A Synthesis of 2-Deoxy-D-[1-11C]Glucose for Regional Metabolic Studies:
Concise Communication

Robert R. MacGregor, Joanna S. Fowler, Alfred P. Wolf, Chyng-Yann Shlue, Robert E. Lade, and Chung-Nan Wan

Brookhaven National Laboratory, Upton, New York

A synthesis of 2-deoxy-D-[1-11C]glucose from H11CN has been developed. This compound is obtained in a radiochemical yield of 30–40% with a synthesis time of 45 min.


The use of 2-deoxy-D-[14C]glucose and autoradiography in animals to determine regional brain glucose metabolism is a widely accepted technique (1–3). Recently this method has been successfully extended to study regional glucose metabolism in humans by utilizing the positron-emitting deoxyglucose analog, 2-deoxy-2[18F]fluoro-D-glucose (FDG(F-18)), and positron-emission tomography (PET) (4–11). The 110-min half-life of fluorine-18 fits conveniently into a clinical study and at the same time results in an acceptable radiation dose to the subject or patient. Note that as the sensitivity of PETT improves with advances in design, the amount of radioactivity required for a study (currently 5–7 mCi) will decrease, thus reducing the absorbed dose even further. The production of FDG (F-18), while now routine and reproducible on a daily basis, still requires the production of 300–1000 mCi of anhydrous 18F-F2, depending on the required delivery of the FDG (F-18). For example, currently at BNL two consecutive human studies are done with each delivery of FDG (F-18). This requires the production of approximately 300 mCi of 18F-F2 (at end of bombardment), which results in 20–25 mCi of FDG (F-18) (12–14). When shipments of FDG (F-18) are made from BNL to collaborating laboratories 100–350 mi distant, larger quantities of FDG (F-18) are required to compensate for delays in transportation and to ensure adequate levels of the product at its destination.

Medical cyclotrons with low deuteron energies (e.g., 8 MeV) place severe constraints on the amount of fluorine-18 that can be produced; thus, production must be maximized in order to allow preparation of adequate daily amounts of this agent.

Carbon-11, another positron emitter, is currently more widely available than 18F-F2. Furthermore, for 1 hr of target bombardment, H11CN can be produced readily in large quantities (~2 Ci) in a nearly carrier-free state at any medical cyclotron installation (15). This makes it more widely available for clinical use the carbon-11 analog, 2-deoxy-D-[1-11C]glucose (C-11 2DG) (1, Fig. 1), at high specific activity. The shorter half-life of C-11 (20.4 min) permits serial metabolic studies at shorter time intervals and a somewhat lower radiation dose than is currently delivered.

For these reasons and others having to do with the metabolic processes being probed, we have developed a synthesis for 2-deoxy-D-glucose utilizing HCN (16). Preliminary reports of the application of this synthesis to the preparation of carbon-11-labeled deoxyglucose have appeared (17,18).

The compound C-11 2DG was prepared from Na11CN in an overall radiochemical yield of 30–40%, with a synthesis time of 40–45 min, by the reaction sequence shown in Fig. 1. We have modified a related scheme for the production of 2-deoxy-D-[1-14C]ribose.
in good agreement with the literature values (47.5%, 52.4%) for 2DG at equilibrium in aqueous solution (25,26). The specific activity of the C-11 2DG is variable, depending on the length of the cyclotron bombardment. The quantity of 2DG produced is 0.25 mg. Therefore, starting with 500 mCi of H\textsuperscript{11}CN, with a synthesis time of 45 min and a radiochemical yield of 30%, 32 mCi of C-11 2DG would be obtained with a specific activity of 128 mCi/mg.

In the course of this work a number of compounds were synthesized and examined as substrates for the initial displacement reaction. D-(--)-arabinose was converted 2,3:4,5-di-O-isopropylidene-D-arabinitol (2) by a four-step sequence using the method reported by Zinner and Kristen (27). The overall yield was 39%. Treatment of (2) with trifluoromethanesulfonic anhydride gave the triflate (3). Although the corresponding tosylate and iodide were also prepared (16) as potential precursors, they proved to be less suited to a synthesis with carbon-11. The tosylate was not sufficiently reactive to allow a rapid displacement by Na\textsuperscript{11}CN. The iodo compound reacted rapidly at elevated temperatures, but the resulting products poisoned the catalyst required in the subsequent reduction. The reactivity of the triflate (3) required that it be prepared immediately before use. The instability of trifluoromethanesulfonic anhydride requires that it be periodically redistilled to ensure reproducibility in the preparation of the triflate. The redistilled material is a clear colorless nonfuming liquid.

Various synthetic methods were examined for the conversion of the nitrite function to the aldehyde. LiAl(OC\textsubscript{2}H\textsubscript{5})\textsubscript{3}H (28) was unsatisfactory, giving amine as the major product. Di-isobutyl aluminum hydride reacted successfully (16) but the exact stoichiometric requirements of this reagent made it unsuitable for synthesis where very high specific activity is required. Raney alloy, which could be used in large excess—less than

![FIG. 1. The synthesis of 2-deoxy-D-[1-\textsuperscript{14}C]glucose (C-11 2DG).](image)

(19), achieving a significantly shorter reaction time and improved yields of C-11 2DG with high specific activity. A synthesis of 2-deoxy-D-[1-\textsuperscript{14}C]glucose, using C-14-labeled cyanide, has been reported as a model for rapid labeling with C-11 (20).

A suitably protected and highly reactive substrate, 2,3:4,5-di-O-isopropylidene-1-O-trifluoromethanesulfonyl-D-arabinitol (3, Fig. 1), was subjected to a nucleophilic displacement reaction with Na\textsuperscript{11}CN to form the corresponding C-11-nitrile (4) in 50 to 60% yield. This compound, although contaminated by some radioactive material that remained at the origin on silica-gel thin-layer chromatography (TLC) with ether hexane (1:1), was used in the next step without further purification. Compound 4 can be obtained in >98% radiochemical purity (Fig. 2a) by silica-gel chromatography if necessary. Simultaneous cleavage of the protective isopropylidene groups, with reduction/hydrolysis of the nitrile to an aldehyde, was accomplished in 60 to 70% yield by a modification of the procedure of van Es and Staskun (21), which involves heating in aqueous formic acid in the presence of Raney alloy (Ni/Al).

Filtration of this reaction mixture through a cation-exchange resin (hydrogen form) removed dissolved metal ions and the C-11-amine that was formed as a side product during the reduction. While stable in 30% formic acid, 2DG is nevertheless acid sensitive (22). It was found that the stability of the column effluent depended on the commercial source of the resin. With some batches of resin, which had been washed extensively (23), evaporation of the effluent resulted in extensive decomposition of the C-11 2DG. For this reason, the effluent of the cation-exchange resin was neutralized by passage through an anion-exchange resin before evaporation of the solvent. Final purification was achieved by flash chromatography (24), giving C-11 2DG with radiochemical purity of >95% by radio-gas chromatography (Fig. 2b) and 96–98% by thin-layer chromatography. The ratio of radioactivity of the α and β anomers (46.8%, 53.2%) in the radio-gas chromatograph is

![FIG. 2. Gas-chromatographic analysis of C-11 compounds. The radioactivity in each 1-min fraction is shown by bars superimposed on the mass profile of added carrier compound. (a) 1-cyano-1-deoxy 2,3,4,5-diisopropylidene-D-[1-\textsuperscript{14}C]arabinitol; (b) trimethylsilyl derivative of C-11 2DG (anomeric mixture).](image)
from this fraction in vacuo and the residue dissolved in U.S.P. saline and passed through a 0.22-µm Millipore filter. The radiochemical purity of the sample was 96–98% by TLC in CH₃CN:H₂O (95:5) and EtOAc:EtOH (1:1), and the radioactivity was congruent with the spot corresponding to carrier 2DG that was spotted with the active sample (I₂ detection). The 2DG could also be visualized in the presence of trifluoroacetic acid vapors, giving a gray spot in about 5 min at 25°C. The chemical yield is ~0.25 mg of 2DG. The final solution also contains ~0.025 mg of D-arabinol, the hydrolysis product of the starting material. The specific activity is 128 mCi/mg at the end of a 45-min synthesis when 500 mCi of H¹¹CN is used. This is the specific activity at the time of calibration, and clearly it will be variable, depending on the length of the cyclotron bombardment. After synthesis, the specific activity is constantly changing, since the material is not carrier-free. This dynamic change during use should be taken into account in adjusting data.

ACKNOWLEDGMENTS

This research was performed under the auspices of the U.S. Department of Energy and supported by NIH Grants No. 3-P41 RR00657 and 5-R01-GM16248.

FOOTNOTES

* Merck.
† On Merck and on Eastman TLC plates.

REFERENCES


26. BARNETT JEG, HOLMAN GD, MUNDAY KA: Structural requirements for binding to the sugar-transport system of the human erythrocyte. Biochem J 131:211–221, 1973