) between $TcOCl_4^-$ and TSA ($[Tc] = 1 \times 10^{-5} M$, Tc:L = 1:4)
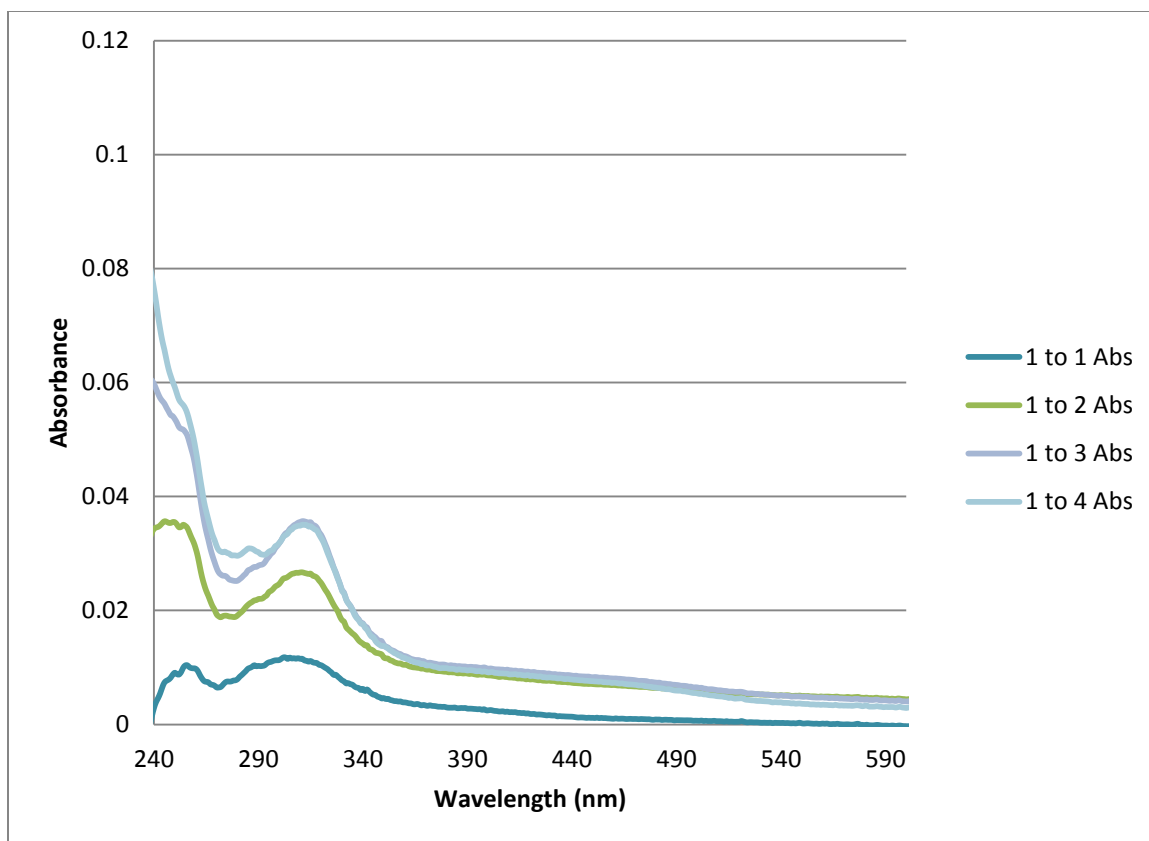
Figure 3.16 UV-visible spectra of the solution obtained after reaction (24 hours) between $TcOCl_4^-$ and TSA ($[Tc] = 3x10^{-6}$ M, Tc:L = 1:1, 1:2, 1:3, 1:4)

The reaction between $TcOCl_4^-$ and TSA was followed over a 24 hours and spectra were regularly recorded (Figure 3.17). The representation of the absorbance at 205 nm, 220 nm (free TSA ligand) and 310 nm is presented in Figure 3.18.
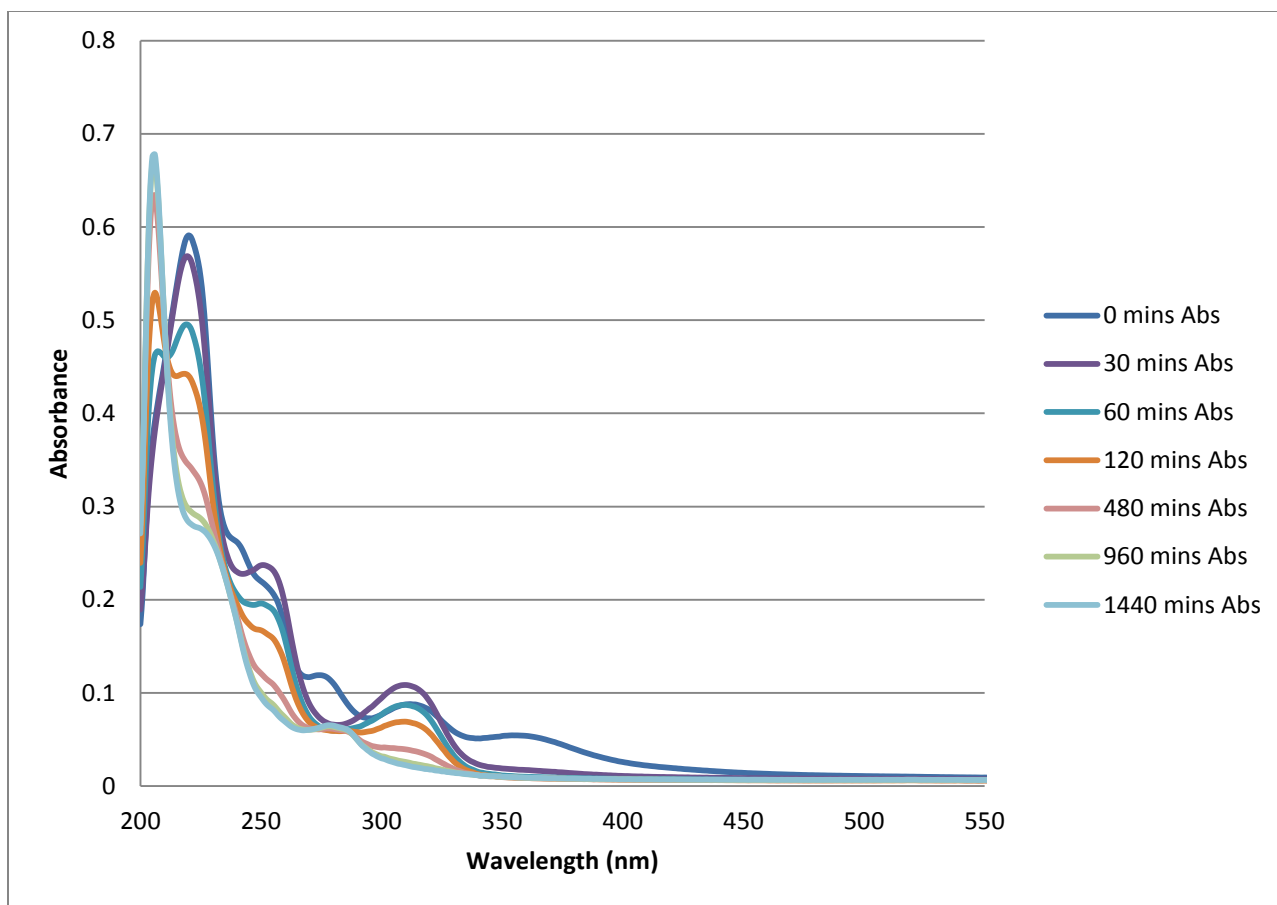
Figure 3.17 - UV-visible spectra as a function of time of the reaction of (n-Bu$_4$N)TcOCl$_4$ with TSA in ethanol. ([Tc]=1x10^{-5} M, Tc:L =1:4)

Analysis of Figure 3.18 is consistent with the presence of various TcO-TSA complexes in solution and the following speciation was postulated :

The complex which exhibits the peak at 205 nm is TcO(TSA)$_2^-$. The complexes which exhibit the peak 260 nm, 274 nm, and 310 nm is TcO(TSA)Cl$_2^-$.

This would make the chemical equation for the reaction as follows:

$$2TcOCl_4^- + 3TSA \rightarrow TcO(TSA)Cl_2^- + TcO(TSA)_2 \qquad \text{Equation 3.4}$$
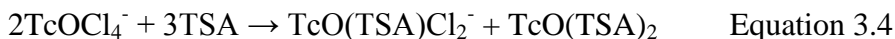
These findings are supported by the presence of a peak at m/z=339in figure 3.15 which has significantly lower abundance than the peak present at m/z=418.78. For the extinction

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coefficient measurements, it was clear that the reaction had gone to completion and all technetium and ligand variables could be determined at ratios of 1:3 and 1:4, but at lower ratios (1:1 and 1:2) and in the kinetic study data is not sufficient to properly postulate the concentration of TSA and $TcO(TSA)_2^-$. For this reason all kinetic data is representative of the formation of $TcO(TSA)Cl_2^-$ and not the other variables.
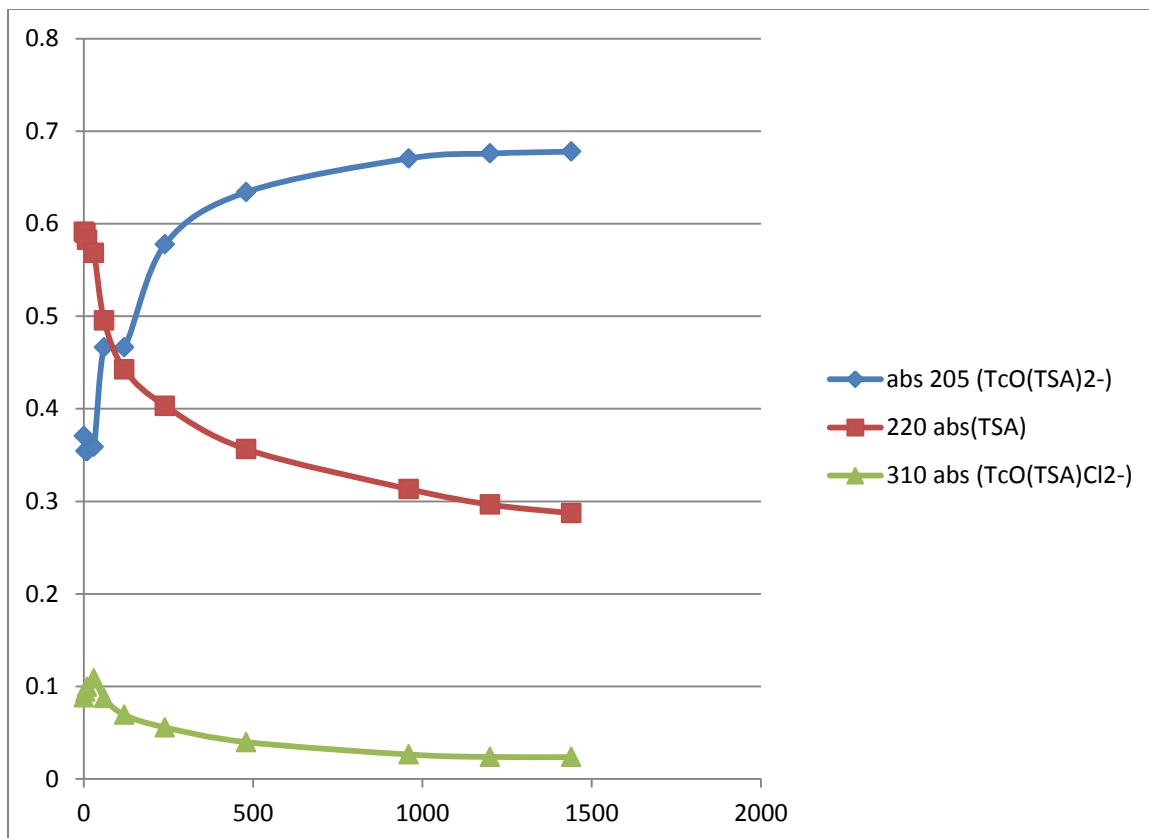
Figure 3.18 - Representation of the absorbance as a function of the time for the solution obtained after the reaction of (n-Bu$_4$N)TcOCl$_4$ with TSA in ethanol. ([Tc] =1x10^{-5} M, Tc:L =1:4). Absorbance at: 205 nm (in blue $TcO(TSA)_2^-$), 220 nm (in red free TSA ligand) and 310 nm($TcO(TSA)$).

Figure 3.19 shows that the $TcO(TSA)Cl_2^-$ concentration increases to a maximum after just 30 minutes, after which the concentration continually decreases. The reaction

rate for the formation of the $TcO(TSA)Cl_2^-$ complexe is respectively $1.95x10^{-8}M^{-1}\cdot min^{-1}$

(See figure A.8).
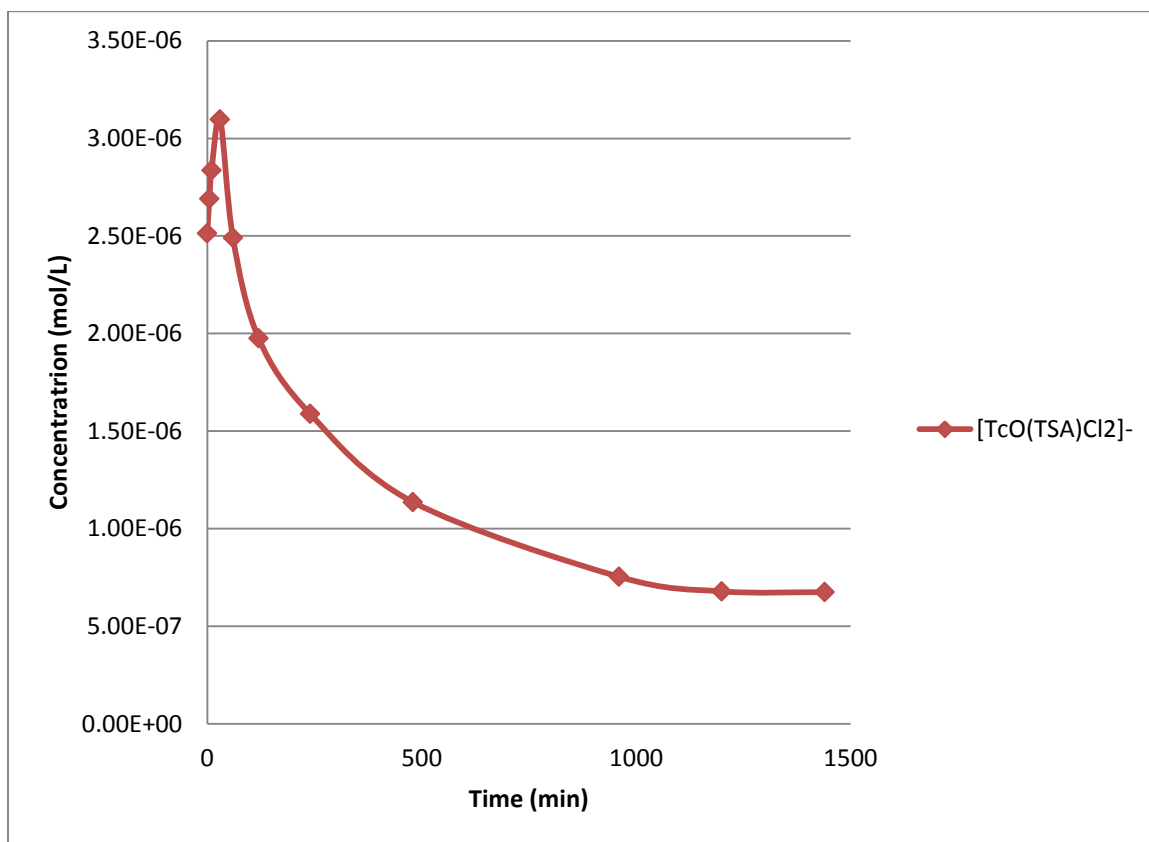
Figure 3.19 - Representation of the concentration of $(TcO(TSA)Cl_2^-)$ as a function of time. ($[Tc] = 1x10^{-5}$ M, Tc:L = 1:4)

Chapter 4: Conclusion and Future Works

In summary, the reaction of bidentate aniline derivatives (2-aminophenol (AMP)) and two thiobenzene derivatives (2-mercaptophenol (MP) and thiosalicylic acid (TSA)) with pentavalent technetium has been investigated for the development of radiopharmaceutical complexes. The $TcOCl_4^-$ complex was used as a precursor and showed reactivity with all the ligand studied.. The Tc: L molar ratio (1:1 and 1:2) were confirmed by electrospray ionization mass spectrometry (ESI- MS). The complexes with a stoichiometry $[TcO(L)_2[$ (L = PDA, AMP, MP, TSA) were identified by ESI-MS. Absorption spectra, extinction coefficient and kinetic formation of these complexes were determined using UV-visible spectroscopy. The results obtained for the various complexes are summarized in Table 4.1.

Complex	r_0 ($M^{-1} \cdot min^{-1}$)	ε ($M^{-1} \cdot cm^{-1}$)	m_{theor} (m/z)	m_{exp} (m/z)
$TcO(PDA)_2^-$	$2.26x10^{-9}$	$1.96x10^4$	323	325.06
$TcO(AMP)_2^-$	$8.99x10^{-12}$	$4.47x10^5$	327	325.03
$TcO(MP)_2^-$	$5.31x10^{-10}$	$1.87x10^4$	363	362.69
$TcO(TSA)Cl_2^-$	$1.95x10^{-8}$	$3.51x10^4$	339	339
$TcO(TSA)_2^-$	N/A	N/A	419	418.78

Table 4.1 – Summary of results for the reaction of (n-Bu$_4$N)TcOCl$_4$ with ligands (PDA, AMP, TSA, MP) in ethanol

The purpose of this study was to establish which ligand would be best suited for radiopharmaceutical applications as time is a major factor in developing ^{99m}Tc complexes. While most of the reactions took about 24 hours to reach completion, the

complex of TcO(TSA)$_2^-$ has the fastest formation rate while the TcO(PDA)$_2^-$ had that fastest reaction rate for the aniline derivatives (Table 4.1).

Concerning the formation mechanisms, it is proposed that the formation of TcO(AMP)$_2^-$ from TcOCl$_4^-$ occurs in two steps. The first step involves the replacement of two Cl- ligands by one AMP ligand (TcOCl$_4^-$ + AMP → TcOCl$_2$(AMP). The second step is the replacement of the remaining Cl- ligands by one AMP (TcOCl$_2$(AMP)$^-$ + AMP → TcO(AMP)$_2^-$). In order to confirm the stepwise formation of TcO(AMP)$_2^-$, it would be of interest to perform ESI-MS measurements after 2 hours, 4 hours and 16 hours of reaction. Similar work should be performed on the TSA complex, and ESI-MS measurements performed after 30 and 60 minutes.

It will be of interest to determine the structure in solution and in solid state of the four complexes studied. X-ray Absorption Fine Structure spectroscopy (XAFS) could be use to determine the structure in solution. If single crystals can be obtained, X-ray diffraction can be use for the solid state structure determination. Along with this structural determination, evaluation of the reaction rate at different temperatures will establish the ideal conditions and parameters for the production of these complexes.

It will also be of interest to transpose the study performed on Tc(+5) to Tc(+6) and Tc(+4). For the hexavalent technetium, it is expected that complexes with the stoichiometry TcN(L)$_2^-$ should form. In this context, the (n-Bu$_4$N)TcNCl$_4$ and (n-Bu$_4$N)$_2$TcCl$_6$ salts have been already synthesized (Appendix I) and preliminary studies show that TcNCl$_4^-$ reacts with ligands. Studies also show that TcCl$_6^{2-}$ should react with

the ligands but these studies had the competing reaction of the formation of TcO_2 as they were performed in perchloric acid.[10,11]

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Appendix

I.   Supplemental Data Tables

Tc:PDA	[TcO(PDA)$_2$]	[TcOCl$_4^-$]	[PDA]	280 abs	ε_{280}
1:1	1.5×10^{-6}	1.5×10^{-6}	0	0.022587	1.5×10^4
1:2	3×10^{-6}	0	0	0.039116	1.30×10^4
1:3	3×10^{-6}	0	3×10^{-6}	0.044676	1.49×10^4
1:4	3×10^{-6}	0	6×10^{-6}	0.058704	1.96×10^4

Table A.1 – Molar absorption determination variables for the reaction (24 hours) of TcOCl4- with PDA

Time	280 abs	[TcO(PDA)2-]	[Tc]	[PDA]
0	6.56×10^{-2}	3.35×10^{-6}	6.65×10^{-6}	3.33×10^{-5}
5	0.063192	3.23×10^{-6}	6.77×10^{-6}	3.35×10^{-5}
10	0.070605	3.61×10^{-6}	6.39×10^{-6}	3.28×10^{-5}
60	0.104993	5.37×10^{-6}	4.63×10^{-6}	2.93×10^{-5}
120	0.117761	6.02×10^{-6}	3.98×10^{-6}	2.80×10^{-5}
230	0.124675	6.37×10^{-6}	3.63×10^{-6}	2.73×10^{-5}
470	0.125555	6.42×10^{-6}	3.58×10^{-6}	2.72×10^{-5}
950	0.127099	6.50×10^{-6}	3.50×10^{-6}	2.70×10^{-5}
1190	0.127489	6.52×10^{-6}	3.48×10^{-6}	2.70×10^{-5}
1400	0.127348	6.51×10^{-6}	3.49×10^{-6}	2.70×10^{-5}

Table A.2 - Time dependent data for the reaction of (n-Bu$_4$N)TcOCl$_4$ with PDA in ethanol. ([Tc] =1×10^{-5} M, Tc:L = 1:4)

AMP:Tc	$[TcO(AMP)_2^-]$	$[TcOCl_4^-]$	[AMP]	$Abs_{236\ nm}$	$\varepsilon_{236\ nm}$
1:1	1.5×10^{-6}	1.5×10^{-6}	0	0.330696	2.20×10^5
1:2	3×10^{-6}	0	0	0.833182	2.78×10^5
1:3	3×10^{-6}	0	3×10^{-6}	1.136302	3.79×10^5
1:4	3×10^{-6}	0	6×10^{-6}	1.340907	4.47×10^5

Table A.3 – Molar absorption determination variables for the reaction (24 hours) of TcOCl4- with AMP

Time (min)	$Abs_{236\ nm}$	$[TcO(AMP)_2^-]$	[AMP]	$[TcOCl_4^-]$
0	0.245221	5.49×10^{-7}	3.89×10^{-5}	9.95×10^{-5}
10	0.246961	5.53×10^{-7}	3.89×10^{-5}	9.94×10^{-5}
30	0.247285	5.53×10^{-7}	3.89×10^{-5}	9.94×10^{-5}
60	0.247865	5.55×10^{-7}	3.89×10^{-5}	9.94×10^{-5}
120	0.248788	5.57×10^{-7}	3.89×10^{-5}	9.94×10^{-5}
240	0.250604	5.61×10^{-7}	3.89×10^{-5}	9.94×10^{-5}
480	0.2461	5.51×10^{-7}	3.89×10^{-5}	9.94×10^{-5}
960	0.248788	5.57×10^{-7}	3.89×10^{-5}	9.94×10^{-5}
1200	0.250125	5.60×10^{-7}	3.89×10^{-5}	9.94×10^{-5}
1440	0.251101	5.62×10^{-7}	3.89×10^{-5}	9.94×10^{-5}
1560	0.251491	5.63×10^{-7}	3.89×10^{-5}	9.94×10^{-5}

Table A.4 - Time dependent data for the reaction of (n-Bu$_4$N)TcOCl$_4$ with AMP in ethanol. ([Tc] =1x10^{-5} M, Tc:L = 1:4)

MP:Tc	$[TcO(MP)_2^-]$	$[TcOCl_4^-]$	$[MP]$	Abs $_{285\ nm}$	ε $_{211\ nm}$
1:1	1.5×10^{-6}	1.5×10^{-6}	0	0.049742	N/A
1:2	3×10^{-6}	0	0	0.030313	N/A
1:3	3×10^{-6}	0	3×10^{-6}	0.097225	3.24×10^{4}
1:4	3×10^{-6}	0	6×10^{-6}	0.111993	1.87×10^{4}

Table A.5 – Molar absorption determination variables for the reaction (24 hours) of TcOCl4- with MP

Time (min)	Abs $_{211\ nm}$	$[MP]$	$[TcO(MP)_2^-]$	$[TcOCl_4^-]$
0	0.271937638	1.46×10^{-5}	3.64×10^{-6}	6.36×10^{-6}
5	0.271649778	1.46×10^{-5}	3.64×10^{-6}	6.36×10^{-6}
10	0.270926476	1.45×10^{-5}	3.63×10^{-6}	6.37×10^{-6}
30	0.269940898	1.45×10^{-5}	3.62×10^{-6}	6.38×10^{-6}
60	0.267573386	1.43×10^{-5}	3.58×10^{-6}	6.42×10^{-6}
120	0.263088584	1.41×10^{-5}	3.52×10^{-6}	6.48×10^{-6}
240	0.258831382	1.39×10^{-5}	3.47×10^{-6}	6.53×10^{-6}
480	0.258794978	1.39×10^{-5}	3.47×10^{-6}	6.53×10^{-6}
960	0.260295406	1.39×10^{-5}	3.49×10^{-6}	6.51×10^{-6}
1200	0.260053366	1.39×10^{-5}	3.48×10^{-6}	6.52×10^{-6}

Table A.6 - Time dependent data for the reaction of (n-Bu$_4$N)TcOCl$_4$ with MP in ethanol. ([Tc] =1x10^{-5} M, Tc:L = 1:4)

Tc:TSA	Abs$_{310\ nm}$	[TcO(TSA)Cl$_2^-$]	[TcO(TSA)$_2^-$]	[TSA]	$\varepsilon_{310\ nm}$
1:3	0.035675	1.00x10^{-6}	2.00x10^{-6}	0.00	3.57x10^4
1:4	0.035053	1.00x10^{-6}	2.00x10^{-6}	3.00x10^{-6}	3.51x10^4

Table A.7 – Molar absorption determination variables for the reaction (24 hours) of TcOCl4- with TSA (Variables at concentratsion of 1:1 and 1:2 were not included as the concentration of both species cannot be determined)

Abs $_{310\ nm}$	[TcO(TSA)Cl$_2$]-
0.088082679	2.51x10^{-6}
0.094308898	2.69x10^{-6}
0.099431358	2.84x10^{-6}
0.108560488	3.10x10^{-6}
0.087278999	2.49x10^{-6}
0.069236711	1.97x10^{-6}
0.055681445	1.59x10^{-6}
0.039838295	1.14x10^{-6}
0.026438527	7.54x10^{-7}
0.023810055	6.79x10^{-7}
0.023664469	6.75x10^{-7}

Table A.8 - Time dependent data for the reaction of (n-Bu$_4$N)TcOCl$_4$ with TSA in ethanol. ([Tc] =1x10^{-5} M, Tc:L = 1:4)
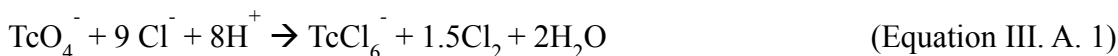
II.   Preparation of tetrabutylammonium nitride tetrachlorotechnetate – (n-Bu4N)TcNCl4

The (n-Bu$_4$N)TcNCl$_4$ salt was prepared from the reaction of impure NH$_4$TcO$_4$ with sodium azide in HCl followed by precipitation with (n-Bu$_4$N)Cl. In this procedure, cold 12 M HCl was added to impure NH$_4$TcO$_4$ (70 mg) and a yellow color (TcCl$_6$$^{2-}$), and evolution of gas were observed. Then, an aqueous solution of NaN$_3$ (200 mg in 0.5 mL of water) was added to the solution which immediately turns orange. The solution was warmed for 20 min at 80 °C. The solution was then separated from a white solid, NaCl. A solution of 350 mg (n-Bu$_4$N)Cl in 2 mL of H$_2$O was added to the orange solution and an orange solid immediately precipitated. The solution was washed twice with H$_2$O and dried at 90 °C for 12 hours. The orange powder was then recrystallized 2 times from 4 mL THF and 12 mL of hexane. The final product was washed twice with hexane.

III.   Preparation of hexachlorotechnetate salts
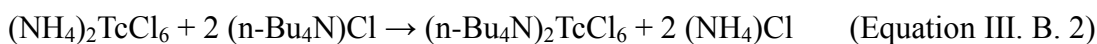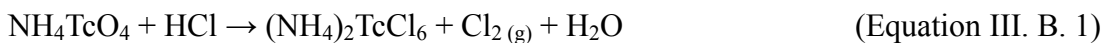
A.   Potassium hexachlorotechnetate – K$_2$TcCl$_6$

The K_2TcCl_6 was synthesized by the reaction between NH_4TcO_4 and warm 12 M HCl/KCl.

$$TcO_4^- + 9\,Cl^- + 8H^+ \rightarrow TcCl_6^- + 1.5Cl_2 + 2H_2O \hspace{2cm} \text{(Equation III. A. 1)}$$

Impure NH_4TcO4 (90 mg) and KCl were added to 2 mL of 12 M HCl in 10 mL Schlenk flask. The solution became green and evolution of chlorine gas was observed. The solution was heated at 110 °C until the complete dissolution of the black compound and appearance of yellow K_2TcCl_6 solid at the bottom of the flask. After complete conversion to K_2TcCl_6 (15 to 20 minutes), the solution was cooled to room temperature. The yellow supernatant was removed and the solid washed two times with 2 mL of cold isopropanol and two times with 3 mL of diethyl ether. The solid was dried under an argon flux with gentle heating.

B. Tetrabutylammonium hexachlorotechnetate – $(n\text{-}Bu_4N)_2TcCl_6$

The synthesis of $(n\text{-}Bu_4N)_2TcCl_6$ was completed by precipitation of K_2TcCl_6 in dilute HCl and an acidic solution of excess $(n\text{-}Bu_4N)Cl$.

$$NH_4TcO_4 + HCl \rightarrow (NH_4)_2TcCl_6 + Cl_{2\,(g)} + H_2O \hspace{1.5cm} \text{(Equation III. B. 1)}$$

$$(NH_4)_2TcCl_6 + 2\,(n\text{-}Bu_4N)Cl \rightarrow (n\text{-}Bu_4N)_2TcCl_6 + 2\,(NH_4)Cl \hspace{0.5cm} \text{(Equation III. B. 2)}$$

A 2 mL solution of K_2TcCl_6(0.001 M) in 6M HCl was prepared. This solution was combined with 3 mL of a 0.01 M (n-Bu$_4$N)Cl solution. A yellow precipitant of (n-Bu4N)$_2$TcCl$_6$ forms and the supernatant was removed. The solution was then washed twice with H_2O and dried at 90°c for 12 hours. The powder was then recrystallized from 2 mL of acetone and 6 mL hexane.

Education:
 Bachelor of Science, Chemistry/Radiochemistry, May 2012
 South Carolina State University

Honors and Awards:
 Golden Key International Honor Society, 2009

 South Carolina State University Honors College Inductee 2009

 South Carolina State University Presidential Scholar Award (Bronze), 2010, 2011, 2012

 South Carolina State University Honors College Mr. Honors, 2010

 South Carolina State University College of Science Mathematics and Engineering Technology Deans Award of Excellence for outstanding Technical Achievement, 2010

 Professional Agricultural Workers Conference Research Oral Presentation winner, 2009

Presentations:

 Childs, K. E.; *Synthesis of Boron-Loaded Liquid, Organic Scintillators for Thermal Neutron Detection.* PAWC, December 6 – 8, 2009.

 Childs, K. E.; Poineau, F.; Czerwinski. K.; *Synthesis of Novel Dinuclear Technetium/Rhenium Compounds,* 246th ACS National Meeting, September 8-12, 2013.

Thesis Title:
Speciation of Pentavalent Technetium Complexes with Aniline and Thiobenzene Derivatives

Thesis Examination Committee:
 Chairman, Kenneth Czerwinski, PhD
 Committee Member, Frederic Poineau, PhD
 Committee Member, David Hatchett, PhD
 Committee Member, Paul Forster, PhD
 Graduate Faculty Representative, Thomas Hartmann, PhD