The Snakes & Ladders of Synthetic Chemistry

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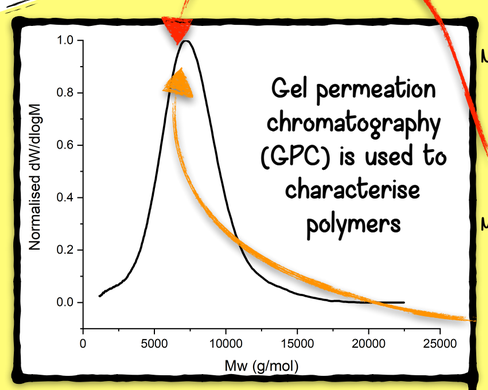
**The life of a synthetic chemist can often feel like a big game of Snakes & Ladders.
Below is a real-life synthesis carried out in the Gibson Group reimagined as a board game.**

START

Your boss has decided that they want some gold nanoparticles coated in glycopolymers, synthesised for use in medical diagnostics, as it will be "novel", "impactful" and justify some grant funding. Your task is to make the particles using common reagents, a Sigma-Aldrich Catalogue and analytical techniques.
Follow the snake to "GO" to begin...

Spectral Support 3



Gel permeation chromatography (GPC) is used to characterise polymers

Calculating PD&DP;

Number average (mean)

$$M_n = \frac{\sum_i N_i M_i}{\sum_i N_i}$$

= 5630 gmol^{-1}

Mass average

$$M_w = \frac{\sum_i N_i M_i^2}{\sum_i N_i M_i}$$

= 6788 gmol^{-1}

$$PD = M_w / M_n$$

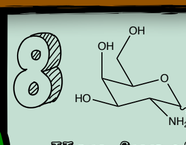
PD = 1.2

$$DP = \frac{M_n - M_w(CTA)}{M_w(monomer)}$$

DP = ~40

Our PD is near to 1, which is good as it means a small dispersity of polymer chain lengths
Progress to 8

8



+ TEA in DMF for 16 hrs at 50 °C

You functionalise your polymer with galactosamine using PFP as a leaving group. You can check the PFP has been removed using ^{19}F NMR, but you can't check sugar addition due to low sugar to monomer ratios.
See Spectral Support 4

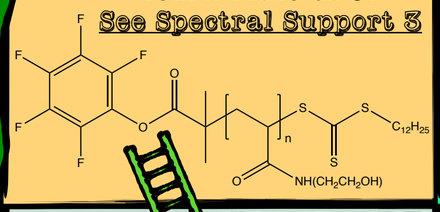
9

Graft your polymers to some gold nanoparticles via a thiol linker.

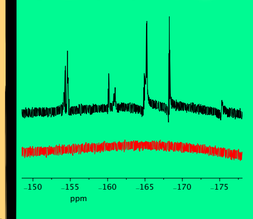
None of your common analytical chemistry techniques can be used to determine if the polymer is on the surface of the gold
See Spectral Support 5

7

You have made your polymer but you need to know the length in monomer units (DP) and the polydispersity (PD) of it. Time to learn some GPC!
See Spectral Support 3



Spectral Support 4

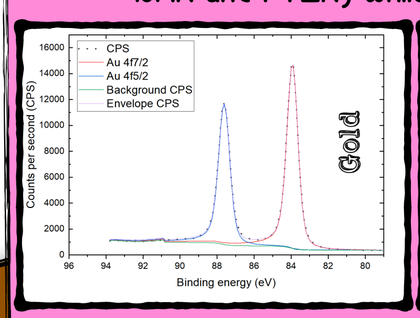


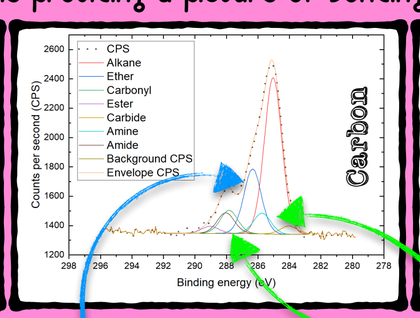
^{19}F NMR before (top) and after PFP removal (bottom)

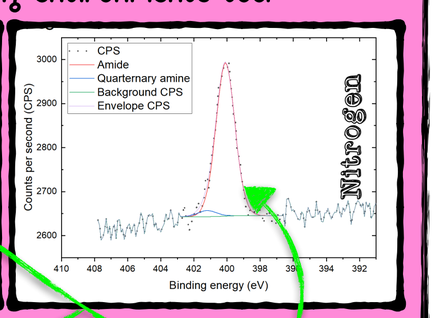
Progress to 9

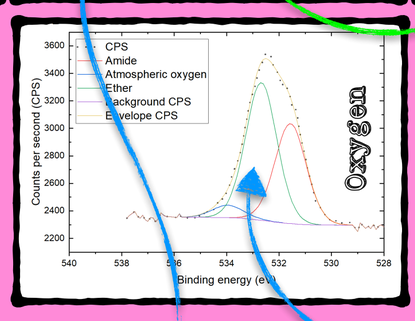
Spectral Support 5

You convince your colleagues in Physics to let you loose on the expensive XPS machine. XPS (X-ray Photoemission Spectroscopy) can be used to probe the surface layer of nanoparticle systems by measuring electron emission from atoms. It is useful to chemists as it can detect nanogram quantities of product (this is beyond the abilities of NMR and FTIR) while providing a picture of bonding environments too.





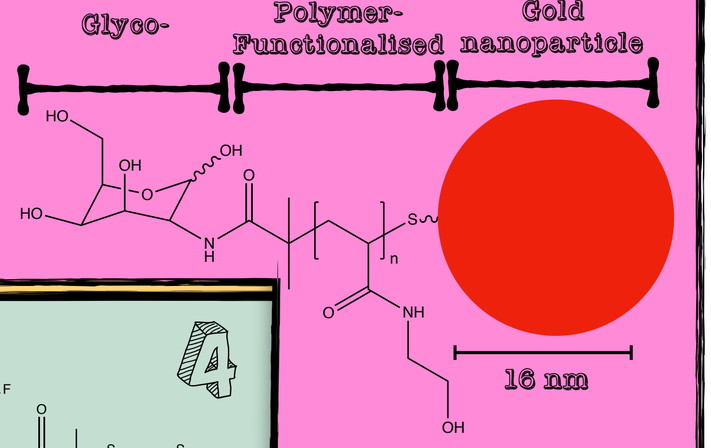




Your carbon and nitrogen spectra both show the presence of amide and amine bonds not found in background contaminants. This shows the presence of the polymer on the gold

The carbon and oxygen spectra both show ether (hydroxyl) peaks far above the background - this shows the presence of the sugar.
Your XPS data has shown the presence of the gold, the polymer and the sugar with the anticipated bonds in the expected ratios, so we have made the product as below!

Product



Progress to 10

RAFT Polymerisation

RAFT is a reversible-deactivation radical living polymerisation technique. It allows for a wide range of functionality, complexity and reaction conditions; while producing a low molecular weight dispersity range and predictable molecular weight polymers. RAFT polymerisation utilises a chain transfer agent ("RAFT agent") to control the reaction, a radical initiator (ACVA) and a vinyl monomer

Can you now safely and competently carry out a RAFT polymerisation?

NO - Follow the snake to the library

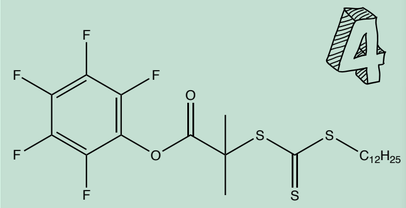
YES - Progress to 7 up the ladder

6

Its a good thing that as a young, naive UG Chemist you didn't think polymer modules were a waste of time, as you need to learn how RAFT polymerisation works
Progress to 6

5

4



You have successfully made the RAFT agent for the polymer synthesis step!
Progress to 5

3

Do you use mass spectroscopy (MS) or NMR to analyse your product?

Mass Spec - the product doesn't "fly" on the ESI follow the snake

NMR - See Spectral Support 2

Spectral Support 2

In your ^{1}H NMR you see a shift to a higher ppm for the dimethyl peak, this is a good indicator that the PFP group has formed an ester bond with the carboxylic acid.
The presence of the aromatic peaks in the ^{13}C is a further indicator that the PFP is present
Follow the ladder to 4

2

+ EDC + DMAP in DCM for 18 hrs at RTP

You want to add a pentafluorophenol (PFP) group, using the above reaction, as PFP is a good leaving group
See Spectral Support 1

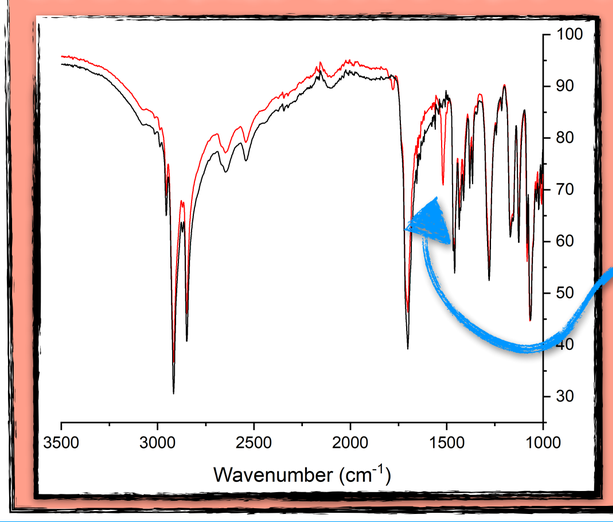
1

You have purchased this reagent from Sigma Aldrich. It is one step away from being your RAFT agent for polymer synthesis
Progress to 2

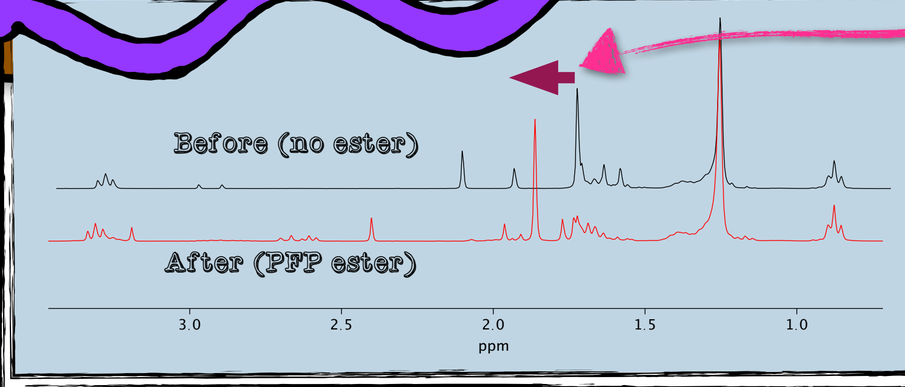
COLLECT STIPEND

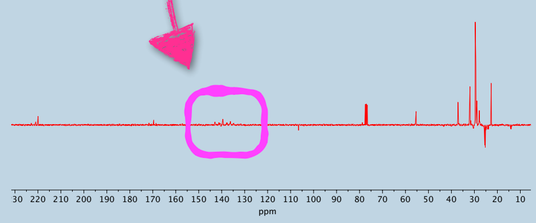
GO

Spectral Support 1



In this synthesis a pentafluorophenol (PFP) group is being added to the reagent (black). We should be able to observe the C-F peak in an FTIR (~1520 cm^{-1}) of the product (red).
This, however, is hardly a conclusive way to determine if we have produced the product.
Progress to 3





10 Summary

You have successfully synthesised a gold nanoparticle system that can be used to sense for protein targets such as Cholera Toxin.
In the Gibson group we use these systems to develop medical diagnostics for the developing world, drug delivery systems and antimicrobials.

Gibson Group Iceni Diagnostics BBSRC bioscience for the future MIBTP Midlands Integrative Biosciences Training Partnership WARWICK