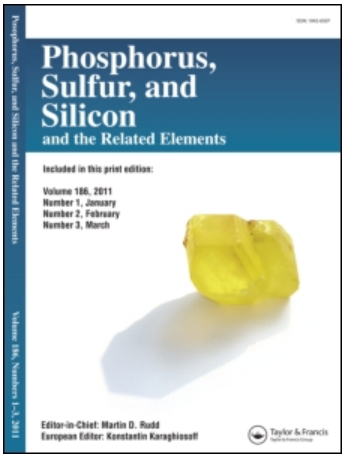


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Rhodium-105 Complexes of Polydentate, Aqueous-Soluble, Phosphine Ligands: New Radiochemical Developments towards Radioimmunotherapy

C. J. Smith; C. Higginbotham; K. V. Katti; W. A. Volkert

To cite this Article Smith, C. J. , Higginbotham, C. , Katti, K. V. and Volkert, W. A.(1999) 'Rhodium-105 Complexes of Polydentate, Aqueous-Soluble, Phosphine Ligands: New Radiochemical Developments towards Radioimmunotherapy', Phosphorus, Sulfur, and Silicon and the Related Elements, 144: 1, 481 — 484
To link to this Article: DOI: 10.1080/10426509908546286
URL: http://dx.doi.org/10.1080/10426509908546286

Phosphorus, Sulfur and Silicon, 1999, Vol. 144-146, pp. 481-484
Reprints available directly from the publisher
Photocopying permitted by license only

Rhodium-105 Complexes of Polydentate, Aqueous-Soluble, Phosphine Ligands: New Radiochemical Developments towards Radioimmunotherapy

C.J. SMITH[b], C. HIGGINBOTHAM[a], K.V. KATTI[ab] and W.A. VOLKERT[a]

[a]*Departments of Radiology,* [b]*Research Reactor,*
University of Missouri-Columbia, Columbia, MO 65211, USA.

The water-soluble, dithio-*bis*(hydroxymethyl)phosphine ligands $(HOH_2C)_2P(CH_2)_xS(CH_2)_3((CH_2)_4COOH)S(CH_2)_xP(CH_2OH)_2$ (X = 2 or 3) were complexed with ^{105}Rh. The new ^{105}Rh-complexes were formed in high radiochemical purity by addition of $^{105}RhCl_3 3H_2O$ to an aqueous solution of the appropriate ligand framework. The new complexes were formed as singular chemical species and did not undergo *in vitro* decomposition for ≤24 hours as indicated by high performance liquid chromatographic analyses. *In vivo* biodistribution analyses of the new complexes indicate that the primary mode of excretion is the renal-urinary pathway. Results of this study suggest the potential development of new radiopharmaceuticals for the treatment of human metastases *via* conjugation of the new ^{105}Rh-complexes to site-specific biomolecular vectors.

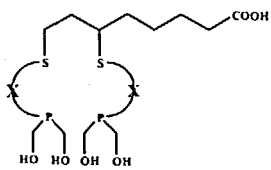
Keywords: Water-soluble; Bifunctional Chelating Agents; (Hydroxymethyl)phosphines

INTRODUCTION

Rhodium-105 is an attractive isotope for radioimmunotherapy due to its ideal nuclear characteristics. For example, Rh-105 has a half-life of 35.5 hours, emits two medium-energy β- particles (0.56 MeV, 70% and 0.25 MeV, 30%), and can be produced in high specific activities (>700 Ci/mmol) in a medium flux reactor.[1] Furthermore, the simultaneous emission of γ rays suitable for imaging (0.319 MeV, 19% and 0.306 MeV, 6%) allows for the monitoring of the *in vivo* efficacy of the treatment.[2]

Efforts into the development of Rh-105 based radiopharmaceuticals have focused upon the use of sulfur, nitrogen and oxygen donor ligands to form stable, kinetically inert Rh(III) complexes. However, the reaction conditions necessary to form these complexes in high yield (≥95%) are sometimes harsh. Therefore, the design and development of new ligand frameworks for the successful chelation of Rh(III), under mild conditions, to form *in vivo* stable, kinetically inert complexes is necessary. Jurisson, Volkert, and co-workers have recently reported the formation of stable Rh(III) complexes formed *via* the use of tetrathiomacrocycles.[3] Our laboratory has recently developed a new class of bifunctional chelating agents based upon a dithio-diphosphine ligand framework of the

type $(HOH_2C)_2P(CH_2)_XS(CH_2)_3((CH_2)_4COOH)S(CH_2)_XP(CH_2OH)_2$ (X = 2 or 3, FIGURE I).[4]



X=2, A; X=3, B

FIGURE I Representative Dithio-diphosphine Bifunctional Chelating Ligand

The presence of soft S and P donor atoms, in combination with the inherent chelate effect imparted upon the metal center by the tetradentate ligating framework, might enhance the stability and kinetic inertness of the Rh(III)-complexes *in vivo*. As part of an ongoing effort toward the development of site-specific diagnostic and therapeutic radiopharmaceuticals at the University of Missouri-Columbia, we herein report the radiosyntheses and biodistribution analyses of the ^{105}Rh-complexes with this new class of bifunctional chelating ligands.

EXPERIMENTAL

Rhodium-105 Production at the University of Missouri Research Reactor

A 16 mg sample of enriched 99.05% ^{104}Ru metal was irradiated for 81 hours in the H-1 position ($\phi_{thermal}$ = 8 x 10^{13} n/cm^{2}s) at the University of Missouri Research Reactor. Separation of the ^{105}Rh from Ru was carried out as previously reported.[5] Approximately 25 mCi (925 MBq) of acidified ^{105}Rh(III)-chloride reagent was supplied and used for the subsequent studies.

Rhodium-105 Labeling of the S_2P_2 Bifunctional Chelating Ligands

A working solution of ^{105}Rh was prepared by addition of 0.1N NaOH to the ^{105}Rh(III)-chloride reagent provided by the MURR. The final pH of this solution was ~5. To 490 µL of this solution, 140 µL of absolute ethanol and 70 µL of the appropriate ligand solution (1 mg/mL stock ligand solution) were added. The final concentration of the ligand solution was 0.1 mg/mL (~ $2x10^{-4}$ M). The solutions were heated at 85°C in a water bath for 1.5 hours and allowed to stand at room temperature for approximately 30 minutes before further analyses were made.

HPLC Analyses of the Rhodium-105-S_2P_2 Complexes

All samples were prefiltered through a 0.22 µm Cameo syringe filter. HPLC analyses were performed using an analytical PRP-1 column (Hamilton, 5µm). The mobile phase consisted of a gradient system with solvent A corresponding to 100% water with 0.1% trifluoroacetic acid and solvent B corresponding to 100% acetonitrile with 0.1% trifluoroacetic acid. The mobile phase started with 100% A from 0-2 minutes followed by a linear gradient from 0% B to 100% B from 2-7 minutes. The gradient remained at

100% B for an additional two minutes before being ramped to 0% B at time 20 minutes for column equilibration. The flow rate of the mobile phase was 1.5 mL/min. The chart speed was 0.5 cm/min. Detection was accomplished radiometrically using an in-line NaI detector for the Rh-105 complexes.

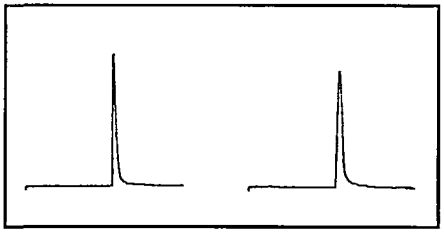
In Vivo Analyses of the Rhodium-105-S_2P_2 Complexes

The biodistribution studies of the new Rh-105-S_2P_2 complexes were determined in Sprague-Dawley (150-250 g) rats anesthetized with sodium pentobarbital (50 mg/kg i.p.). The rats were injected with 5μCi (185 kBq) of complex in 30 mL of saline *via* a cannulated right jugular vein. Tissues and organs were excised from the animals at 2 hours post-injection (p.i.). Subsequently, the tissues and organs were weighed and counted in a NaI well counter and the percent injected dose (%ID) and %ID/g of each organ or tissue calculated. The %ID in whole blood was estimated assuming a whole-blood volume of 6.5% the total body weight.

RESULTS AND DISCUSSION

HPLC Analyses of the Rhodium-105-S_2P_2 Complexes

The ^{105}Rh-complexes of ligands A and B were produced in high yields (~90%) upon heating the ligand solution ($2x10^{-4}$ M) with a neutralized solution of $^{105}RhCl_3$. The HPLC chromatograms representing the purified ^{105}Rh-complexes of A and B are shown in FIGURE II.



Complex of A (6.90 min) Complex of B (7.06 min)

FIGURE II HPLC Chromatographic Profiles of the ^{105}Rh-complexes

Each of the chromatograms show a single species with retention times of 6.9 and 7.0 minutes. Subsequent analysis of the ^{105}Rh-complexes showed little or no decomposition at 24 hours post-complexation. The chloroform-saline partition coefficients for each of the new complexes was <0.0001±0.0001, indicating the extreme hydrophilic nature of the species.

In Vivo Analyses of the Rhodium-105-S_2P_2 Complexes

Preliminary biodistribution data in anesthetized rats showed that each of the new complexes cleared efficiently from the bloodstream, and were excreted primarily through

the renal-urinary pathway. Table I lists the biodistribution analyses at 2 hours post-injection for each of the new species.

TABLE I Biodistribution of 105Rh-complexes in Rats at 2 Hours Post-injection

Organ	^{105}Rh-232 -complex	^{105}Rh-333-complex
Brain	0.019	0.000
Blood	3.076	3.598
Heart	0.074	0.153
Lung	0.140	0.146
Liver	3.166	4.316
Carcass	11.989	13.539
Spleen	0.023	0.068
Stomach	0.220	1.692
Large Intestine	0.230	0.195
Small Intestine	9.575	17.693
Kidneys	3.041	3.544
Urine	71.260	58.352

The primary clearance route for the new complexes is the renal-urinary pathway (TABLE I). However, there appears to be additional clearance of ^{105}Rh-activity for the complexes of ligand B *via* the hepatobilary pathway. This could, in part, be due to the additional CH_2 linkage in the 333 ligand framework as compared to the 232. However, the effective clearance from blood and other non-target tissue reflects the degree of polarity imparted upon each of the new complexes by the hydroxyalkyl-functionalized phosphines.

CONCLUSIONS

The new dithio(hydroxylalkyl)phosphine bifunctional chelating ligands, reported in this study, represent an important step toward the development of *in vivo* stable radiolabeled complexes. Furthermore, the successful chelation of this new class of ligands to rhodium-105 presents enormous scope toward the development of radiolabeled biomolecules (e.g. peptides or proteins) for use in the design of therapeutic radiopharmaceuticals for the treatment of various metastatic cancers. Additional radiolabeling procedures and biodistribution analyses are currently underway to further ascertain the *in vitro* and *in vivo* properties of the new ^{105}Rh-complexes.

References

[1] M.R.A. Pillai, J.M. Lo, and D.E. Troutner, *Appl. Radiat. Isot.* **41**, 69, (1990).
[2] M. Venkatesh, N. Goswami, W.A. Volkert, E.O. Schlemper, A.R. Ketring, C.L. Barnes, and S. Jurisson, *Nucl. Med. Biol.* **23**, 33, (1996).
[3] N. Goswami, R. Alberto, C.L. Barnes, and S. Jurisson, *Inorg. Chem.* **35**, 7546, (1996).
[4] H. Gali, S.R. Karra, V.S. Reddy, W.A. Volkert, and K.V. Katti, *(Submitted for Publication).*
[5] B. Grazman and D.E. Troutner, *Appl. Radiat. Isot.* **39**, 257, (1988).