PREPARATION OF ^{18}F-β-D-GLUCOSYL FLUORIDE

Alberta E. Lemire and Mary F. Reed
Department of Radiation Medicine, University of Kentucky
Medical Center, Lexington, Kentucky 40506
Received August 31, 1977
Revised October 3, 1977

SUMMARY

A rapid procedure for the synthesis of β-D-glucosyl fluoride labelled with the short-lived, positron-emitting radionuclide, ^{18}F, is described. Accelerator produced ^{18}F, as Ag^{18}F, is reacted with tetra-O-acetyl-α-D-glucosyl bromide, and the product is hydrolyzed with NaOMe producing ^{18}F-β-D-glucosyl fluoride with a radiochemical yield of 15%, based on the activity of the initial reaction mixture corrected for decay, and a purity of about 87%. Purification by TLC gave approximately 200 μCi of product with a specific activity of at least 4.4 μCi/mg.

This glucose analog is of interest as a metabolic tracer and as a potential tumor localizing agent.

Key Words: Fluorine-18, β-D-Glucosyl Fluoride, Sugar, Tumor Localizing

INTRODUCTION

In recent years increasing research has been directed toward the preparation of radiopharmaceuticals incorporating the short-lived, positron-emitting radionuclide ^{18}F (half life 110 min). The proliferation of compact medical cyclotrons and the advent of emission computed axial tomography for positron emitters seems to insure that the field will become even more active in the years to come. Palmer et al (1) and Robinson (2) have comprehensively

0362-4803/78/0015-0105$01.00

reviewed progress to date in this field.

The substitution of fluorine for hydrogen or hydroxyl in organic molecules produces "analog" molecules that often demonstrate either unchanged or very subtly changed biological behaviors (2). Thus ^{18}F labelled compounds may find use as analog metabolic tracers.

A group of monofluorinated compounds of particular interest are the fluorinated sugars. Depending upon which of the six possible positions that F for OH substitution has occurred (3,4), substitution of fluorine for hydroxyl in these sugars leads to considerable modification in transport across mammalian membranes and changes in enzymatic action. Although the enzymology of fluorocarbohydrates has been rather extensively studied, little is known of their metabolic fate in vivo, and the importance of preparing suitably labelled fluorocarbohydrates for such studies has been pointed out by Kent (5).

The subtle changes in the enzymology of fluorocarbohydrates as opposed to ordinary carbohydrates also suggests that this group of substituted compounds may have interesting potential as tumor localizing radiopharmaceuticals. Wassenaar et al (6) have pointed out that many tumors have extensive glycolytic activity. This activity could well be due to differences in isozyme profiles; for example, there is a marked difference in the isozyme profile for normal liver and certain hepatomas (7). Thus ^{18}F-fluorosugars appear to be particularly promising for tumor localizing studies. For these reasons we have initiated a study of the potential of a series of ^{18}F-fluorosugars as tumor localizing radiopharmaceuticals and in this paper report the facile synthesis of the first fluorosugar tested, ^{18}F-β-D-glucosyl fluoride.

EXPERIMENTAL

Production of ^{18}F. Fluorine-18 was produced by the $^{20}Ne(d,\alpha)^{18}F$ reaction on the University of Kentucky Van de Graaff Accelerator. This procedure has been described previously (8). AgF labelled with ^{18}F was prepared by washing the glass target chamber insert by rotating for ten minutes with a slurry of 100 mg AgF in 20 ml of dry CH_3CN. Best recovery of activity was achieved by allowing the AgF to stir in the dark with the CH_3CN for 20 minutes prior to use in order to

achieve maximum dissolution. In a typical run a solution containing about 10 mCi of ^{18}F activity would be thus obtained.

Preparation of ^{18}F-β-D-glucosyl fluoride. The procedure followed (except for the use of H-OH resin rather than water extraction to remove excess fluoride) is essentially that reported by Hall, Manville, and Bhacca (9) for the preparation of "cold" β-D-glucosyl fluoride for NMR studies.

One hundred mg of tetra-O-acetyl-α-D-glucosyl bromide in 5 ml of dry CH_3CN was added to the $Ag^{18}F$ wash solution, and the mixture was stirred in the dark for 15 minutes. The solution was filtered through a fine glass fritted disc, and the filtrate stirred with 1 g H-OH resin (Rexyn 300) and 1 g 4A molecular sieves for 5 minutes and once again filtered. The filtrate was then evaporated to a syrup under vacuum in a water bath at 40°C.

On an aliquot of the syrup a TLC (Eastman Silica Gel G, EtOAc or MeOH solvent) showed that 87-99% of the activity corresponded to a spot that moved with the same Rf as an authentic sample of tetra-O-acetyl-β-D-glucosyl fluoride which had been prepared by standard literature methods and agreed in melting point 85° [lit 86-89°, 88° (10)], ^{13}C NMR (11) and proton NMR (9) with the published data. Proton and ^{13}C NMR of the syrup in a "cold" synthesis on the same scale also agreed with the published data. The remaining activity stayed at the origin and was probably due to ^{18}F-fluoride. The radiochemical yield of tetra-O-acetyl-β-D-glucosyl fluoride was 18.4 to 19.4%, based on the activity of the initial reaction mixture and corrected for decay.

The syrup was dissolved in 2 ml of dry MeOH and hydrolyzed by stirring with 0.45 ml of NaOMe solution (100 mg NaOMe in 10 ml dry MeOH) for 5 minutes and then adding 1 g of H^+ resin (Rexyn 101) and stirring for a further 5 minutes. The supernatant MeOH solution was then removed with a syringe.

The radiochemical yield, corrected for decay, of the β-D-glucosyl fluoride at this point was 15.1%. Typically 1 mCi of product was obtained. The purity as monitored by TLC (silica gel plates, MeOH solvent) was generally about 87% with the residual activity remaining at the origin, probably due to fluoride. The purity of the β-D-glucosyl fluoride was generally slightly less than that of the initial tetra-O-acetyl-β-D-glucosyl fluoride. This small decrease was probably

due to a side reaction of the β-D-glucosyl fluoride with NaOMe causing elimination of HF (12). A ^{13}C NMR spectra of this syrup in a same scale "cold" synthesis agreed with the published spectra for β-D-glucosyl fluoride (11).

Further purification could be achieved by spotting the MeOH solution on a preparative TLC plate (silica gel, 250 μ thickness) and developing in MeOH. The band with Rf =.72 was scraped off and stirred with 10 ml of normal saline. The saline solution was separated from the silica G by filtration and the product recovered with 70% recovery efficiency in 8 ml of saline. Approximately 200 μCi of β-D-glucosyl fluoride was obtained with a specific activity of at least 4.4 μCi/mg based on 100 mg of starting material. The overall radiochemical yield for this purified product, corrected for decay, was 8.2%. It was shown by TLC to be 92-97% pure, which is of the level of purity suggested to be acceptable by Palmer et al (1) for radiopharmaceuticals labelled with short-lived isotopes.

While the total activity recovered is somewhat low at this point, it is still sufficient for tissue distribution studies in animals. It may also be noted that we are severely limited by the modest capability of the Van de Graaff accelerator to produce ^{18}F. Cyclotron production of ^{18}F can easily lead to curie amounts, and hence the synthesis described herein when carried out with cyclotron produced ^{18}F should give product in an amount and with a specific activity suitable for clinical studies in humans.

ACKNOWLEDGEMENT

Research supported in part by Grant PO1-CA-17786 awarded by the National Institute of Health, DHEW.

REFERENCES

1. Palmer A.J., Clark J.C. and Goulding R.W. - Int. J. Appl. Radiat. Isot. 28: 53 (1977).
2. Robinson G.D. in Radiopharmaceuticals, Subramanian G., Rhodes B.A., Cooper J.F. and Sodd V.J. eds, The Society of Nuclear Medicine, Inc., New York, 1975, p. 141.
3. Taylor N.F. in Carbon-Fluorine Compounds, Chemistry, Biochemistry, and

Biological Activities, Elliott K. and Birch J. eds, Elsevier Press, Amsterdam, 1972, p. 216.

4. Burnett J.E.G. - Ibid., p. 95.
5. Kent P.W. - Ibid., p. 212.
6. Wassenaar W., Tator C.H. and Batty H.P. - Cancer Res. 35: 785 (1975).
7. Sato S., Matsushima T. and Sugimura T.L. - Cancer Res. 29: 1437 (1969).
8. Reed M.F., McEllistrem M.T. and Pettit W.A. - Phys. Med. Biol. 20: 493 (1975).
9. Hall L.D., Manville J.F. and Bhacca N.S. - Can. J. Chem. 47: 1 (1969).
10. Micheel F., Klemer A., Nolte M., Nordiek H., Turl L. and Westermann H. - Ber. 90: 1612 (1957).
11. Bock K. and Pedersen C. - Acta Chem. Scand. [B] 29: 682 (1975).
12. Micheel F. and Klemer A. - Adv. Carb. Chem. 16: 85 (1961).