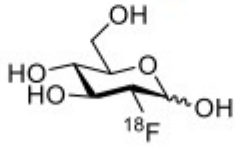
Problem 21. Fluorinated radiotracers

Fluorodeoxyglucose, namely the ^{18}F isotopomer 2-deoxy-2-[^{18}F]fluorodeoxyglucose (^{18}F-**FDG**), is a compound used in cancer diagnostics in a technique called positron emission tomography (PET). In this technique, the patient is treated with a radiotracer which is preferentially taken up by cancer cells. Upon radioactive decay, a positron is formed which rapidly annihilates with a nearby electron. A pair of γ-photons flying in opposite directions are produced and detected. This allows for the localization of the tumour with high sensitivity and spatial resolution.



^{18}F-**FDG**

21.1 The isotope ^{18}F is produced by a proton bombardment technique. Which isotope of which element is used for the production of ^{18}F?

$$^{17}O + p \rightarrow {}^{18}F$$

Since the amount of ^{18}F-**FDG** used in PET is very low, the dose is defined by units of radioactivity instead of the more commonly used molar concentration.

21.2 What is the amount of ^{18}F-**FDG** (in moles) present in one dose of 300 MBq (3×10^8 s^{-1})? The half-life of ^{18}F is 109.771 min.

Dato che il decadimento radioattivo segue una cinetica del primo ordine, si applica la seguente equazione:

$$\ln\frac{A_0}{A} = k\,t \qquad \text{da cui si ottiene} \qquad k = \frac{\ln\frac{A_0}{A}}{t} \qquad \text{quindi} \qquad k = \frac{\ln 2}{t_{1/2}}$$

Dopo un secondo di reazione, il rapporto A_0/A si ottiene da $\ln\frac{A_0}{A} = \frac{\ln 2}{109.771}\ \frac{1}{60} = 1{,}95241\ 10^{-4}$

$A_0/A = 1{,}000105247$ mentre il numero di atomi di ^{18}F che decadono al secondo è $A_0 - A = 3\ 10^8$ atomi.

Da questi dati si ricavano gli atomi che producono un segnale di 300 MBq cioè $A_0 = 2{,}850798\ 10^{12}$ atomi.

Questa quantità può essere convertita in moli $n = \frac{atomi}{N} = \frac{2{,}850798\ 10^{12}}{6{,}022\ 10^{23}} = 4{,}73387\ 10^{-12}\ mol$ ^{18}F-FDG

Il valore in moli cercato è quindi $n = 4{,}73\ 10^{-12}$ mol

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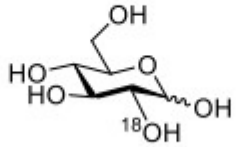
Assume that all molecules of ^{18}F-**FDG** decay to ^{18}O-**glucose**, which eventually undergoes standard biochemical transformation into carbon dioxide and water.



^{18}O-**glucose**

21.3 At what time point will the chemical energy of ^{18}O-**glucose**, produced by the decay of ^{18}F-**FDG**, be equal to the total energy of γ-photons not yet released from the remaining ^{18}F-**FDG**? In other words, at which time point would decomposing all obtained ^{18}O-**glucose** into CO_2 and H_2O produce the same amount of energy as the radioactive decay of all remaining ^{18}F-**FDG**? The heat of combustion of glucose is 2 800 kJ mol^{-1}.

L'energia chimica totale prodotta dalla trasformazione del ^{18}O-glucosio in CO_2 e H_2O è:

$$E_{tot} = (2{,}8\,10^{6}\ J/mol)\ (4{,}73387\,10^{-12}\ mol) = 1{,}32548\,10^{-5}\ J$$

L'energia dei fotoni prodotti dal decadimento radioattivo di un ^{18}F-FDG è data dall'annichilimento di un positrone ed un elettrone, quindi corrisponde all'energia delle loro due masse secondo Einstein:

$$E = mc^2 = (2\ \ 9{,}109\,10^{-31}\,kg)\ (2{,}998\,10^{8}\,m/s)^2 = 1{,}63743\,10^{-13}\ J$$

L'energia totale dei fotoni prodotti dal decadimento radioattivo del ^{18}F-FDG è quindi:

$$E_{tot} = n\ N\ E = 4{,}73387\,10^{-12}\ \ 6{,}022\,10^{23}\ \ 1{,}63743\,10^{-13}\ = 4{,}66789\ \ 10^{-1}\ \text{J}$$

Assumendo che *(x)* sia la frazione di ^{18}O-glucosio convertito in CO_2 e H_2O ed (1-x) sia la frazione di ^{18}F-FDG che deve produrre la stessa energia sotto forma di radiazione gamma, si può scrivere:

$x\,(1{,}32548\,10^{-5}) = (1-x)\,(4{,}66789\,10^{-1})$ da cui si ricava x = 0,9999716 quindi (1-x) = 2,8395 10^{-5}

Da questo dato si può ottenere il tempo necessario per arrivare a questo punto della reazione:

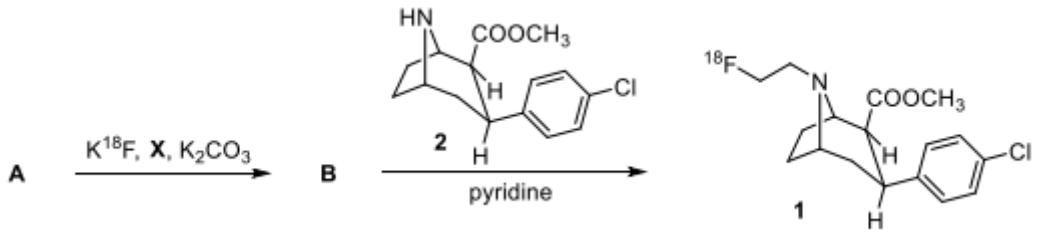
$$t = \frac{\ln\frac{A_0}{A}}{k} \qquad t = \frac{\ln\frac{1}{2{,}8395\,10^{-5}}}{6{,}314483\,10^{-3}} = 1657{,}98\,\text{min}$$

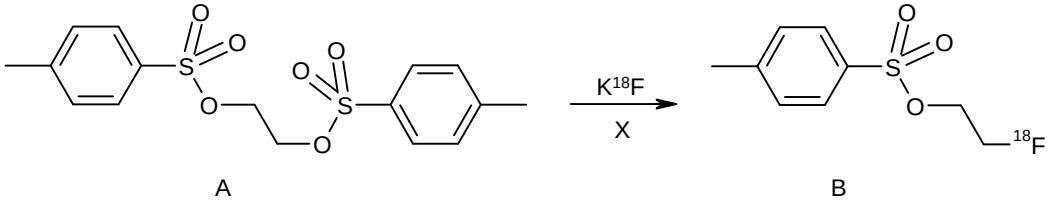
quindi 1658 minuti (27 h 38 min)

Nevertheless, ^{18}F-**FDG** is not the only fluorinated radiotracer in use. Compound **1** is a radiotracer used in the diagnostics of Parkinson's disease (PD). Molecule **1** binds to the dopamine transporter (DAT), a membrane protein characteristic of dopaminergic neurons. Degeneration of this class of neurons is a symptom of PD. Therefore, targeted imaging of neural cells expressing DAT is advantageous in the diagnostics of the neurodegenerative disorder.

A freshly synthesized sample of K^{18}F reacts with ditosylate **A**, producing monofluorinated precursor **B**. Molecule **B** further reacts with amine **2** to give the final radiotracer **1**.

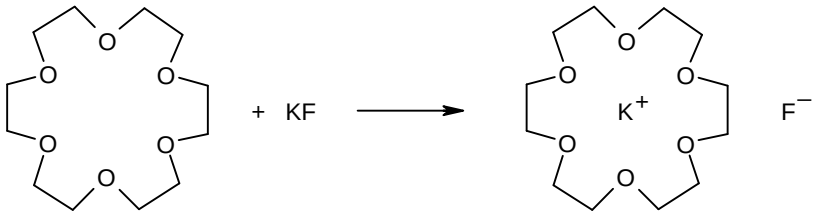
21.4 Propose the structures of tosylates **A** and **B**. What additive **X** is required to render the fluoride anion nucleophilic enough that the reaction runs to completion within minutes?





A B

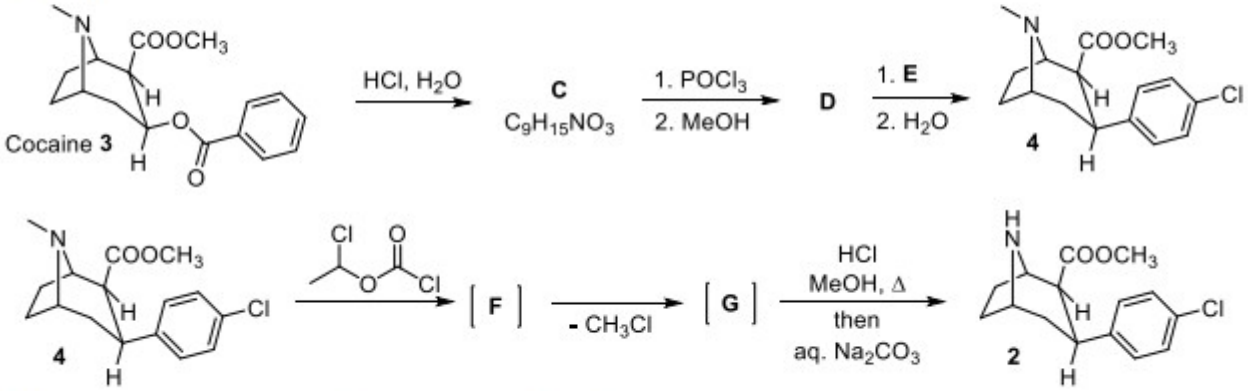
Per rendere nucleofilo lo ione fluoruro e per poterlo avere in soluzione con il reattivo A, si deve usare il reattivo X, questo è un etere corona che sequestra lo ione potassio e lascia libero lo ione fluoruro.



X

Amine **2** can be easily produced by a sequence of reactions starting from cocaine (**3**), a natural product from plants of the *Erythroxylaceae* family.

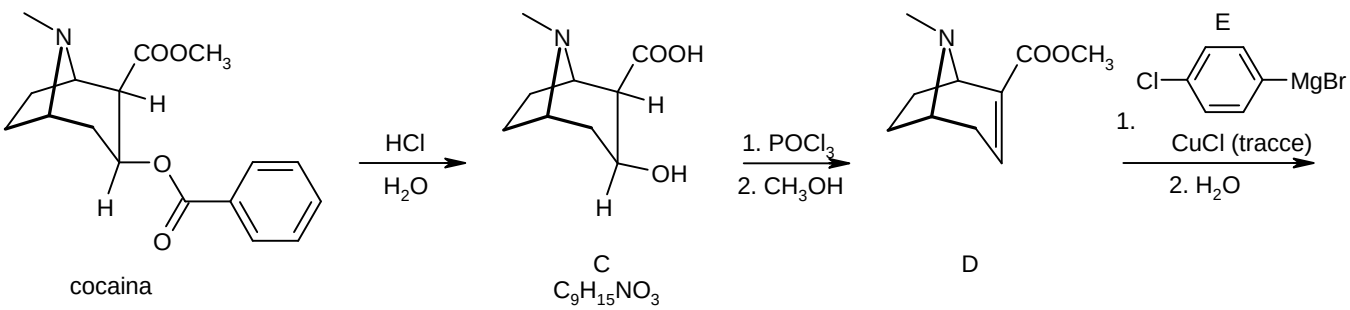
The synthesis starts with acid-catalyzed hydrolysis of cocaine (**3**) leading to compound **C** ($C_9H_{15}NO_3$). Subsequent elimination with $POCl_3$ produces, after a methanolic workup, compound **D**. Addition of magnesium-containing reagent **E** to compound **D** provides, after subsequent aqueous workup, precursor **4**. The final step in the synthesis of secondary amine **2** involves demethylation with 1-chloroethyl chloroformate followed by workup with aqueous sodium carbonate.



21.5 Draw the structures of compounds **C** to **E**.

21.6 Compound **4** is not the only stereoisomer which can be formed by the addition of **E** to **D**. Draw the structures of all the stereoisomers which are unwanted side-products of the transformation.

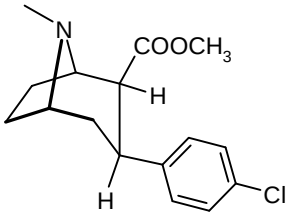
21.7 The mechanism of demethylation of **4** involves the formation of acylated intermediates **F** and **G**, and subsequent liberation of amine **2** with acidified hot methanol. Draw the structures of intermediates **F** and **G**.



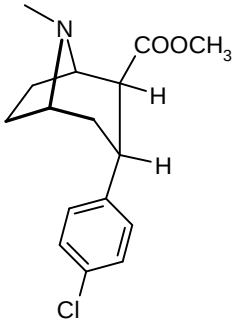
cocaina

C
$C_9H_{15}NO_3$

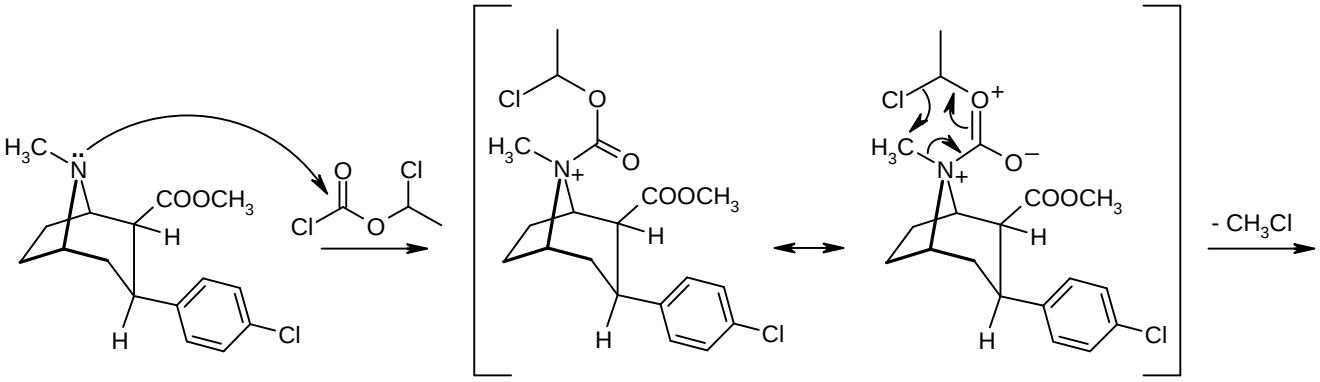
D



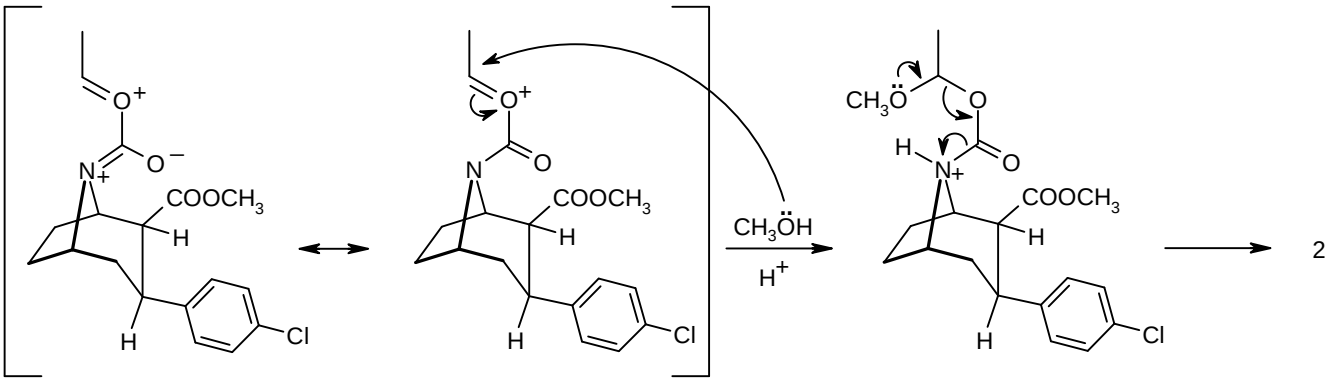
4
prodotto richiesto



prodotto indesiderato



4 F



G

Soluzione proposta da Mauro Tonellato - Padova