

## Synthesis and Characterization of $^{14}\text{C}$ Polyvinylphosphonic Acid

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### SUMMARY

Ten mCi of  $^{14}\text{C}$  ethylene was converted to 1.16 mCi of  $^{14}\text{C}$  PVPA by oxidative phosphonation with phosphorus trichloride and molecular oxygen, dehydrohalogenation with triethylamine in ether, polymerization, and hydrolysis. The polymer had a specific activity of 12 uCi/mg and a radiochemical purity over 99%.

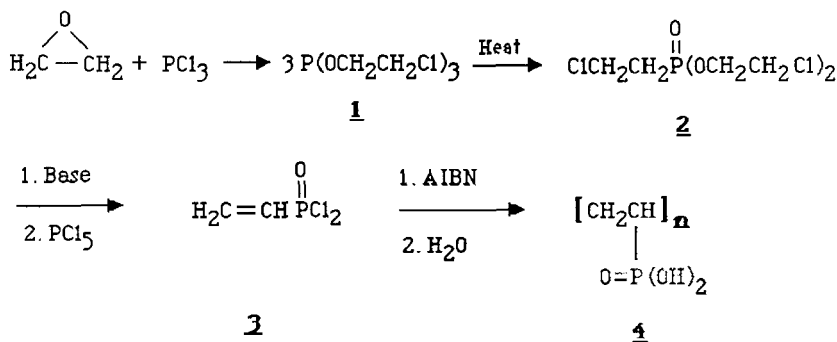
**Key words:**  $^{14}\text{C}$  synthesis, polyvinylphosphonic acid, vinyl phosphonyl dichloride, 2-chloroethylphosphonyl dichloride.

### INTRODUCTION

Polyvinylphosphonic acid (PVPA, **4**) is manufactured commercially as a finish for photographic films<sup>1</sup>. It has been shown to have anticariogenic activity in rats<sup>2</sup> and to inhibit plaque and gingivitis formation *in vivo*<sup>3</sup>.

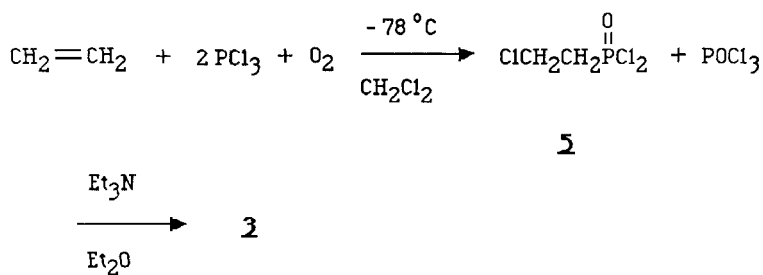
Synthesis of radiolabelled PVPA was necessary to supply material for studies of its metabolic fate and pharmacology. Radiolabelling by the phosphonation of polyethylene using a  $^{32}\text{P}$  reagent has been reported<sup>4</sup>, but, since the procedure gives less than complete phosphonation, it was not adaptable to the present case. A commercial procedure for the preparation of PVPA is shown in SCHEME 1. Labelling phosphorus by this route would require using large amounts of the short-lived hazardous  $^{32}\text{P}$  isotope in an inefficient protracted linear sequence. As an alternative, we decided to synthesize  $^{14}\text{C}$  PVPA.

## SCHEME 1



SCHEME 1 is also not very attractive for the synthesis of  $^{14}\text{C}$  PVPA. The starting material,  $^{14}\text{C}$  ethylene oxide, is not generally commercially available. There are four steps to the monomer **3** which proceed with only moderate overall yield. In addition, the sequence requires the loss of two-thirds of the radioactivity in the phosphorus pentachloride cleavage step to generate **3**. We therefore investigated the oxidative phosphonation of ethylene shown in SCHEME 2 as an alternate route to the monomer<sup>5</sup>.

## SCHEME 2



A ten-fold excess of phosphorus trichloride was used in order to allow for the competitive formation of phosphorus oxychloride. A six-fold volume of methylene chloride solvent and a low reaction temperature were chosen to maximize the dissolution of ethylene and its retention in the reaction mixture. Gas scrubbers were used in line with the gas flow from the reaction vessel to further minimize escape of ethylene. The oxygen was introduced into the system at a relatively slow rate with vigorous stirring in order to minimize formation of the by-product 1,2-dichloroethane<sup>6</sup>. The product 2-chloroethylphosphonyl dichloride, **5**, was dehydrohalogenated in ether solution with triethylamine. The monomer **3** was polymerized neat

using azobisisobutyronitrile (AIBN) as the initiator. Anhydrous conditions were maintained throughout until completion of the polymerization.

## EXPERIMENTAL

$^{14}\text{C}$  labelled ethylene was supplied from New England Nuclear in breakseal bulbs containing 5 mCi, each. Solvents were ACS reagent grade and stored over 4A molecular sieves. Phosphorus trichloride was distilled immediately prior to use.

NMR spectra were obtained from a Bruker MSL-300 spectrometer with a 10 mm probe, deuterium lock, and without proton decoupling. Size exclusion HPLC was done on a Toyosoda TSK column eluting with pyrophosphate buffer and using a refractive index detector. Radioisotope measurements were made by liquid scintillation counting in Aquasol II cocktail with a Beckman LS-6800 instrument.

### Oxidative Phosphonation:

$^{14}\text{C}$  ethylene (nominal 10.3 mCi, 1 mmol) was transferred from breakseal bulbs to a vacuum trap along with 200 mg (7.1 mmol) of ethylene. The reaction apparatus, consisting of a 50 mL flask, two high efficiency gas scrubbers, and a 20 mL bubbler, was assembled as shown in Figure 1. The system was purged with dry argon. The flask was charged with a solution of 30 mL of phosphorus trichloride in 70 mL of methylene chloride, and each scrubber with 5 mL phosphorus trichloride in 30 mL of methylene chloride. The terminal bubbler contained 10 mL of neat sulfuric acid. The flask and scrubbers were chilled to  $-78\text{ }^{\circ}\text{C}$  in dry ice-acetone baths. The trap containing the ethylene was then connected to the gas inlet. The solution in the flask was stirred vigorously while the ethylene was swept into the reaction vessel with a stream of dry oxygen. Flow was then held to about 5-8 mL/min. for five hours, during which time the reaction went to completion. The apparatus was then allowed to come to room temperature under a static argon atmosphere overnight. Analysis of the system found 9.0 mCi in the flask, 1.5 mCi in the first scrubber, 0.08 mCi in the second, and 0.001 in the terminal sulfuric acid bubbler.

The contents of the flask and scrubbers were combined and distilled at atmospheric pressure under argon to a head temperature of  $90\text{ }^{\circ}\text{C}$ . The residue was transferred to a 10 mL roundbottomed flask for distillation under vacuum. The pressure was gradually reduced to 5.5 Torr while collecting the phosphorus oxychloride distillate at dry ice-acetone temperature. The 2-chloroethylphosphonyl dichloride product (**5**) was collected at a head temperature of  $65\text{-}70\text{ }^{\circ}\text{C}$ . The product was obtained as

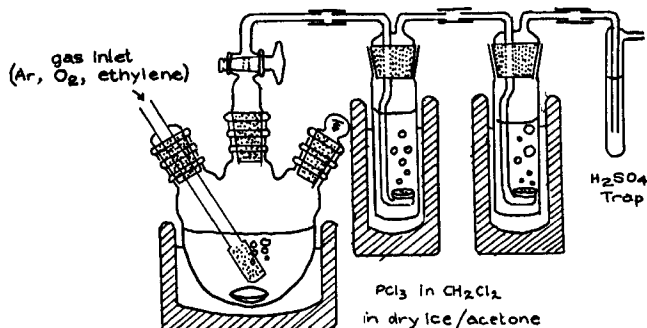


Figure 1. Apparatus for the oxidative phosphorylation of ethylene.

1.23 g (6.8 mmol, 83%) of colorless oil with an activity of 9.0 mCi. A total activity of 1.57 mCi was found in the initial methylene chloride and the phosphorus oxychloride distillates.

### Dehydrohalogenation of **5**:

The 1.23 g (6.8 mmol) portion of **5** obtained above was dissolved in 10 mL of anhydrous diethyl ether. The solution was stirred under argon at 0 °C and 0.98 mL (excess) of triethylamine was added. The mixture was stirred 1 h, then filtered through a glass frit under argon pressure. The filtrate was distilled, first at atmospheric pressure to remove ether, then under vacuum. The product **3** was 0.317 g (2.19 mmol, 32%) of colorless liquid with an activity of 2.9 mCi.

### Polymerization of **3**:

A 0.011 g (3 mole %) portion of azobisisobutyronitrile (AIBN) was added to the 0.317 g (2.19 mmol) of **3** obtained above and the resulting solution was stirred at 75 °C under an argon atmosphere 96 h. The crude poly(vinylphosphonyl dichloride) was converted to PVPA by dissolving it in 5 mL of water, then transferred to a dialysis bag made from 3500 Dalton-cutoff cellulose tubing. The solution was dialyzed against two separate 500 mL portions of water for 18 h each. The diffusate contained about 1.7 mCi and the retentate showed 1.2 mCi of activity. The retentate was reduced to about 0.6 mL *in vacuo*, then freeze dried. The purified <sup>14</sup>C PVPA (**4**) was obtained as a pale yellow resinous solid in 0.0974 g yield.

## RESULTS AND DISCUSSION

A 0.05 mL portion of an aqueous solution of **4** (0.0012 g/mL) was passed through a gel permeation size exclusion HPLC column. The elution profile is shown in Figure 2. The material eluted largely as a single, fairly narrow peak in a region between where peaks from PVPA standards, known by light scattering data to be 15 and 20 KD, appeared. All radioactivity was recovered in samples collected within this region, as well.

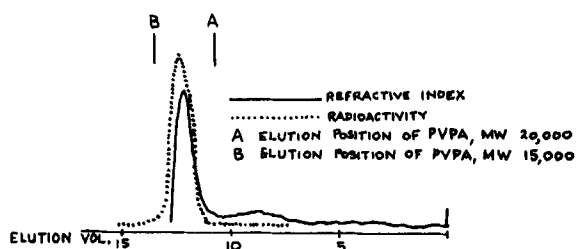


Figure 2. Size exclusion HPLC of **4**.

The  $^{31}\text{P}$  nmr spectrum of a solution of 1.57 mg of **4** in 2.00 mL of deuterium oxide is shown in Figure 3, along with a separate spectrum of vinylphosphonic acid in deuterium oxide. The polymer shows a single broad peak at 31 ppm, well separated from that of vinylphosphonic acid at 16 ppm. The signal-to-noise ratio of the spectrum is such that as little as 1 % monomer would have given a detectable signal.

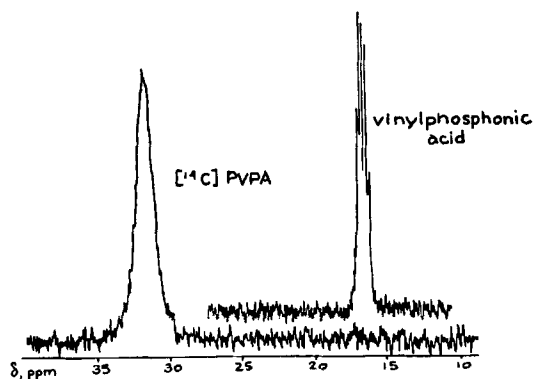


Figure 3. Phosphorus NMR spectra of **4** and vinylphosphonic acid.

All the activity of the starting ethylene was recovered in the reaction flask and scrubbers during the oxidative phosphorylation reaction. This implies that all the ethylene reacted with none passing through the system

to be lost into the atmosphere. The oxidative phosphorylation is a complex process involving the generation and reaction of chlorine and chloroethyl radicals<sup>6</sup>. Although our procedure was developed to provide an optimized yield of **5**, a significant amount of 1,2-dichloroethane is formed as a byproduct. This accounts for the radioactivity found in the methylene chloride and phosphorus oxychloride fractions during distillation of the crude product mixture.

Difficulties encountered in this work arise from the extreme sensitivity to moisture of the reagents and intermediates. The yield in the dehydrohalogenation reaction was considerably less than the 80% we routinely obtained in cold runs. Yields should improve considerably if the sequence were run in a glove box under an anhydrous atmosphere.

The polymerization follows the procedure used for the commercial production of PVPA. Commercial samples typically show 12-14% monomer present, by proton NMR, and lose from 30 to 70% of their starting weight upon purification by dialysis as 3500 Dalton cutoff. The results of our polymerization are consistent with results obtained in those preparations of PVPA. Thus, from a manageable and inexpensive quantity of starting material, using a simple method, we acquired <sup>14</sup>C PVPA of sufficient quality and quantity for a number of useful pharmacology experiments.

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