

Oxidation of 2-[¹⁸F]Fluoro-2-Deoxyglucose to 2-[¹⁸F]Fluoro-1,3-Propanedial

A Novel F-18 Precursor for Positron Emission Tomography (PET) Radiotracers

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ABSTRACT and INTRODUCTION

Positron emission tomography (PET) is a noninvasive imaging technique that utilizes beta-emitting radionuclides to quantitatively assess biological processes and diseases *in vivo*. Due to the short half-lives of the nuclides commonly used in PET (e.g., carbon-11, 20.4 min; fluorine-18, 109.8 min), there is a need for versatile precursors and rapid methods to incorporate them into molecules. To address this need, we have investigated the feasibility of using sodium periodate (NaIO₄) for the rapid conversion of 2-[¹⁸F]fluoro-2-deoxyglucose ([¹⁸F]FDG) to 2-[¹⁸F]fluoro-1,3-propanedial ([¹⁸F]FPD), a new reagent with the potential to label proteins. Studies were carried out by modeling radioactive (hot) reactions using nonradioactive (cold) reactions. Preliminary cold investigations involved oxidizing D-glucose, 2-deoxy-D-glucose (2DG), and [¹⁹F]FDG in the presence of excess NaIO₄ and monitoring product formation over time by ¹H and ¹⁹F-NMR in D₂O. Subsequent studies involved the investigation of temperature on reactions, performing reactions in H₂O to observe ¹⁹F-¹H J coupling, and using H₂O₂ to assess pH effects. Results from the ¹H-NMR studies suggest the formation of formic acid ($\delta = 8.25$ ppm) in each case as predicted. In the case of 2DG, the presence of a doublet at $\delta = 8.45$ ppm suggests the presence of 1,3-propanedial. The ¹H spectrum of the oxidation of [¹⁹F]FDG lacks a clear di-aldehyde resonance; however, a doublet of triplets ($\delta = -215.1$ ppm) in the ¹⁹F spectrum suggests the formation of the desired product. Further analysis by ¹⁹F-NMR suggests over-oxidation of the FDG intermediates occurs with time and elevated temperatures resulting in the formation of NaF. This observation was supported by analyzing a hot [¹⁸F]FDG oxidation by radio-thin layer chromatography. By quenching the reaction with ethylene glycol over-oxidation was prevented and thus allowed -215.1 ppm intermediate to be studied. Using H₂O₂ to oxidize FDG resulted in a clean one product reaction without defluorination demonstrating the need for acidic reaction conditions. Thus, we have shown that it is feasible to oxidize [¹⁸F]FDG using NaIO₄ to form [¹⁸F]FPD; however, H₂O₂ provides more desirable reaction conditions. Further studies are needed to assess optimal hot reaction conditions and to develop a method of detection for the detection of [¹⁸F]FPD.

Goals

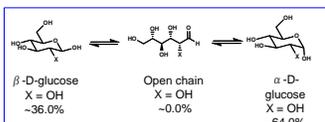
- To assess the feasibility of using NaIO₄ to form [¹⁸F]FPD from [¹⁸F]FDG.
- To understand the effects of temperature, NaIO₄ concentration, and pH on the reaction.
- To establish appropriate reaction conditions.
- To successfully use NaIO₄ to oxidize [¹⁸F]FDG to form [¹⁸F]FPD.
- Ultimately, to label a compound with [¹⁸F]FPD.

Pros

- ✓ Increase in specific activity.
- ✓ Potential to label proteins.
- ✓ Fast reaction at high temps.
- ✓ Well known reactions.
- ✓ Accessible, economical reagents
- ✓ **FDG IS EVERYWHERE!!**

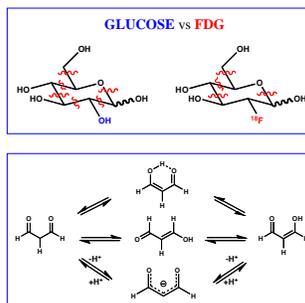
Cons

- ✗ Many side reaction possibilities.
- ✗ Complex equilibrium.
- ✗ Few suitable solvents.
- ✗ Over-oxidation.



For monosaccharides, an equilibrium exists between the closed ring hemiacetal and the open chain form allowing epimerization between α and β anomers.

REACTIONS and RATIONALE



Consequences of Chemoselectivity

The oxidation of D-glucose yields formaldehyde and formic acid as the complete cleavage of the pyranose ring occurs. 2-fluoro-2-deoxy-D-glucose (FDG) lacks a hydroxyl group at the C-2 position. Thus oxidation should not occur at this position 2-fluoro-1,3-propanedial (FPD)

Complex Equilibrium

1,3-propanedial can exist in many forms depending on the nature of the solvent. In polar solvents 1,3-propanedial has been shown to exist in the trans-enol form while in nonpolar solvents, the cis-enol form is preferred due to stabilization through intramolecular hydrogen bonding.

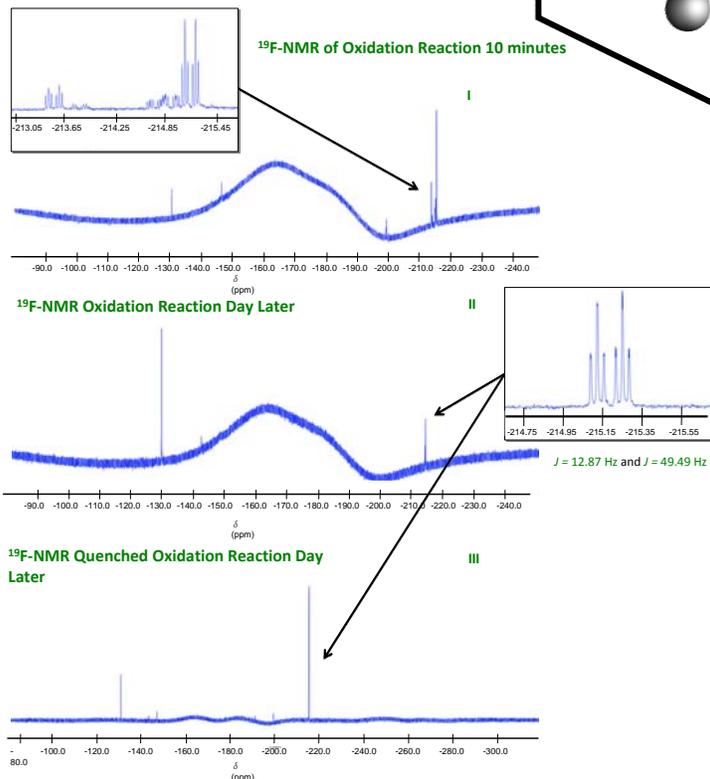
Potential Impact

PET has become a widely available imaging technique. At least 95% of the United States population lives within a 75 mile radius of a PET center. Thus this research can have a significant impact on much of the nation as FDG is widely available.



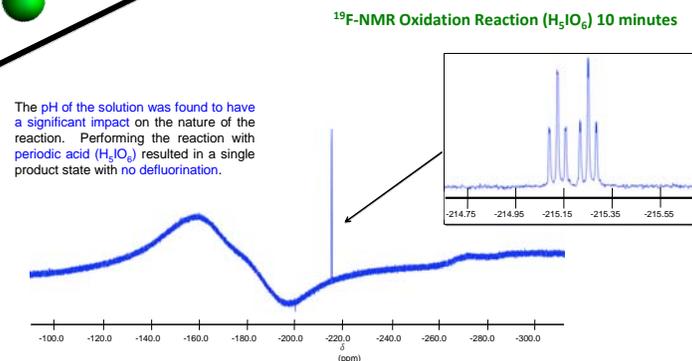
J.C. Patterson II and M.L. Mosley: PET Availability in the US, *Mol Imaging Biol* (2005)

METHODS, DATA, AND RESULTS



All reactions were performed in a small vial using 2.0 mg of FDG and 500 μ L of a 200mM NaIO₄ solution. Figure I depicts the ¹⁹F spectrum of the oxidation of FDG using NaIO₄. Upon reaction, several fluorinated intermediates were observed, and some FDG ($\delta = -199.1$ ppm) remained. When the reaction was allowed to continue overnight (Figure II), a two product system was reached. One intermediate ($\delta = -131.1$ ppm, s) was found to correspond to NaF and is believed to be a result of over-oxidation of FDG by NaIO₄ resulting in defluorination. The other intermediate ($\delta = -215.1$ ppm, dt) displays J-coupling constants and splitting characteristic of FPD. To prevent defluorination (Figure III), excess NaIO₄ was removed by quenching the reaction with Et(OH)₂. Quenching resulted in a two intermediate state where the proposed FPD intermediate was favored.

DATA and RESULTS CONTINUED (pH EFFECTS)



CONCLUSIONS

- NaIO₄ provides a feasible method for forming FPD
- Over oxidation occurs at higher temperatures and longer reaction times.
- Over oxidation results in defluorination of the -215.1 ppm intermediate.
- Oxidation at 50°C for 10 minutes followed by quenching the reaction with ethylene glycol produces an intermediate which is stable overnight in solution.
- The reaction is pH sensitive and using H₂O₂ results in a one product system.

FUTURE WORK

- Further investigation of -215.1 ppm ¹⁹F resonance.
- Using this methodology to successfully convert [¹⁸F]FDG into a new precursor.
- Development of a method for the detection of the new [¹⁸F]FPD precursor.
- Labeling of a compound using the new ¹⁸F precursor.

ACKNOWLEDGEMENTS

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