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Bifunctional Chelates of Rh-105 and Au-199 as Potential Radiotherapeutic Agents

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Performance Report
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Introduction

Since last year we have:

1) Continued the synthesis of pentadentate bifunctional chelating agents based on diethylene triamine,

2) Studied the chelation of Rh-105, Au-198 (as a model for Au-199) and Tc-99*m* with these agents as well as chelation of Pd-109, Cu-67, In-111, and Co-57 with some of them,

3) Synthesized a new class of potential bifunctional chelating agents based on phenylene diamine,

4) Investigated the behavior of Au-198 as a model for Au-199,

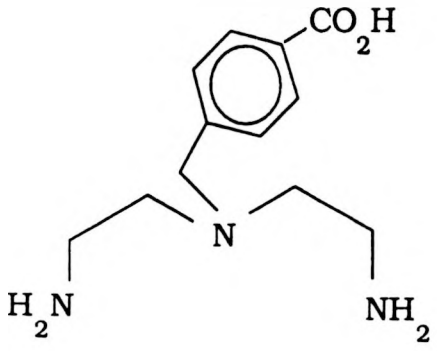
5) Begun synthesis of bifunctional chelating agents based on terpyridyl and similar ligands, and

6) Continued attempts to produce tetradentate bifunctional chelates based on diaminopropane.

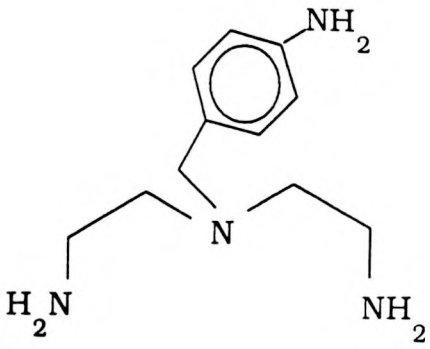
Each of these will be addressed below.

1. Pentadentate bifunctional chelating agents

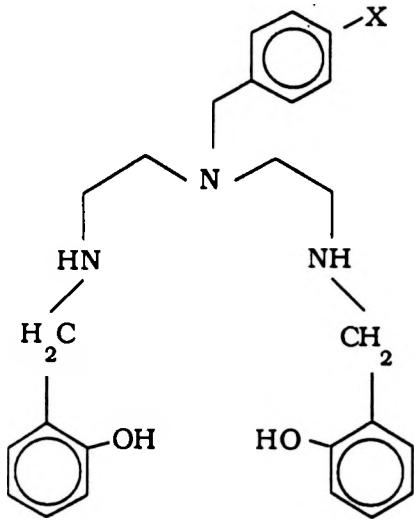
Last year we noted the ease with which a triamine could be derivatized to produce the ligands **1a** and **1b** and with which the pentadentate ligands **2a**, **2b**, and **2c** could be further prepared. This year we prepared the similar ligand **3** as a non-bifunctional model compound. In addition, we prepared a class of similar compounds based on pyrrole carboxaldehyde **4a** and **4b** and other non-bifunctional model compounds **5** and **6**. Structures for the pyrroles ligands and synthetic schemes are shown in Figs. 1-4. A scheme similar to that for **6** was used for **5**. Ligands were characterized by proton NMR.



1a



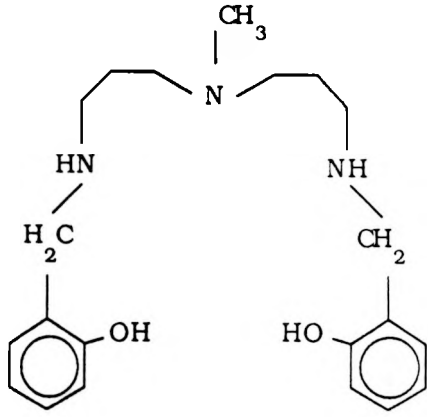
1b



2a X = NO_2

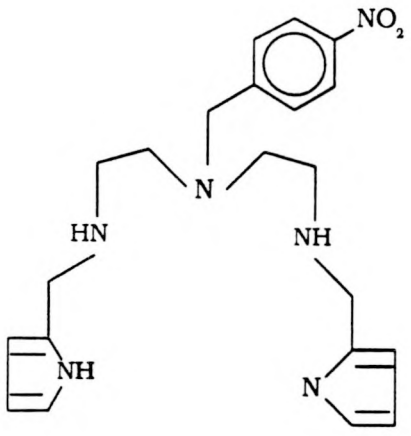
2b X = NH_2

2c X = H

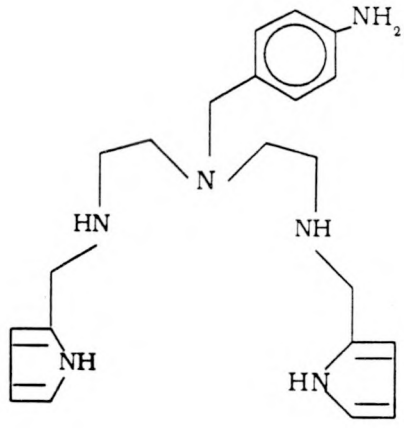


3

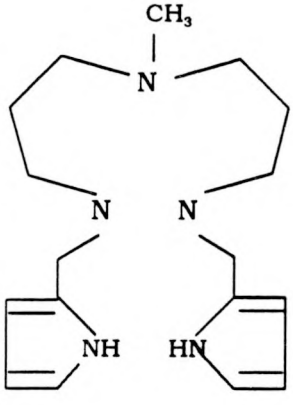
FIG. 1



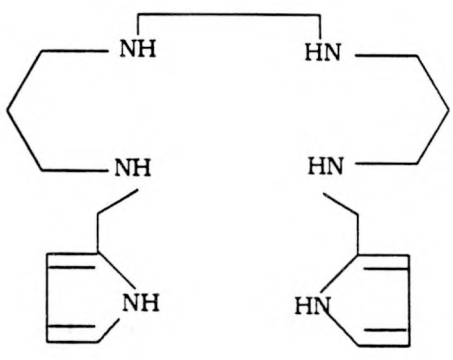
4a



4b



5



6

FIG. 2

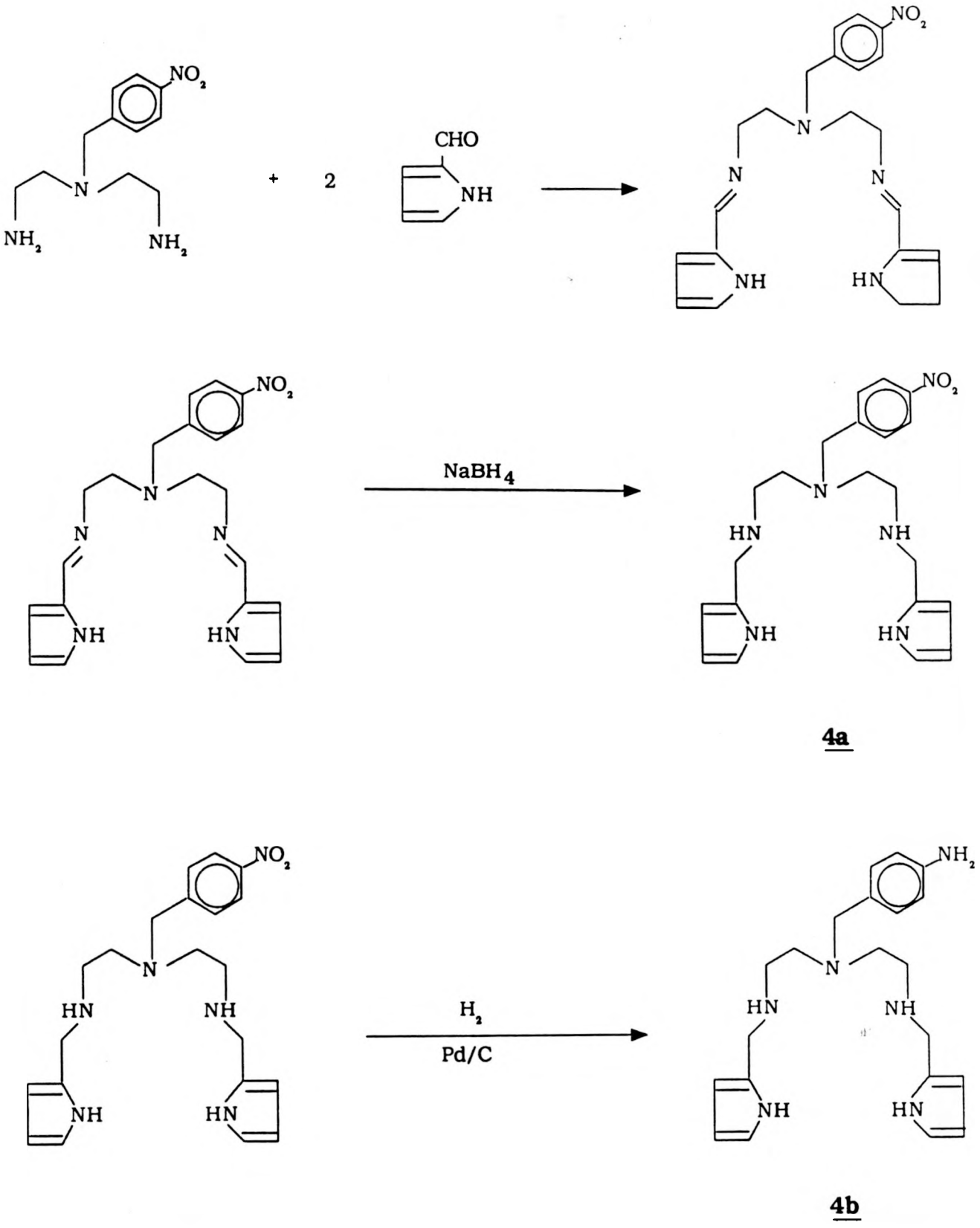
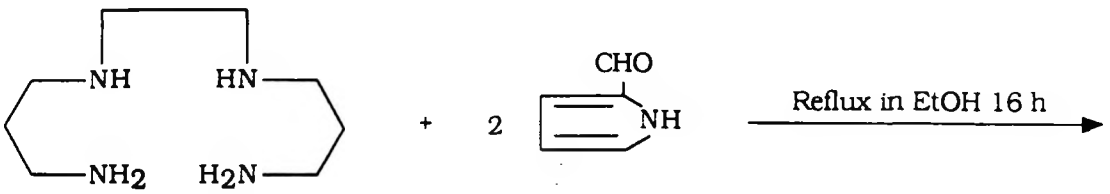
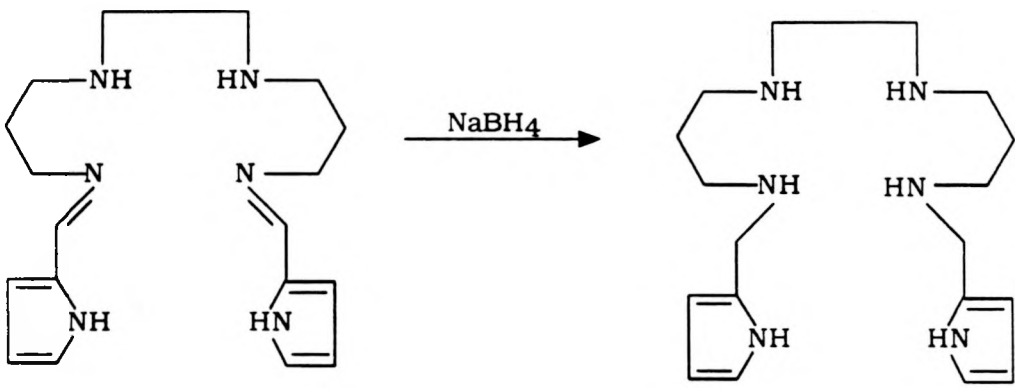

NO2
NH2
NH2
+ 2
CHO
NH
NO2
N
N
N
NH
HN
NaBH4
NO2
N
N
N
NH
HN
NO2
N
HN
NH
NH
HN
4a
H2
Pd/C
NH2
N
HN
NH
NH
HN
4b

FIG. 3


NH
HN
NH2
H2N
+
2
CHO
NH
Reflux in EtOH 16 h


NH
HN
N
N
NH
HN
NaBH4
NH
HN
NH
HN
NH
HN

6

FIG. 4

2. Chelation of radionuclides with ligands 2-3 and 4-6

One of our goals was to see if the properties of the pyrrole ligand complexes were as good as those we had found earlier with the phenols. Therefore we undertook a study of the extent of complexing found with these ligands with Rh-105, Au-198, Tc-99*m*, Pd-109, Cu-64 and 67, Co-57, and In-111. Typical experiments for chelation studies are described below.

Rh-105 $RhCl_3$ $3H_2O$ carrier (0.1 mmol) in ~2ml saline buffered at pH 9 with $NaHCO_3$ was spiked with Rh-105 and refluxed for 15 minutes. One mL of an ethanolic solution of the ligand (1.25 mmol) was added, and the solution refluxed for 1.5 hour. Uncomplexed rhodium is carried on MgO (1). The extent to which the Rh-105 was carried when 50 μL of the solution above was diluted to 0.4 mL in saline and mixed with 50 mg MgO was taken as a measure of the uncomplexed rhodium.

Au-198 Au-198 was prepared by irradiating 1 mg of gold wire for 15 minutes at flux of ~8×10^{13} n/cm^2 sec at the University of Missouri Research Reactor to give ~1 mCi of activity. The wire was dissolved in 1 mL of aqua regia which was then evaporated to dryness. The solid was taken up in 1 mL distilled water, the solution taken to dryness, and the solids redissolved in 1 mL distilled water to give a solution ~5×10^{-3} M in $AuCl_4^-$ at pH 4-5. The solution above (100 μL, 5×10^{-4} mmol) was mixed with 0.5 mL of an ethanolic solution of the ligand (2.5×10^{-3} mmol) and allowed to stand for 1 hour. The best method for estimating the yield for gold complexes was extraction into $CHCl_3$ ($AuCl_4^-$ is not extracted) or TLC using acetone as the solvent ($AuCl_4^-$ moves, the complexes do not).

Tc-99*m* Tc-99*m* complexes were prepared in a usual radiopharmaceutical fashion in which 200 μL of a saturated solution of stannous tartrate was added to 5 mL of a saline solution buffered at pH ~8-9 with $NaHCO_3$ in which TcO_4^- was ~10^{-7} M and the ligand 10^{-4} M. Complex yield was estimated by extraction into $CHCl_3$.

Pd-109 Pd-109 was prepared by irradiating ~1 mg of palladium wire for ~15 min in a flux of 8×10^{13} n/cm^2•sec. The irradiated target was transferred to a glass vial and dissolved in one mL distilled water. The solution was evaporated to remove excess acid and the residue taken up again in distilled water, the evaporation repeated, and the residue redissolved. In a typical complexation reaction, 200 μL (0.5 μmol) of an ethanolic solution of the ligand was mixed with 300 μL (0.5 μmol) of Pd-109 solution and 600 μL of ethanol and allowed to stand for 2 hr at room temperature. Complexation yields were estimated by MgO adsorption.

Cu-64,67 Cu-64 was prepared as above by irradiating ~1 mg copper for 15 min and dissolving in 8 M HNO_3. The pH of the solution was adjusted to 4. Cu-67 was prepared by the (n,p) reaction on an enriched Zn-67 ZnO target. The Cu-67 was separated from the target by an ion exchange method and delivered as a no-carrier-added product (We wish to thank Dr. Kurt Zinn of

MURR for supplying the Cu-67.). Complexes were prepared by a method similar to that for Pd-109.

Co-57 Co-57 was purchased from Dupont as $CoCl_2$ in 0.5 M HCl at a specific activity of 10 mCi/mL. This solution was used to spike a 10^{-3} M solution of $CoCl_2$. Complexes were prepared by mixing 100 µL (0.5 µmol) of an ethanolic solution of the ligand with 25 µL (0.025 µmol) of the $CoCl_2$ solution and 100 µL saline. The pH was adjusted to 6 or 9, and the solution allowed to stand for 2 hr at room temperature. Complex yields were estimated by TLC using acetone as a solvent. The $CoCl_2$ migrated with the solvent front, and the complex remained near the origin.

In-111 In-111 was obtained from Dupont as In(III) in citrate buffer at a specific activity of 0.3 mCi/mL. No carrier was added. Complexes were prepared in a manner similar to that for Co-57. In some cases solutions were buffered at pH 6 with acetate and others at pH 9 with bicarbonate. Yields were estimated by adsorption on MgO.

Conjugation to proteins was demonstrated by using human gamma globulin (Sigma 4386). In a typical experiment with Rh-105 the complex was prepared as described above, extracted into $CHCl_3$ and thiophosgene added to the organic phase to form the isothiocyanate derivative (hereafter called the activated complex) of the bifunctional chelate. The organic phase was separated and evaporated to remove solvent and excess thiophosgene. The residue was taken up in 0.1 mL DMF and added to 2 mL of 5×10^{-5} M protein (assuming average molecular weight of 150000) and allowed to stand at room temperature for 3 hr. The estimated amount of rhodium, based on extraction efficiencies, was ~2.5×10^{-5} mmol. A similar blank experiment was run in which no thiophosgene was added so that no covalent coupling should have occurred.

The amount of conjugation or coupling to the protein was estimated by loading 100 µL of the solution on a G-75 Sephadex column and eluting with saline. The eluent was collected in 2-mL fractions and the radioactivity of each fraction measured on a NaI(Tl) well scintillation counter. The percentages of activity in the protein peak and in the uncoupled complex peak were calculated by dividing the amount of activity in the fractions comprising each peak by the total amount added to the column.

Results are summarized in Table 1. High complex yields were

Table 1. Complexation and coupling yields with Rh-105

I.	Ligand	**4b**	**5**	**6**
II.	Complex yield, %	80	98	95
III.	Extraction in $CHCl_3$, %	28	21	18
IV.	Extraction of activated complex in $CHCl_3$, %	61	37	50

V.	Coupling yield, %	97	70	94
VI.	Overall coupling yield, %	60	26	47
VII.	Blank, %	16	7	4

[3] VI = IV x V

achieved with all ligands but extraction into $CHCl_3$ was low. There was, however, higher extraction of the activated complex and high coupling yields were found, especially with **4b** and **6**. There was also significant coupling with **5**. The coupling achieved with **5** and **6**, which we believe to be through an unbound pyrrole(2), suggests that for rhodium a simpler approach to the synthesis of bifunctional ligands can be taken. Bis adducts of multidentate linear amines may be satisfactory if one of the adducts, pyrrole in this case, is not bound and free for coupling. We confirmed this by synthesizing the bis pyrrole of ethylene diamine and found its rhodium complexes could also be coupled. This is consistent with our earlier work with the tridentate ligands **1a** and **1b** which showed that the stability and kinetic inertness of the rhodium complexes were high enough that three bound nitrogens were sufficient.

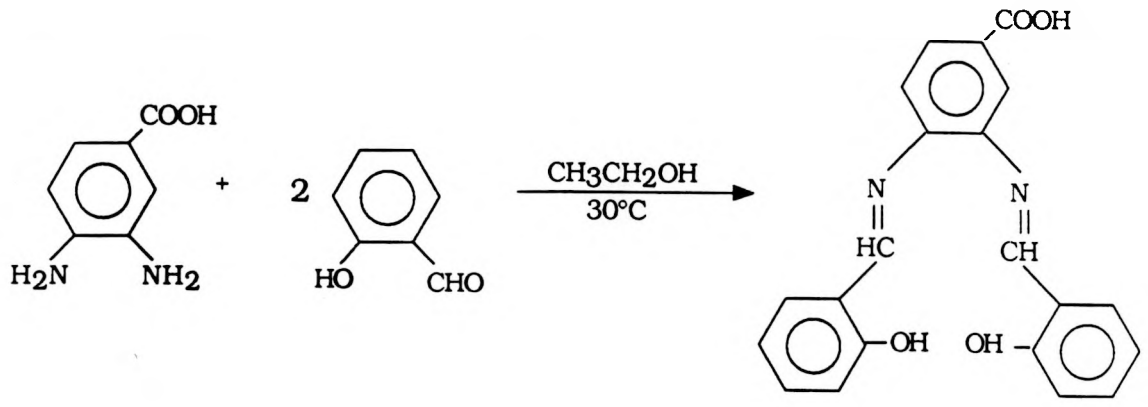
We therefore performed similar studies for complexes of **4b** and **6** for a number of other radionuclides to compare with our previous work with **2b**. The results are shown in Table 2. Yields are given by symbols to indicate percentage ranges since the actual yields vary somewhat with reaction conditions. It can be seen that for these metals the phenol ligand is more

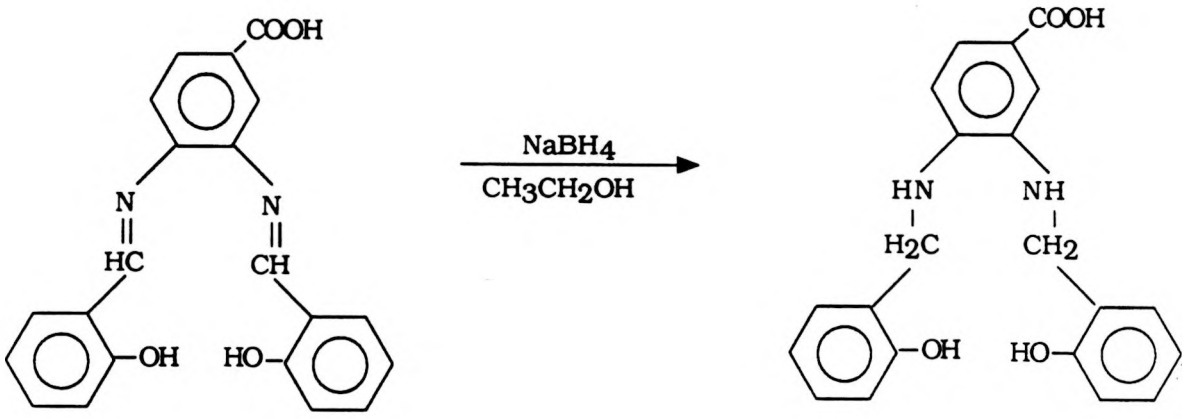
Table 2. Complexation and coupling yields (%)

	2b		**4b**		**6**	
Radionuclide	comp.	coup.	comp.	coup.	comp.	coup.
Tc-99	+++	+++	++	++	++	++
Pd-109	+++	+++	a	a	a	a
Cu-64,67	+++	+++	+++	++	+++	++
Co-57	+++	++	+++	++	+++	+
In-111	+	-	-	-	-	-

a Insoluble complexes were formed
+++ 80 - 100%
++ 50 - 80%
+ 20 - 50%
- < 20%

generally useful than the pyrroles. None of the ligands gave satisfactory results with In-111. Results with Au-198 will be discussed below.


COOH
H_2N
NH_2
+
2
HO
CHO
CH_3CH_2OH
30°C
N
HC
N
CH
OH
OH


COOH
N
HC
N
CH
OH
HO
$NaBH_4$
CH_3CH_2OH
HN
H_2C
NH
CH_2
OH
HO

7 **8**

FIG. 5

3. Bifunctional chelating agents based on phenylene diamine

As another approach to the development of bifunctional ligands we have investigated the use of 3,4-diamino benzoic acid to synthesize ligands by condensation with salicylaldehyde to give a functionalized derivative, **7**, of the well-known ligand, salphen. This Schiff base ligand was also reduced to the amine form, **8**. The synthetic schemes are given in Fig. 5.

Complexation with Rh-105 was accomplished in a manner similar to that described in Part 2. Results of some typical preparations are shown in Table 3.

Table 3 Complexation of Rh-105 with ligand 7 and 8

Ligand	**7**	**8**	**7**	**8**
Reflux time (min)	10	10	120	120
Complex yield (%)	66	76	69	83

The complexes were not extracted into $CHCl_3$ from the reaction mixture but showed 30-40% extraction after buffering at pH 4. Complex yields did not decrease after standing for 24 hr.

A Rh-105 complex of **7** was prepared by mixing 2.5 mL of a bicarbonate/saline solution at pH 9 containing 2.2×10^{-3} mmol rhodium carrier spiked with Rh-105 tracer with 1 mL ethanol containing 5×10^{-3} mmol ligand and refluxing for 2 hr. The estimated complex yield was ~70%. The mixture was dried and the residue dissolved in 2 mL DMSO with ~70% going into solution. A portion of this solution (0.5 mL, ~4×10^{-4} mmol rhodium) was diluted to 2 mL with DMF and 10^{-2} mmol each of the buffer $(C_2H_5)_3N$ and the coupling agent, isobutylchloroformate, IBCF, added. The solution was allowed to stand at room temperature for 1 hr.

A portion of this activated complex (0.1 mL, ~2×10^{-5} mmol rhodium) was added to 1 mL of a solution of human gamma globulin containing 5×10^{-5} mmol protein. After 24 hr at room temperature, the coupling was measured as before. The yields were nearly 100%, among the best we have obtained. A blank (no activating agent added) showed ~20% taken up by the protein. Similar results were obtained for HSA, except that the blank was much higher, ~40%.

We also investigated use of these ligands with Tc-99m. Its complex with **8** was prepared as in Part 2 at pH 4. Extraction into $CHCl_3$ was ~70%. However, extraction into ethyl acetate was >95%, indicating nearly complete complexation. There was no decrease in yield after 24 hr.

Human gamma globulin was labeled in the way just described for rhodium except that incubation was only for 3 hr. At that time ~55% of the activity was found in the protein fraction. However, only ~90% of the total activity was recovered from the column suggesting a possible aggregation of protein leading to a colloid not passing the column. After 20 hr, the yield

was reduced to ~40% indicating some decomposition of the complex. Similar results were obtained when CH_3CN was used as the solvent in preparing the activated complex.

These results are encouraging for Rh-105 and we intend to consider further studies of the reactions of Rh-105 complexes with **7** and **8**. These ligands do not appear as useful for Tc-99m. We are also synthesizing a similar ligand with oximes as the terminal chelating groups and will investigate its use with both Rh-105 and Tc-99m.

4. <u>Radiochemistry with Au-198</u>

The secondary goal of this work is the investigation of the use of Au-199 because of its desireable nuclear properties. It is, however, simpler to do preliminary chemical studies using Au-198 which can be prepared by direct neutron activation. Because of the general usefulness of ligand **2b** (See Table 2) with a number of metals we elected to study its use with gold. The general method of complexing is described above. At pH 3-5 60-70% of the resulting complex could be extracted into $CHCl_3$ while less than 1% of the uncomplexed gold could be extracted. In addition, the uncomplexed gold moved with the solvent front on acetone TLC while the complex remained at the origin. When the pH of the gold solution was raised to 6-9 before addition of the ligand, less than 20% extraction was observed. However, when a small amount of gold solution at pH 4-5 was added to a ligand solution already at pH 8 up to 80% of the resulting complex could be extracted. On electrophoresis the uncomplexed gold moved toward the anode while the complex remained at the origin. Thus, although it is not completely characterized, these results indicate the formation of a complex of gold with **2b**.

It has been shown by others (3) that Au-199 in no-carrier-added form can be used for direct labeling of proteins. We did similar experiments with low specific activity Au-198. To 2 mL of 5×10^{-5} M human gamma globulin in citrate buffer ranging from 3 to 7 pH was added 10 μL of Au-198 stock solution (~5×10^{-5} mmol) and the solution incubated at room temperature for 5 hr. More than 90% labeling was seen in all experiments. This result is consistent with that of Ref. 3 in which 95% labeling was achieved using inert gold (spiked with Au-195) at a gold/protein molar ratio of 1.

We then attempted to couple the gold complex of **2b** to human gamma globulin using the methods already described. When $2\text{-}3 \times 10^{-6}$ mmol of activated gold complex was added to 5×10^{-5} mmol protein the apparent labeling was ~80%. However, the same result was obtained when a blank was run using unactivated complex. A similar pair of results was obtained using ligand **4b**. This may be due to the transchelation of the gold from the ligand to the protein.

Again following the example of Ref. 3 we searched for a simple ligand

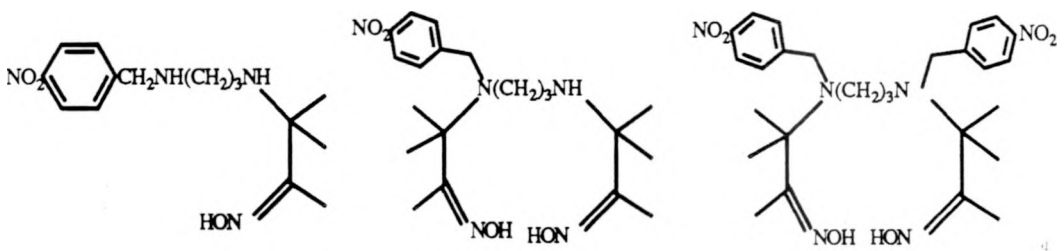
which might bind gold tightly enough to prevent direct labeling of protein and which might also be used to challenge directly labelled protein. We chose the linear tetramine 1,4,8,11-tetraazanonane, TA. We have shown earlier (4) that a bifunctional chelating agent with this backbone is an effective complexing agent for technetium, copper, palladium and rhodium. The complex was prepared by mixing Au-198 solution and then ligand in aqueous solution at pH 4-5 and in ligand/metal ratios of 4 to 100. The product was not extracted into $CHCl_3$ and there was movement toward the cathode on electrophoresis. Complexation yields were estimated at ~80%. When this complex was mixed with human gamma globulin only 16% was found in the protein fraction. This may have been due to uncomplexed gold.

The apparent stability of this N-coordinating ligand suggests that amines may be good backbones for bifunctional chelates of gold. One such approach using terpyridyl is described below in part 6.

5. Tridentate and tetradentate ligands based on 1,3-diaminopropane.

One goal for this past year has been to synthesize some ligands that would have the capability to bind to Rh(III) and have a functional site available for coupling to a monoclonal antibody. The ligands would first possess an $-NO_2$ group which could then be reduced to an amine functionality. The amine functional group would be the desired moiety for the coupling reaction with the monoclonal antibody protein.

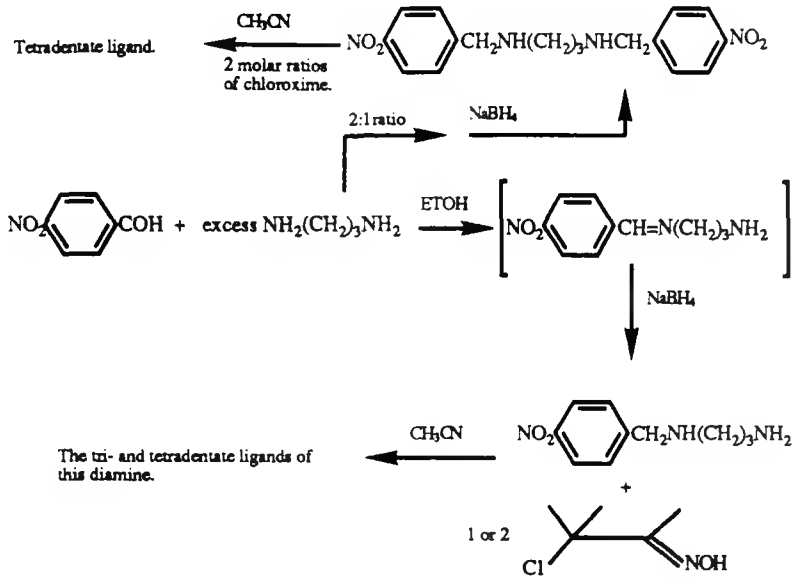
Three new ligand have been synthesized and characterized, one tridentate and two tetradentate ligands all of which contain an amine oxime functionality for metal binding. The chemical structures of these three ligands **9**, **10**, and **11** are as follows:



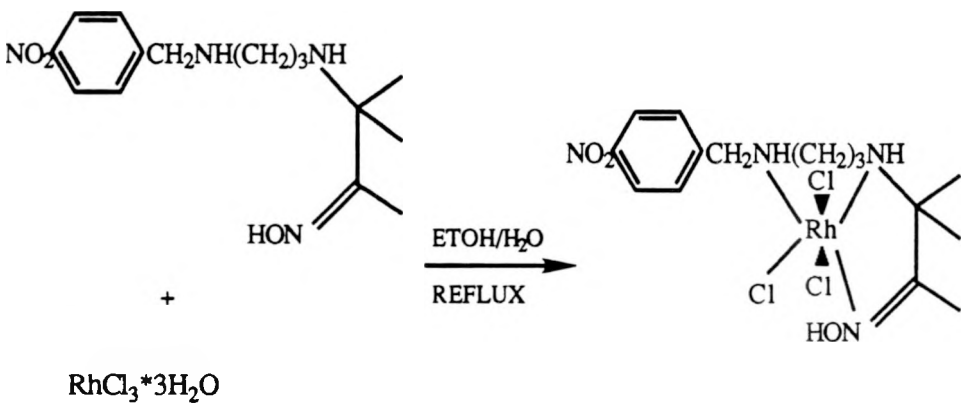
9 **10** **11**

The synthetic schemes used to produce these three ligands are very

similar and are outlined below:



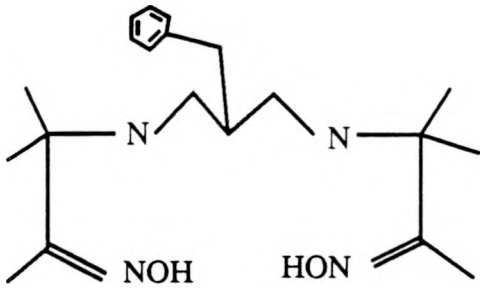
Attempts to synthesize complexes of all of these ligands have been made but only one of the ligands, **9**, has had its complex characterized. The formation of this complex, and its structure are found below:



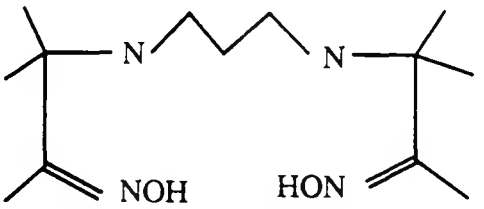
$RhCl_3*3H_2O$

In addition, some radiochemical Au studies were done. Since another part of this year's work was to develop some ligands that would complex with Au(III) to give inert complexes and have a functional group that could be coupled to a monoclonal antibody, some of the amine oxime ligands that were being developed for Rh(III) needed to be tested with Au(III). The syntheses of the complexes were attempted on a large scale first. However, the Au(III) solutions that were reacted with the amine oxime ligands afforded Au reduced to its zero oxidation state. The next step was to react these solutions together but on a more dilute scale; therefore, a

radiochemical study was conducted on two of our amine oxime ligands. The ligands used (PnAO & BPnAO) were:



BPnAO



PnAO

A 0.1mL of 2.5 x10^{-3}M $AuCl_4^-$ was reacted with a five-fold excess of the ligands above and was compared to a standard's behavior when TLC, paper chromatograghy and gel-electrophoresis experiments were conducted. The standard in all cases was $AuCl_4^-$. The following observations were made:

1. In the TLC experiment a small portion of the activity moved with either of the ligand samples, (<20%) moved in acetone whereas almost 50% of the standard's activity moved.

2. When saline was used as the mobile phase more of the activity moved in the standard sample than in the ligand samples: standard~90%, PNAO ~56% and BPNAO ~15%.

3. In the paper chromatography experiment not much of the activity moved in any of the samples(<13%) with acetone as the mobile phase.

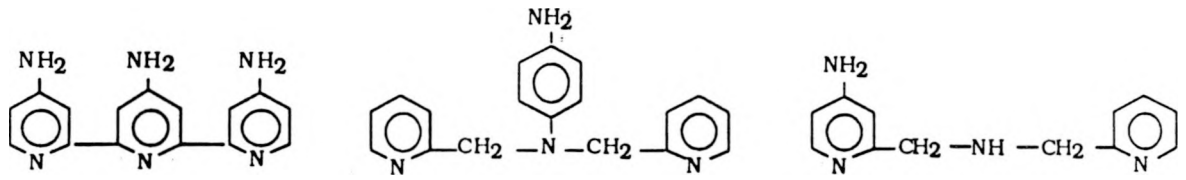
4. When saline was the mobile phase most of the activity moved in the standard(~96%) with decreasing amounts of activity moving in the ligand samples(~78%/PNAO and ~57%/BPNAO).

5. In the gel-electrophoresis experiment the standard's activity moved toward the anode whereas the ligand sample's activity remained stationary.

All of this indicates that the ligands are reacting with the $AuCl_4^-$ in some fashion. It is possible that the oxime group is reducing the gold complex to its metallic state since a lot of its activity does not move in some of these experiments. This possibility would not be surprising since this reduction has been demonstrated to occur when the reactions are done on a larger scale. Work is underway to test this hypothesis by reducing the oxime moieties of PnAO and conducting the same experiments with the resulting ligand.

6. Work on Terpyridyl Based and Related Bifunctional Ligands for Au(III) Studies

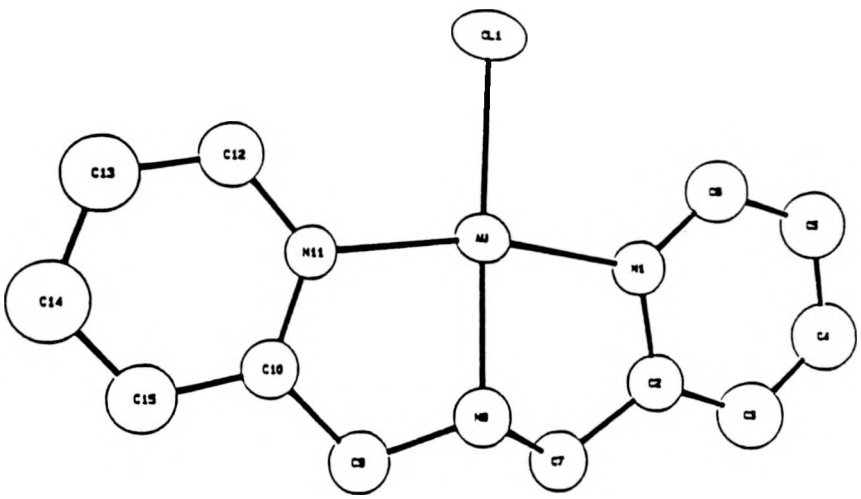
In this area we are in the intermediate stages of work on developing our ligands. We are attempting initially to synthesize the following three bifunctional ligands:



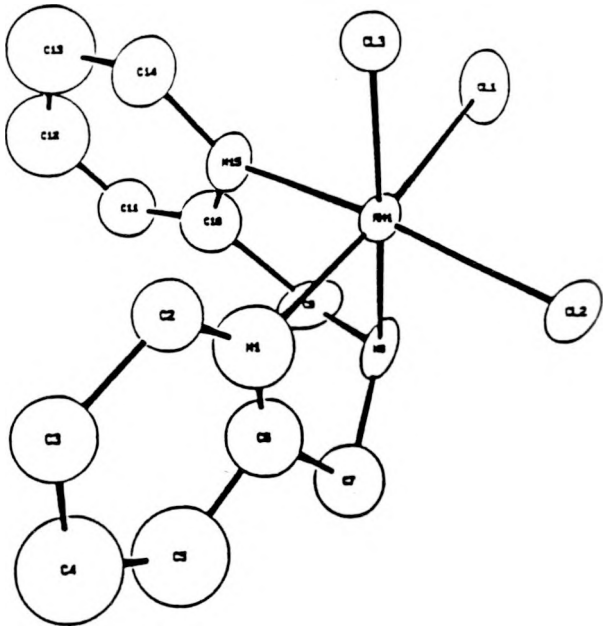
12 **13** **14**

The starting material(terpyridyl) for ligand **12** is commercially available, and the three step synthesis for **12** is in the literature(5). We have successful reproduced the first two steps and characterized the products by PMR. The third step has also been done, but the product is not yet fully characterized.

For ligand **13** the intermediate dipicoylamine was first synthesized. It was prepared according to the procedure given by Romary et al(6) by the reaction between 2-picolyl amine and 2-picolyl chloride. The product was purified by vacuum distillation of the free base, followed by recrystallization of the trihydrochloride. The reaction between dipicolylamine(DPA) and $HAuCl_4$ was carried out at various pH values, and no pure products could be isolated when 1:1 ligand to metal ratio was used. When the reaction was carried out using 2:1 ligand to metal ratio, and at pH 7.0, in water, crystals separated out on addition of a small amount of $NaClO_4$. These were recrystallized from acetonitrile as dark reddish, brown crystals. The crystal structure of that compound is shown below.



Reaction of rhodium trichloride with DPA in water/ethanol mixture yielded yellow crystals with the structure from X-ray below.



In order to functionalize DPA for protein binding(ligand **13**), the reaction between para-nitrobenzylchloride and DPA is under study, but the products of reduction of the nitro compound are not yet characterized. It is also planned to prepare 4-nitro-2-picolyl amine,which would then be reacted with 2-picolylchloride to get ligand **14**, another functionalized DPA . For both ligand **13** and ligand **14** the nitro group will be reduced to obtain the desired amino compounds.

Studies with 198-Au on complexation with DPA showed some complexation, but the results from this initial study are still not conclusive.

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3. P. Anderson, A.T.M. Vaughn, N.R. Varley, Nucl. Med. Biol. 15 p 293-297, (1988)

4. a) F.M. Chen, Ph.D. Thesis, University of Missouri, 1985.
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6. Romary,J.K.; et al; J.C.S.(C), 1968, 2884.

PUBLICATIONS

In the list of publications and presentations the following initials will be used

DET = David E. Troutner
EOS = Elmer O. Schlemper
CJ = Christy John
MRAP = M.R.A. Pillai
JML = Jem-Mau Lo

1. "Labeling of proteins with ^{105}Rh", CJ, MRAP, JML, DET, Appl. Radiat. Isot. **40**, 701 (1989)
2. "Labeling of human serum albumin with ^{105}Rh-cysteine complexes", JML, MRAP, CJ, DET, Ibid., in press
3. "Radiochemical purity evaluation of rhodium-105 complexes by magnesium oxide", JML, MRAP, CJ, DET, Ibid., in press
4. "Labeling of hematoporphyrin with ^{105}Rh and binding studies with human gamma globulin", MRAP, JML, DET, Ibid., in press
5. "Labeling of proteins using (^{105}Rh)Rh-4-(p-aminobenzyl)-diethylenetriamine", MRAP, JML, CJ, DET, Nucl. Med. and Biol., in press
6. "Radiochemical studies of technetium complexes of tetradentate amine phenols", MRAP, CJ, JML, DET, Appl. Radiat. Isot., accepted
7. "Pentadentate amine phenol complexes of ^{99m}Tc", DET, MRAP, CJ, JML and K. Misellati, Proceedings of third Int. Symp. on Tc in Chemistry and Nucl. Med., Padova, Italy, Sept. 1989, accepted.
8. "μ-oxo-bis-oxo-dinuclear complex of technetium(V) with amine phenol ligands: Synthesis, characterization, and x-ray crystal structure", MRAP, CJ, JML, EOS, DET, Inorg. Chem., accepted
9. "Rhodium complexes of some bidentate secondary amine-oxime ligands and application to labeling of proteins", G. Ergun-Efe, MRAP, EOS, DET, Inorg. Chem., submitted
10. "Labeling of human gamma globulin with (^{105}Rh) rhodium using a new pentadentate bifunctional ligand", MRAP, CJ, DET, Bioconjugate Chem., submitted
11. "Technetium complexes of pentadentate amine phenol ligands", MRAP, CJ, JML, M. Corlija, DET, Appl. Radiat. Isot., submitted

PRESENTATIONS or POSTERS

Society of Nuclear Medicine, Annual Meeting, St. Louis, June 1989

1. "Labeling of human IgG with Rh-105 complexes derived from diethylenetriamine", MRAP, CJ, JML, DET
2. "Synthesis, characterization, and x-ray structures of amine phenol complexes of Tc(V)", CJ, MRAP, JML, EOS, DET
3. "Radiochemical studies of Tc-99*m* complexes of tetradentate amine phenols", MRAP, CJ, JML, DET
4. "Evaluation of Tc-99*m*-tetradentate amine phenols as potential cell labeling radiopharmaceuticals", M. Corlijia, MRAP, CJ, JML, DET, T.J. Hoffman, W.A. Volkert, and R.A. Holmes

Third Int. Symp. on Tc in Chemistry and Nuclear Medicine, Padova, Italy, Sept. 1989

5. "Pentadentate amine phenol complexes of Tc-99*m*", DET, MRAP, CJ, JML, and K. Misellati

American Chemical Society, Midwest Regional Meeting, St. Louis, Nov. 1989

6. "Synthesis, characterization, and structure of some new rhodium(III) complexes as potential radiopharmaceuticals", T. Kilcoin and EOS

American Crystallographic Association, National Meeting, Seattle, July 1989

7. "Stucture of some Tc(V) and Pd(II) complexes of reduced tetradentate ligands derived from salicylaldehyde and diamines", MRAP, CJ, JML, EOS, DET

EDUCATION AND TRAINING

Post-doctoral

Dr. M.R.A. Pillai finished a stay of two years at the University of Missouri on this project and returned to his postion as Scientific Officer at the Bhabha Atomic Research Center, Bombay, India. He will use the experience gained from this project in his continued work in the development and evaluation of radiopharmaceuticals.

Graduate

Two Ph.D. theses were completed and degrees awarded in December, 1989:

Guler Ergun - "Rhodium(III) complexes with bidentate a-amine oxime ligands containing secondary amine nitrogens"

Khaled Misellati - "Labeling of proteins with prechelated radionuclides"

Mr. Tim Kilcoin completed the comprehensive examination for the Ph.D. degree. Mr. Lixin Lang will take the comprehensive examination during the Winter, 1990 semester. Mr. Nihal Weerasinghe and Mr. Prahlad Singh passed departmental qualifying examinations and have begun work on the Ph.D.

All of the above except Mr. Singh have received partial support from this project. The remainder of the support as well as full support for Mr. Singh has come from University of Missouri sources.

Undergraduate

Mr. David Klug and Mr. Matt Hansen, Hughes Foundation Undergraduate Research Interns, are doing undergraduate research projects as part of the project. Miss Cathy Sprowls is assisting with library research. All are undergraduate majors in the Department of Chemistry.