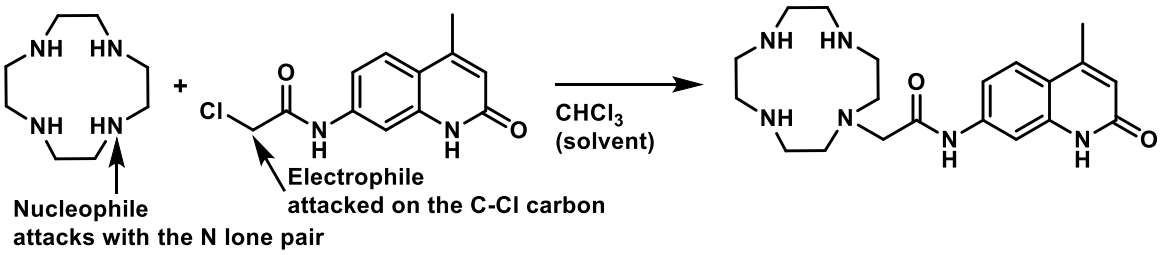
Homework 5 – 2017/05/03

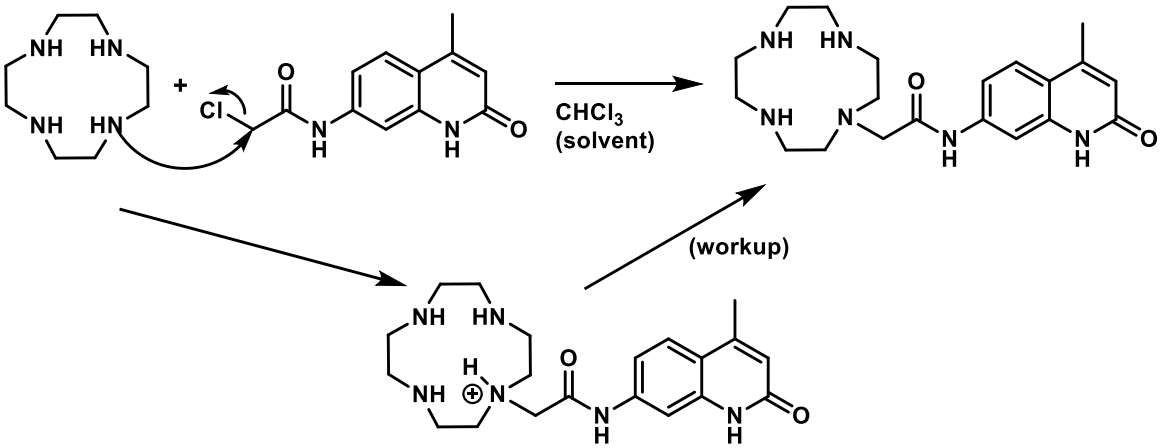
1) A PhD student carries out the following reaction:



a) Identify the nucleophile and the electrophile!

See scheme

b) Draw the mechanism of the reaction!



c) What type of reaction is this?

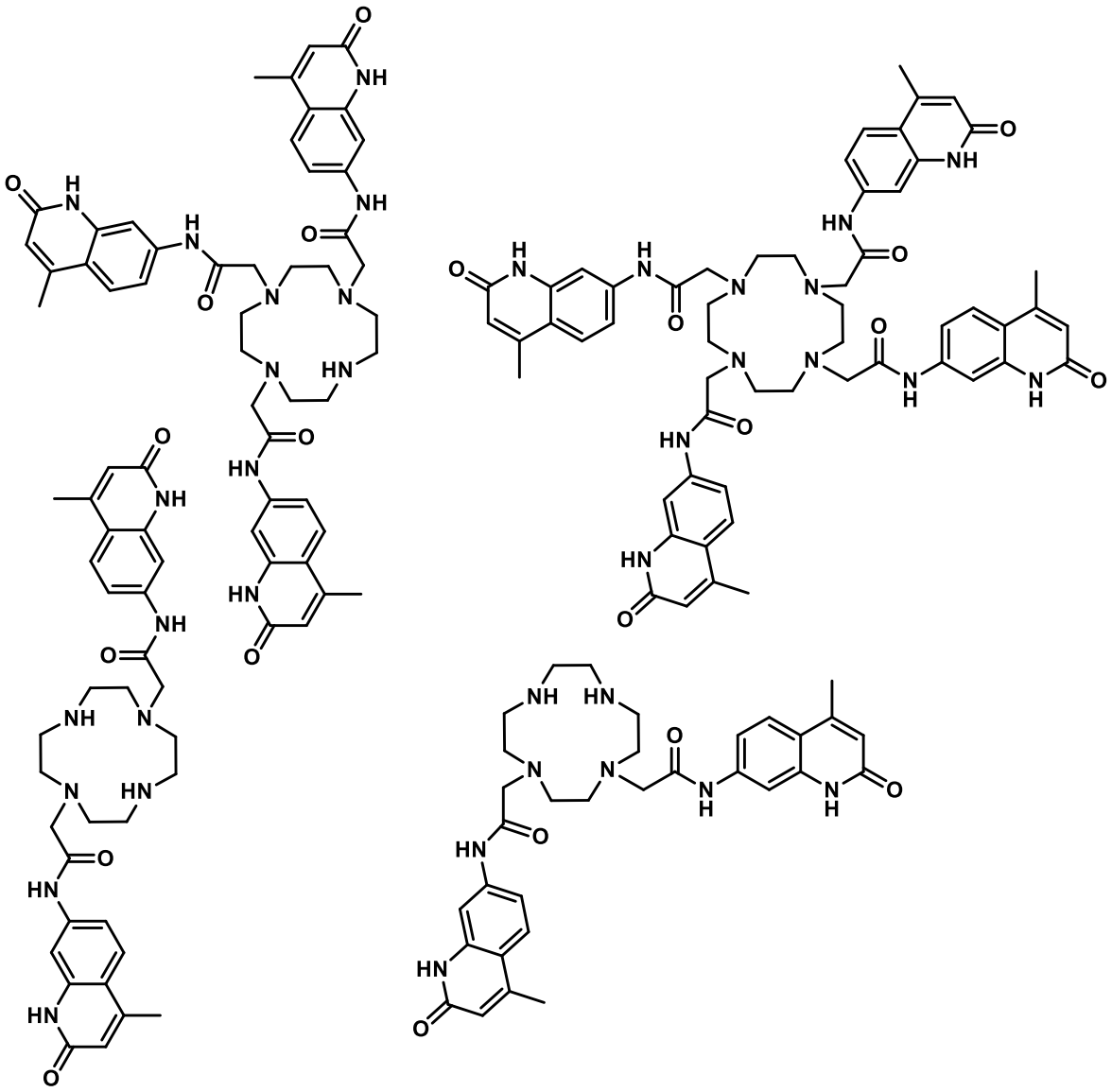
Bimolecular nucleophilic substitution. The Cl is sitting on a primary C, which is not going to give a stable carbocation, so S_N1 is excluded. Furthermore, the carbonyl group which is attached to the same carbon is very electron-withdrawing, which would decrease the stability of that already very unstable carbocation even more. So this is an S_N2.

d) What is (are) the by-product(s)? What happens to them during the reaction? Is their formation a problem for this reaction?

One equivalent of HCl is formed. As there are in total four secondary amines, this is not a problem, as you can afford to protonate one. In fact, this is even helpful, see below (part *e*).

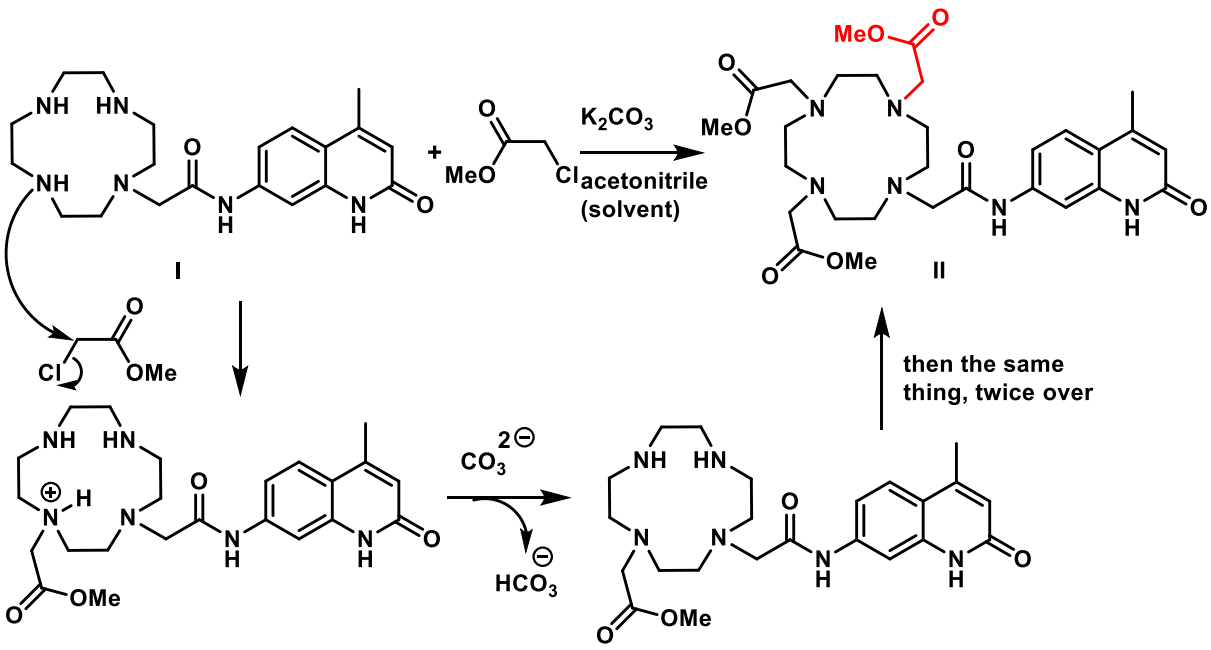
e) Do you expect any side-products to form? (I mean stuff that this poor student really would not wish to see forming.)

The product still contains three nucleophilic secondary nitrogen atoms, that can go on reacting with the electrophile – in fact their nucleophilicities are similar to that of the starting material's. This means that doubly, triply and even four-fold alkylated products can form.

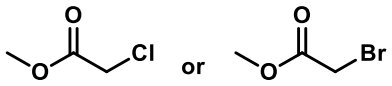


However, this turns out not to be a major problem. The reason is the following. There is no added base in the reaction, and it is run in $CHCl_3$, which is a solvent that is not good at solubilizing separated ions (such as a proton). So after the first S_N2-reaction, the proton stays close to the monoalkylated macrocycle (see scheme on previous page). This makes the alkylated macrocycle positively charged, and thus less nucleophilic than the starting material. During workup we add some base and to get rid of the proton, but by then there is no more alkyl halide to do unwanted reactions.

*2) After successfully performing the reaction, the student took the product (**I**) and used it to prepare a new compound (**II**).*



*a) What is **reagent X**?*



The reagent is the electrophile in the reaction. You need something that can contains the group marked in **red**, plus a good leaving group. The leaving group can be a halide (Br or Cl for example). You're gonna need at least three equivalents of the reagent, as you're substituting three secondary nitrogens.

b) Draw the mechanism.

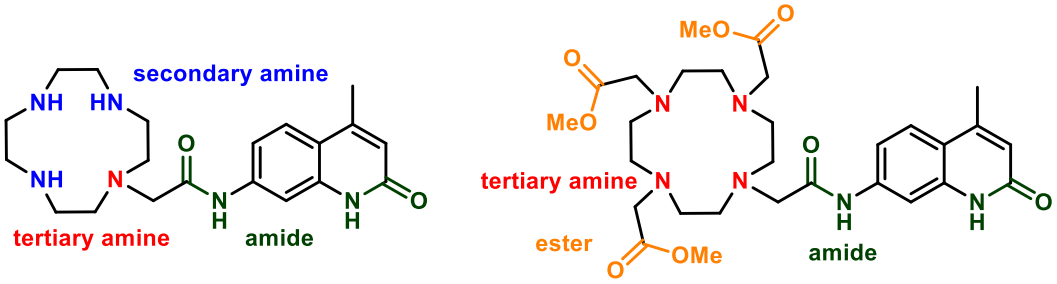
See scheme.

c) How many equivalents of K_2CO_3 do you need?

Three, to take care of the three equivalents of HCl (or HBr) by-product. Here you need all the secondary amines as nucleophiles, so you have to make sure that they are not protonated.

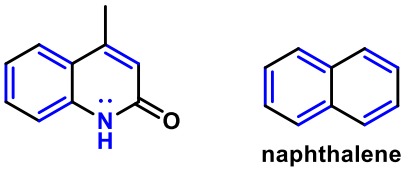
To be honest, the first protonation of the base gives you bicarbonate, which is still a decent base. So one equivalent of K_2CO_3 can take care of 2 equivalents of HCl. But K_2CO_3 is cheap, and it's easy enough to dump in 3 equiv, instead of worrying whether HCO_3^- is good enough.

*d) Identify the functional groups in **I** and **II**.*

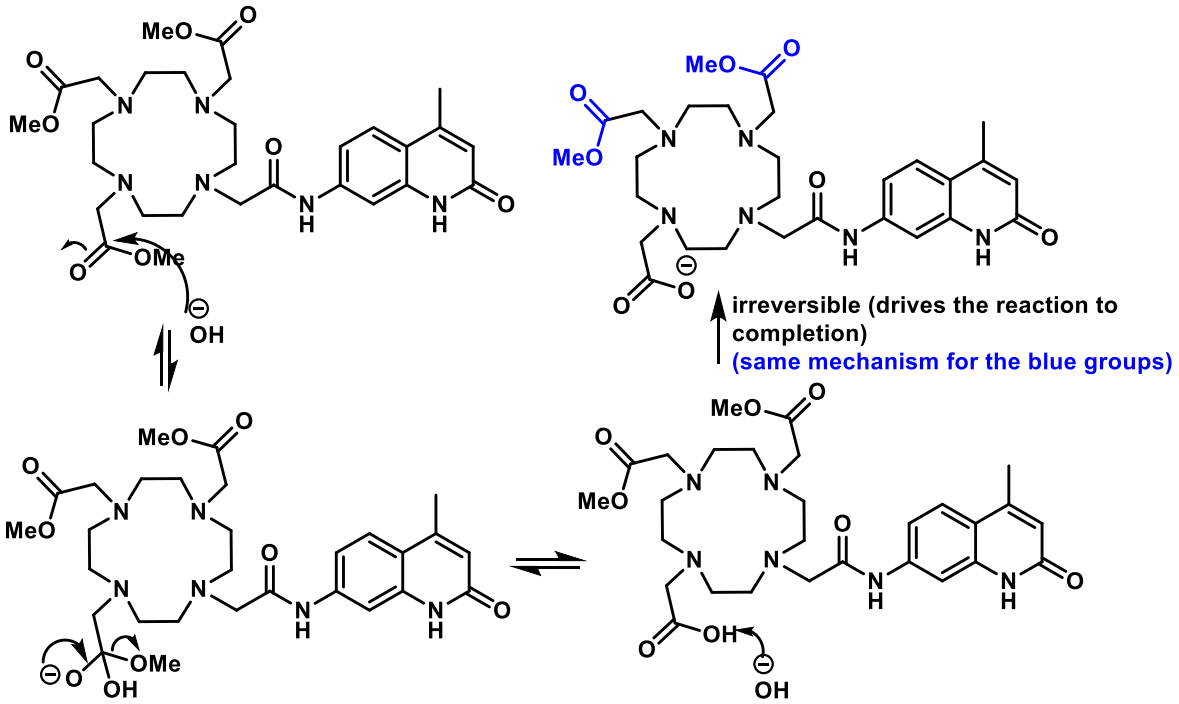


*e) In what region do you expect the part highlighted in **red** to absorb (λ_{max})? If you need help, compare it to the structures in Homework 3.*

The conjugation seems about as extended as in naphthalene (see electron pairs marked in blue), which absorbs in the UV. The actual λ_{max} for **II** is around 320 nm, which indeed is in the UV.



f) You can hydrolyze the methyl esters to the carboxylates ($RCOO^-$) with aqueous NaOH solution. Draw the product and the hydrolysis mechanism! Why do you form the carboxylates under these conditions, and not the carboxylic acids (RCOOH)?

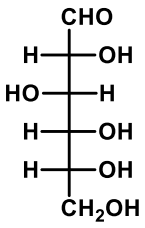


You get carboxylates because there is a base in the reaction mixture that is strong enough (NaOH, pK_a ~ 13.8) to essentially quantitatively deprotonate the carboxylic acids (pK_a ~ 4-5, see below for how this value was estimated).

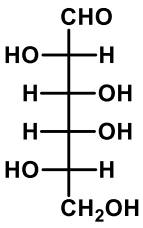
g) Do you expect the final product to dissolve in water? Why or why not?

The product contains three carboxylic acids with pKa's around 4-5, and three amines with pKa's around 9-10. These values are not far from those seen in amino acids, which are water-soluble. Of course the product is a bit larger than an amino acid, but it also has three of both functional groups; this makes it likely to be water-soluble. (*In fact, it is water-soluble, which can make purification a real nightmare.*)

3) a) Draw the Fischer projection of the open-chain forms of D-galactose and L-galactose.

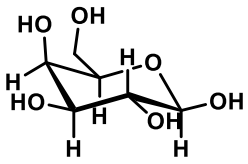


D-Glucose

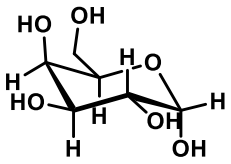


L-Galactose

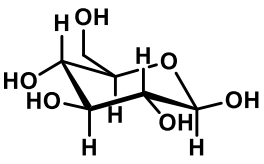
b) Draw the pyranose forms (chair) of β-D-galactose, α-D-galactose, β-D-glucose, and β-D-mannose (see Table 16.1 for D-aldoses; page 428 in the 2nd edition).



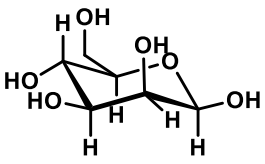
β-D-Galactose



α-D-Galactose

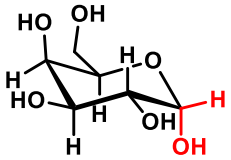


β-D-Glucose

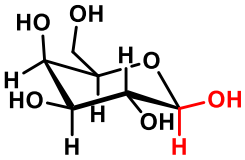


β-D-Mannose

c) What is the relationship between α-D-galactose and β-D-galactose?



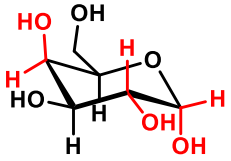
α-D-Galactose



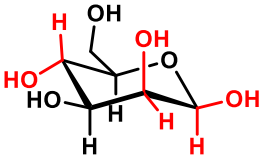
β-D-Galactose

They are C-1 epimers (see the red-marked part).

d) What is the relationship between α-D-galactose and β-D-mannose?



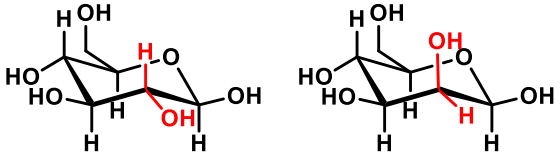
α-D-Galactose



β-D-Mannose

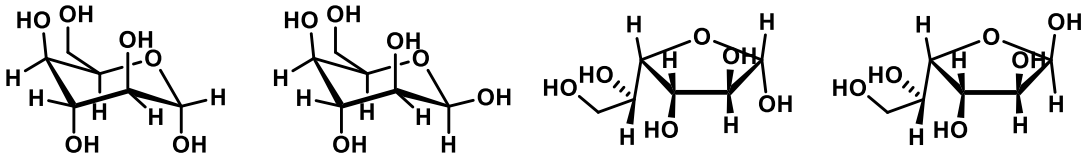
They are diastereomers (see the red-marked parts).

e) What is the relationship between β-D-glucose and β-D-mannose?



They are C2-epimers (see the red-marked part).

f) Draw the possible pyranose and furanose forms of D-idose.



*4) If you put live bacteria in a solution containing Ln complexes similar to **III**, after a while you will find some of the complex inside the (still live!) cells. Our initial hypothesis was that the cellular uptake was due to the β-D-galactose unit.*

a) How would you test this hypothesis? You can assume to have access to any instruments or chemicals you need, and the PhD student can make any fancy compounds.

b) Surprisingly, even complexes lacking a sugar are taken up, through what seems to be active transport. How would you, a biologist, try to figure out what is happening?

This is still work in progress, so I'll not make it public. If you're a student taking organisk kemi I and would like to know the answer, please contact me.