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Low energy cyclotron production and cyclometalation chemistry of iridium-192

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HIGHLIGHTS

- Cyclotron production, radiochemical isolation, cyclometalation chemistry of radio-iridium.
- Osmium electroplating, irradiation with 12.7 MeV protons at different current intensity.
- Target dissolution using H_2O_2 and HCl.
- Iridium purification by ion exchange chromatography.
- Radiosynthesis of iridium cyclometalate compounds.

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ABSTRACT

This work demonstrates the labelling of a novel class of iridium lumophore with radioiridium, as proof-of-feasibility for producing and using the medically useful isotope iridium-192. Natural osmium was electroplated onto silver target backings in basic media and irradiated for up to two hours with ≤ 20 μA of 12.8 MeV protons. A range of iridium isotopes were generated, characterized and quantified using γ-spectroscopy methods. The target material was removed from the backings via oxidative dissolution with hydrogen peroxide, and the iridium radioisotopes isolated using an anion exchange resin. Both no-carrier-added as well as carrier-added formulations were then used in subsequent cyclometalation reactions.

1. Introduction

Radiometals have opened new fields of study in nuclear medicine, taking advantage of their varied chemical and nuclear properties to enable both imaging and therapeutic applications (Rey, 2010; Thorp-Greenwood and Coogan, 2011). Multi-functional radiopharmaceuticals (RP) enable simultaneous applications across imaging or therapy modalities, with many emerging RPs based on a metallic radionuclide as either the signalling and/or therapeutic component. With ~80% of the known elements classifying as metal in nature, a large array of chelate chemistry has been developed over time. A number of avenues are therefore available to facilitate different labelling scenarios, including incorporation of metallic radioisotopes into targeting moieties that range from small molecule constructs to large biological target vectors (i.e. peptides, proteins, antibodies, etc.). The goal of this work was to produce, isolate and apply iridium-192, and demonstrate its use through cyclometalate chemistry to achieve a new, highly emissive, multifunctional RP for further study.

Luminescence cell imaging (LCI) is a cell histology technique that uses high resolution optical microscopy to image emissive compounds, generating detailed cell micrographs that are used to visualize the molecular interactions of a compound with the host. This technique has been integrated into multifunctional radiopharmacy, with many examples working in conjunction with PET or SPECT (Brindle, 2008; Chiang et al., 2012; Thorp-Greenwood and Coogan, 2011).

The excellent photophysical properties of iridium cyclometalate compounds (Chi and Chou, 2010) have generated interest for their use in LCI (Lo and Zhang, 2012; Thorp-Greenwood, 2012). Both the cyclometalating and ancillary ligands are easily modified to include biological targeting moieties (Lo et al., 2013; Mandal et al., 2012; Steunenberg et al., 2012). Despite the current relevance of such a project, to the best of our knowledge, a radiosynthesis of an iridium cyclometalate compound has not yet been reported. This

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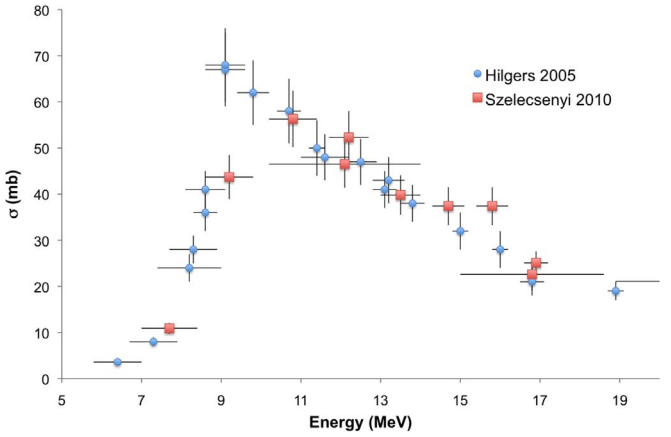

Fig. 1. Excitation functions of ^{192}Os(p,n)^{192}Ir (Hilgers et al., 2005; Szelecsényi et al., 2010).

may be due to the impractical conditions of the conventional synthesis, including lengthy (> 10 h) reflux, use of dehalogenating agents and difficult post-reaction workup (Sprouse et al., 1984). However, new developments in microwave synthesis, along with improvements in aqueous organometallic chemistry, have dramatically reduced reaction times (Alam et al., 2013; Konno and Sasaki, 2003; Saito et al., 2004; Wu et al., 2010) and have opened a growing number of metal transformations that can be achieved in aqueous media and in the presence of oxygen.

Iridium-192 ($T_{1/2}$=73.8 d; EC 4.8%; β^- 95.2%; $E_{\beta max}$=179 keV) currently plays a role in nuclear medicine, albeit somewhat far from targeted radiopharmacy. Using neutron activation of a ^{191}Ir wire, low specific activity ^{192}Ir brachytherapy sources are routinely generated and used globally for the treatment of several cancers (Habrand et al., 1991; Mate et al., 1998; Rostelato et al., 2008). Proton, deuteron, and alpha particle-induced reactions have also been demonstrated in the production of this isotope (Hilgers et al., 2005; Szelecsényi et al., 2010; Tárkányi et al., 2007). Specifically, the excitation function of the ^{192}Os(p,n)^{192}Ir reaction has been published (Hilgers et al., 2005; Szelecsényi et al., 2010) (Fig. 1) and represents the most easily accessible transmutation method. Hilgers et al. (2005) compared the cyclotron production of ^{192}Ir against neutron-induced, reactor-based production with regard to the manufacture of brachytherapy sources. Reactor production was found, for this purpose, to have a higher cross-section and lower co-production of the long-lived metastable ^{192m}Ir ($T_{1/2}$=241 a) (Hilgers et al., 2005). In vivo applications with RPs, however, typically require a higher specific activity that may only be achieved using particle accelerators.

Here we report a complete methodology for the production of radio-iridium on a low energy medical cyclotron, its radiochemical isolation, and the labelling of representative cyclometalate compounds.

2. Experimental

2.1. Materials and instrumentation

Naturally abundant powdered osmium metal (99.95%, 20 mesh; isotopic composition shown in Table 1) and iridium trichloride hydrate ($IrCl_3 \cdot 3H_2O$) were purchased from Alfa Aesar International (Ward Hill MA, USA). All solvents, acids, bases and reagents were purchased from Sigma Aldrich (Oakville ON, Canada) and used as received. Conventional column chromatography was performed using silica gel (Silicycle, 230–400 mesh), while anion exchange chromatography was performed using Biorad 1 × 8 anion exchange resin. Microwave reactions were performed on a Biotage Initiator system. Nuclear Magnetic Resonance (NMR) spectra were measured on a Bruker AV400 instrument at 298 K, and mass spectra were obtained with the positive ion mode electro-spray ionization [ESI(+)] source on an Agilent 6210 time-of-flight liquid chromatography/mass spectrometry (MS) system. High Performance Liquid Chromatography (HPLC) separations were performed on an Agilent 1200 instrument with a Phenomenex Jupiter C18 column, a UV detector set to 250 nm, and a Gabi NaI γ-ray detector. Scanning Electron Microscopy (SEM) and Energy Dispersive X-ray analysis (EDS) was performed on a FEI Dualbeam 235 instrument.

Table 1
Isotopic composition of naturally abundant osmium.

^{A}Os	186	187	188	189	190	192
% Abundance	1.59	1.96	13.24	16.15	26.26	40.78

2.2. Target preparation

Targets were prepared as described previously (Chakrabarty et al., 2001; Greenspan, 1969; Hilgers et al., 2005; Szelecsényi et al., 2010). Briefly, 500 mg of OsO_4 was placed in 2 mL of nitric acid and brought to reflux in a distillation apparatus at atmospheric pressure. The OsO_4 vapor formed was absorbed by a receiving solution of deionized (DI) H_2O. The low pH of this solution was adjusted to neutral with a 12 M solution of KOH. An aliquot was then added to an aqueous electrolyte bath containing sulphamic acid (H_3NSO_3, 0.908 g, 9.35 mmol), disodium phosphate (Na_2HPO_4, 0.167 g, 1.18 mmol), and sodium hydroxide (NaOH, 0.165 g, 4.13 mmol) to achieve a total volume of 65 mL. The resulting brown solution was brought to reflux for 5 min, after which a color change to yellow was observed. A portion of this bath was set aside to act as a replenishing solution during the electroplating.

Elemental silver target plates were machined to discs of 35 mm diameter and 1 mm thickness. A target plate holder was fashioned to mask a geometry matching that of the cyclotron beam (10 mm diameter). The entire holder was then submerged in the electrolytic bath and the system brought to 70–80 °C with vigorous stirring. A voltage and current of 3.0 V and 50 mA were applied, respectively, for 90 min and replenishing solution added as needed.

2.3. Target irradiation

All irradiations were performed on the TRIUMF TR13 cyclotron, a 13 MeV, self-shielded negative hydrogen ion cyclotron. Targets were mounted in a module specifically designed for this TR13 cyclotron (Fig. 2). The target interfaced directly with the cyclotron extraction port, separated from the cyclotron vacuum by a 25 μm aluminum foil. The aluminum entrance foil and the beam side of the target plate were each cooled with a 65 L min^{-1} at 10 psig

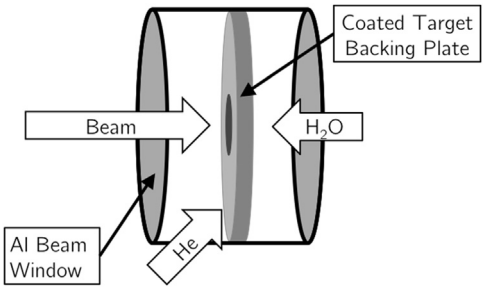

Fig. 2. Schematic of the target holder used for all irradiations.