MICROSCALE SYNTHESIS OF PHOSPHORUS TRICHLORIDE LABELED WITH HIGH SPECIFIC ACTIVITY ^{33}P*

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SUMMARY

Milligram quantities of high specific activity ^{33}P-labeled phosphorus trichloride are synthesized from carrier-free ^{33}P-labeled phosphoric acid (^{33}P-H_3PO_4).

Special apparatus were constructed for this synthesis. Carrier-free ^{33}P-H_3PO_4 is converted to lead phosphate in the presence of carrier by metathesis with lead oxide. Upon hydrogen reduction of the lead phosphate, elemental phosphorus is liberated and reacted with chlorine to form phosphorus pentachloride. Subsequent reduction in a specially constructed phosphorus reductor yields the phosphorus trichloride which is collected and sealed in an ampul.

The procedures described are applicable to routine production of millicurie or multicurie quantities of several ^{33}P-labeled phosphorus intermediates.

Key Words: Phosphorus-33, Phosphorus Trichloride, Phosphorus Pentachloride, Radio-synthesis

INTRODUCTION

Phosphorus trichloride (PCl_3), phosphorus pentachloride (PCl_5), and phosphorus oxychloride ($POCl_3$) are important intermediates in the synthesis of many organophosphorus compounds. The availability of these intermediates labeled with high specific activity radiophosphorus-33 (^{33}P) offers potential advantages for synthesis of labeled pharmaceuticals for pharmacological studies or even radiotherapeutic applications (1).

Phosphorus-33 (25.2-day half-life, 0.25 MeV pure beta emitter) is produced by an (n,α) reaction with ~60% isotopically enriched ^{36}Cl (3 x 10^5 year half-

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life) and is recovered carrier-free as the orthophosphate (2). Curie amounts of ^{33}P can be converted into compounds containing less than 50 mg of total phosphorus. A curie of ^{33}P has negligible mass (6.4 micrograms) and therefore carrier phosphorus must be added.

The syntheses of radiolabeled $^{32}PCl_3$, $^{32}PCl_5$, and $^{32}POCl_3$ have been well documented in the literature (3-15). In previous work, reduction of phosphoric acid or alkaline earth phosphates to liberate elemental phosphorus has been carried out using carbon at high temperature as the reductant, followed by chlorination to produce PCl_3, PCl_5, and $POCl_3$ (3-5). Direct production by carbon reduction and simultaneous chlorination has also been reported (6). Our objective was to develop a rapid procedure for routine production of semi-micro quantities of these phosphorus intermediates at the multicurie level which could be adapted to glove box operation.

EQUIPMENT DESIGN AND MATERIALS

The apparatus shown in Fig. 1 was developed in our laboratory for the in-line production of PCl_3.

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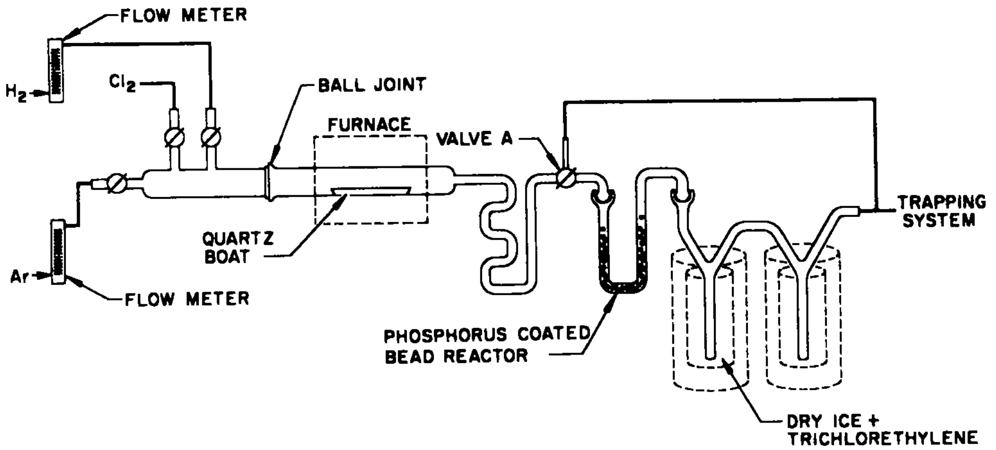

Fig. 1. Schematic of Apparatus for $^{33}PCl_3$ Production.

The reduction tube (48 cm length x 2.5 cm diam) is of Vycor, sealed to Pyrex at both ends through the use of graded seals. Reactant and carrier gases (hydrogen, chlorine, and argon of >99% purity) are introduced through a glass manifold with Teflon stopcock valves. Connection to the reduction tube is through a ball joint (35/20). A 110-volt split tube furnace (20-cm length x 3-cm internal diam, Hevi Duty Electric Co., Milwaukee, WI) with a maximum rating of 1000°C is used during the 2-3 hr reduction stage of the synthesis. Located at the end of the reduction tube is a Teflon stopcock (valve A). The straight-through portion of the stopcock is drilled to match the tubing inside diameter to afford clear passage of reaction products. This valve allows carrier and reaction gases (argon, hydrogen, and chlorine) to be diverted during specific stages of the process and prevents them from interacting with other components of the system. All gases exiting the apparatus are passed through charcoal and water scrubbers to trap and recover any lost reaction products. A U-shaped reductor (constructed with 10-mm diam Pyrex tubing) containing 3-mm diam borosilicate glass beads (Kimble Div., Owens-Illinois, Inc., Toledo, OH) coated with purified red phosphorus is connected to the reduction tube directly after valve A. The phosphorus is purified by boiling with distilled water and filtering off the phosphorus. This process is repeated 2-3 times until no traces of acid are detected in the filtrate. After drying overnight in a desiccator under high vacuum, ∿200-300 mg of the phosphorus are added to 50 g of glass beads in a 125-ml Erlenmeyer flask which has been purged with argon. (This and following operations are done in an argon-filled box to minimize oxygen contamination.) The flask is stoppered and vigorously shaken until an even coating of red phosphorus appears on the beads. The U-tube reductor is filled as follows: a plug of glass wool is placed at the exit; the tube is filled about one-half with uncoated glass beads of the same diameter; the remaining half is filled with the coated beads. No glass wool is inserted at the entrance of the reductor.

The Y-condenser/receivers (constructed with 5-mm diam Pyrex glass tubing) are used to condense, collect, and redistill the PCl_3 product. The specific design of the Y-condenser evolved after numerous attempts with other designs. The condenser must quickly cool the PCl_3 vapor in the carrier gas (normal flow of 30-40 cm^3/min) below the dew point, allowing sufficient time for droplets to form and disengage from the gas stream. The PCl_3 is collected in the bottom of the stem of the Y-condenser. The entire length of the Y-condenser is maintained at -77°C with solid CO_2-trichlorethylene slush. Efficiency of the Y-condenser under these conditions is >99%.

EXPERIMENTAL METHODS

Preparation of $Pb_3(PO_4)_2$

$$3PbO + 2H_3PO_4 \rightarrow Pb_3(PO_4)_2 + 3H_2O$$

Carrier-free ^{33}P obtained in the form of orthophosphoric acid in 1 *N* HCl is subjected to prepurification by cation exchange to insure that no cations other than hydrogen are present. The carrier solution of H_3PO_4 is made up with a known amount of phosphorus.

Carrier solution equivalent to 20 mg phosphorus is added to a 50-ml Teflon-coated beaker containing the desired amount of carrier-free ^{33}P-H_3PO_4 solution. The beaker contents are evaporated down to incipient dryness several times with a small volume of concentrated nitric acid to remove all chlorides. The residue is taken up in a minimal amount of water for transfer to a 76 x 16 x 10 mm silica boat (Amersil, Inc., Hillside, NJ) containing 238 mg PbO (1.06 mmoles) spread in a thin layer on the bottom. Secured by a clamp, the boat is partially immersed in an ultrasonic water bath and the metathesis is allowed to proceed for one hour. After metathesis, the boat containing the $Pb_3(PO_4)_2$ is placed under a heat lamp and the contents dried for one hour.

Reduction of $Pb_3(PO_4)_2$ with Hydrogen

$$Pb_3(PO_4)_2 + 8H_2 \rightarrow 3Pb + 2P + 8H_2O$$

The boat is transferred to the reduction tube and placed in the center of the furnace. Argon gas (helium can be used if argon is not available) is passed through the entire train at 50 cm^3/min for 30 min (to flush air out of the system). Argon flow is stopped and hydrogen is introduced at 25 cm^3/min; valve (A) is adjusted to bypass the reductor. The furnace is turned on and the voltage is regulated (45 to 90 volts maximum) so that the temperature gradient approximates the heating curve in Fig. 2. As the temperature rises, water may appear in the cool exit tube; superficial water comes off at a furnace temperature of ∿300°C; water of reduction appears at ∿500°C. The water evaporates and passes out in the sweep gas. Small amounts of PH_3 may appear at 600°C. Escaping phosphorus species are absorbed in the water scrubber and activated carbon trap. Elemental phosphorus, ranging in color from white to dark red, starts collecting in the cooler distal portions of the tube while the furnace temperature is ∿650°C (10).

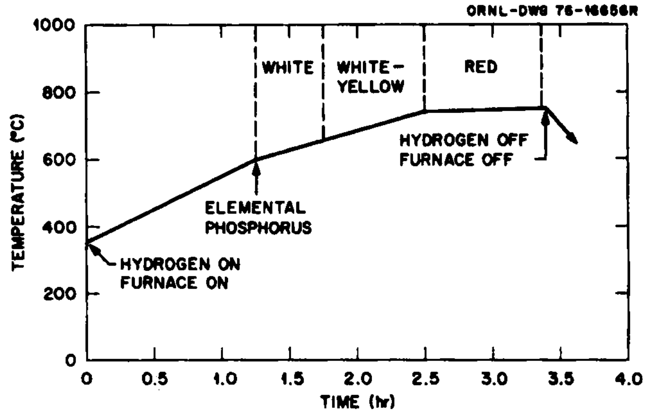

Fig. 2. Temperature Gradient Profile for Hydrogenation of $Pb_3(PO_4)_2$.

The phosphorus is liberated more readily as the temperature rises; 1-1 1/2-hours at 650-800°C is usually sufficient for reduction of all the $Pb_3(PO_4)_2$. The gas flow is reduced to 10-20 cm^3/min during the collection of elemental phosphorus to minimize losses by vaporization and entrainment. At the end of the reduction, the heat is turned off, the furnace is removed, the hydrogen is stopped, and 10-20 ml/min argon is turned on to flush hydrogen out of the tube. At this point the process is most vulnerable to oxygen contamination; the pressure of the oxygen-free gas in the tube must not fall below atmospheric pressure.

Chlorination of Phosphorus to PCl_5

$$2P + 5Cl_2 \rightarrow 2PCl_5$$

An excess of oxygen-free chlorine gas is introduced into the argon-filled tube at virtually zero flow rate. The progress of the reaction is easily observed: yellowish-white PCl_5 rapidly forms on the walls. One-half hour is allowed to ensure that the reaction goes to completion. Valve (A) is closed during most of the chlorination period to minimize PCl_5 losses. The excess chlorine is then flushed out with 10-20 cm^3/min of argon.

Reduction of PCl_5

$$3PCl_5 + 2P \rightarrow 5PCl_3$$

Valve (A) is readjusted to allow carrier gas to flow through the reductor. Dewars containing solid CO_2-trichlorethylene slush (-77°C) are placed around the Y-traps so that the tubes are completely immersed in the slush.

The PCl_5 deposit is heated with a hot-air gun (Master Appliance Corp., Racine, WI) and sublimed in a 10-20 cm^3/min stream of argon through the reductor (also heated with the hot-air gun). The PCl_3 formed in the gas phase in the reductor collects in the bottom of the Y-tube condenser/receiver. The radiophosphorus specific activity is diluted 3:5 by this reaction.

The $^{33}PCl_3$ (∿0.090 ml) which is collected may be redistilled to the second trap, if desired, by replacing the first -77°C dewar with an 80°C water bath, cooling the second trap, and continuing the argon flow at 10-20 cm^3/min. The purity with respect to $POCl_3$ is only slightly improved but most of the elemental white phosphorus (nonradioactive, from the reductor) dissolved in primary distillate is left behind. The sacrifice in yield is usually not justified (a loss of 10-20%), however, unless the small amount of elemental phosphorus does interfere with a subsequent organic synthesis. Purity with respect to $POCl_3$ contaminant in the PCl_3 product could be improved slightly if stringent prepurification measures were taken to specifically remove O_2 and H_2O from the gases and red phosphorus employed.

The bottom tip of the Y-tube condenser/receiver containing the $^{33}PCl_3$ product is directly sealed off from the base of the Y-tube. The product is initially chilled with the CO_2-trichlorethylene slush, a moderate vacuum is pulled on the system, and the tube is sealed using a micro gas-oxygen torch. The ampul formed is ∿3 cm in length. Visual inspection of the product should reveal a clear liquid with no sign of crystals at -77°C ($POCl_3$ contamination). A small amount of yellow deposit may occur in the ampul after storage for a few days, which results when white α-phosphorus in solution (nonradioactive, from the reductor) polymerizes and condenses out as yellow-orange phosphorus.

Product Analysis

The chemical purity of the PCl_3 was determined nondestructively using a combination of NMR and laser Raman spectroscopic analysis (16) and was found to average 92% PCl_3 and 8% $POCl_3$. The NMR analysis was used to calibrate the Raman spectral intensities. The presence of the $POCl_3$ contaminant is thought to be due to oxygen contamination within the phosphorus-coated bead reductor and minute traces of oxygen in the inert carrier gas stream.

The product contains <5% ^{32}P activity which is formed by the (n,α) reaction on the ^{35}Cl in the enriched ^{36}Cl target. The ratio of the ^{32}P to ^{33}P activities in the carrier-free H_3PO_4 is determined by the method of Brown (17).

The chemical yield is determined by assaying the ^{33}P activity with the bremsstrahlung radiation of the sealed ampul (due to the interaction of ^{33}P and ^{32}P in the surrounding glass walls. The bremsstrahlung is measured in a Capintec, Model CRC-2N, gross ionization chamber (Capintec, Inc., Mount Vernon, NY) that has been appropriately calibrated with ^{32}P and ^{33}P standards. The Capintec calibration setting is zero since the bremsstrahlung detected (a meter reading of ∿50 μCi or less) represents a significantly larger amount of ^{32}P and ^{33}P activity actually present (greater than 0.5 mCi ^{32}P and 50 mCi ^{33}P). Therefore, the most sensitive calibration setting is required. The validity of this technique has been tested by destructive radiochemical analyses (18). The chemical yield is calculated from the ratio of the ampul activity to the known amount of activity introduced into the silica boat, and the specific activity is determined by the amount of carrier H_3PO_4 added to the boat. Chemical yields have averaged better than 90%. Specific activities of PCl_3 products can be varied over a wide range. To date, typical runs have been made at 100 mCi/mmole of $^{33}PCl_3$ with a product of 75-150 mCi.

DISCUSSION

The production of elemental phosphorus using a gaseous reductant at relatively low temperature, followed by chlorination with chlorine gas, was the most operable procedure to meet our requirements, *viz*: utilization of only semi-micro quantities of phosphorus, high radioactivity, need for high yield, and sealed ampul packaging for handling and assay. Many phosphates (Ca, Mg, rare earth, Fe, Zn) and gaseous reductants (H_2, CO, PH_3) were tried with little success, confirming observations made in the thorough treatise on the hydrogen reduction of phosphates by Hutter (19). The hydrogen reduction of lead phosphate was determined to be the most practical procedure.

Attempts to chlorinate elemental phosphorus directly to PCl_3 by adding only the stoichiometric amount of chlorine were only partially successful at best, there being a great tendency for the reaction to proceed to PCl_5. Therefore, an excess of chlorine was used to convert the phosphorus to PCl_5 which was then reduced by red phosphorus to PCl_3.

The reduction of PCl_5 to PCl_3 in the vapor phase by a thin film of red phosphorus is perhaps an original contribution of this work, as is the condensation of minute quantities of PCl_3 vapor out of carrier gas (Ar or He) in a trap at -77°C.

With minor modifications, the process and apparatus used can be adapted to collect ^{33}P-labeled PCl_5, $POCl_3$, and even elemental phosphorus.

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