CHEM 191
Module 4
Structures and reactions of biological molecules

Lecture 5
Reactions of Carboxylic Acids and Their Derivatives

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Module 4 Lecture 5
Learning objectives

Learning Objectives:

- Recognise different carboxylic acid derivatives, and understand and predict their reactivity
- Understand the mechanism for nucleophilic acyl substitution reactions, including acid catalysed ester hydrolysis and ester formation
- Recognise that many lipids are carboxylic acid derivatives
- Recognise a phospholipid and a triglyceride and appreciate the role of fatty acid esters in cell membranes and lipid storage.

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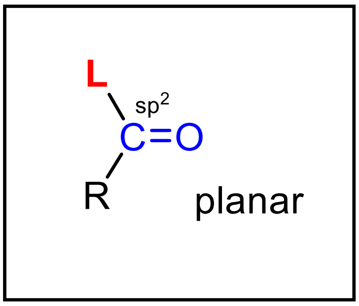
Geometry and polarisation

- Geometry similar to aldehydes/ketones
- C=O, made up of one sigma bond, one pi bond



R = carbon, **L** = any atom other than carbon

- Depending what the **L** group is, the C of C=O can be further polarized

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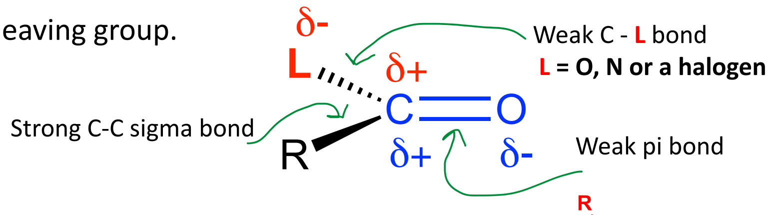
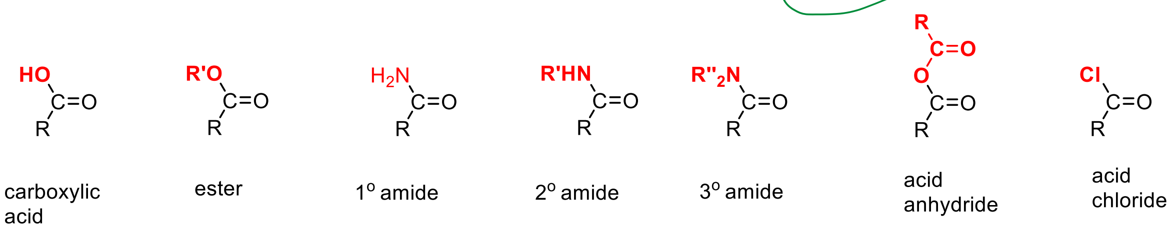
Carboxylic acid derivatives

- In lectures 3 and 4 we discussed the **addition reactions** of aldehydes and ketone
- Carboxylic acid derivatives can undergo **substitution reactions** since there is a weaker C-**L** bond and **L** can be a leaving group.





- Different carboxylic acid derivatives have different reactivity towards **nucleophilic acyl substitution** (structures above drawn in no particular order)

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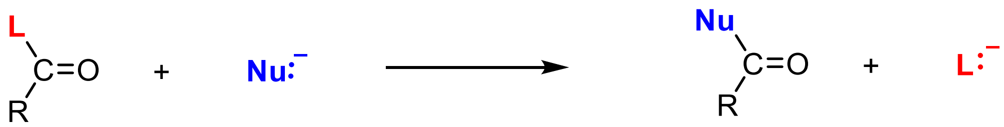
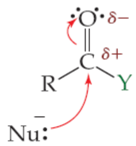
Nucleophilic acyl substitution

- An incoming nucleophile ends up **substituting** with the **leaving group**



- **Mechanism** – the same tetrahedral intermediate forms as we have seen before, but this then reforms the carbonyl pi bond because a **leaving group** is present

Figure 29.33



an acid chloride, anhydride or ester

R = H, alkyl, aryl
Y = Cl, OR, OCOR

Pages 1356-1358

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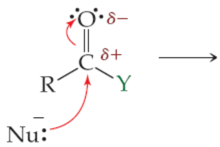
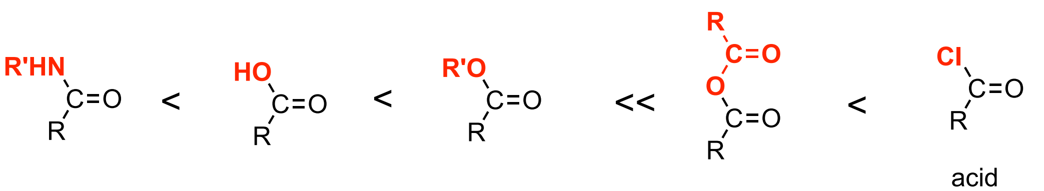
Nucleophilic acyl substitution

- Reactivity is governed by several factors
  - The electronegativity of the carbonyl carbon
  - The stability of the leaving group
  - The nucleophilicity of the nucleophile



an acid chloride, anhydride or ester



amide | carboxylic acid | ester | acid anhydride | acid chloride

$\delta+$ of carbonyl carbon **small** $\delta+$ of carbonyl carbon **large**

least reactive to nucleophilic acyl substitution most reactive

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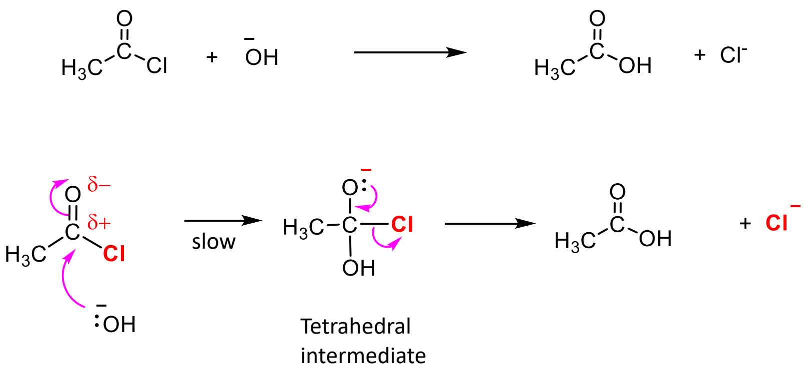
Acid chlorides and anhydrides are the most reactive

- δ+ on C of C=O is sufficient to attract weak and strong nucleophiles
- E.g. nucleophilic acyl substitution with a strong nucleophile -



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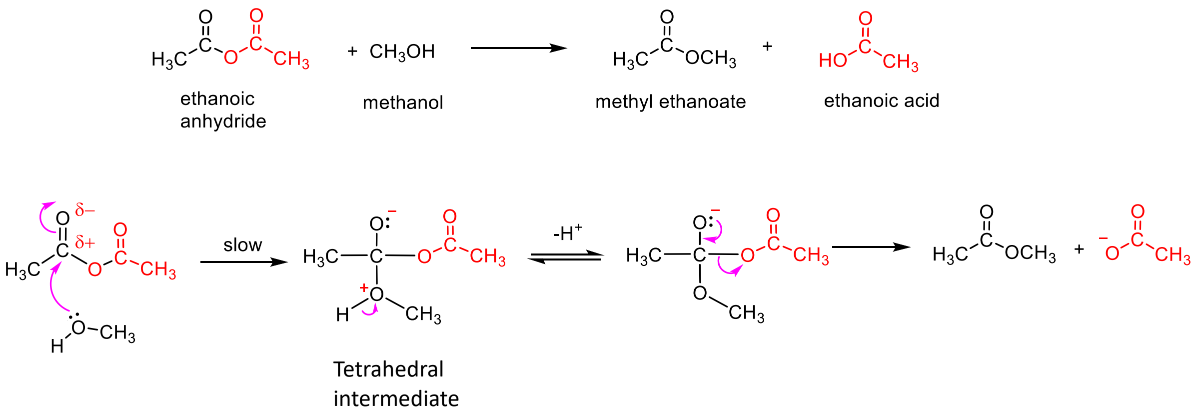
Acid chlorides and anhydrides are the most reactive

- δ+ on C of C=O is sufficient to attract weak and strong nucleophiles
- E.g. nucleophilic acyl substitution with a weaker nucleophile, a deprotonation step is required -



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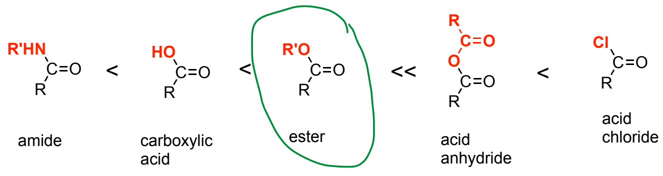
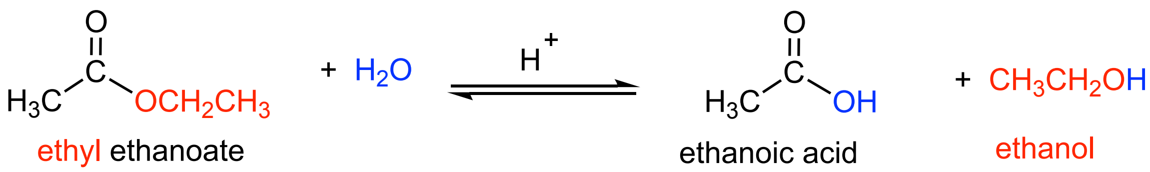
Esters are the next most reactive to nucleophilic acyl substitution

- Quite a lot less reactive than acid anhydrides
- Generally, need to make a better E+ before reaction can easily occur, this can be via acid catalysis



- **Acid catalysed ester hydrolysis** is a nucleophilic acyl substitution



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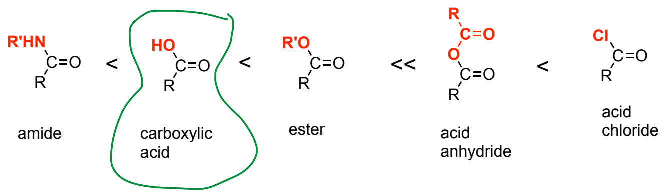
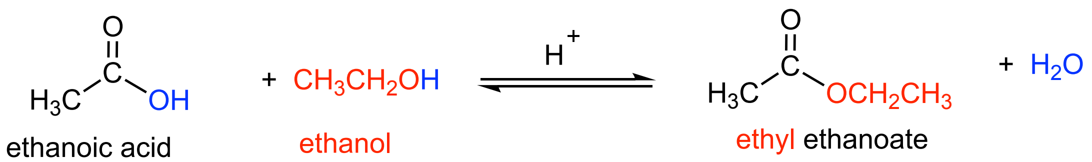
Carboxylic acids are the next most reactive to nucleophilic acyl substitution

- Again, need to make a better E+ before reaction can easily occur, this can be via acid catalysis



- **Acid catalysed ester formation** is a nucleophilic acyl substitution



- This reaction, and acid catalysed ester hydrolysis, are both reversible….. the mechanism is…..

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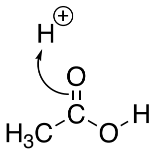
Mechanism – acid catalysed ester formation

The reverse reaction is **acid catalysed ester hydrolysis**
HOMEWORK – draw out the reverse reaction showing arrows



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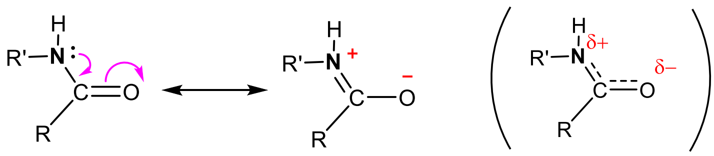
Amides are the least reactive in nucleophilic acyl substitution reactions

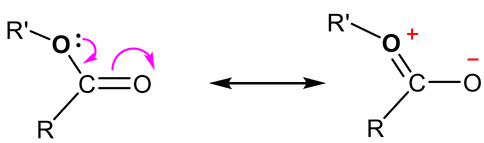
- Because they are the least electrophilic



real structure

Note: C-N bond has partial double-bond character (shorter than single bond, more difficult to break and to rotate). This is very significant for nitrogen. *Revisit in peptide lecture 7.*

- Less significant for oxygen as it is more electronegative.



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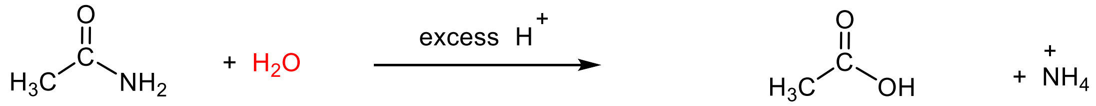
Amides are the least reactive in nucleophilic acyl substitution reactions

- Substitution is possible but very forcing conditions are required
  - Acid catalysed with heat
  - Or, strong base, heat



ethanamide — Reaction requires heat — ethanoic acid

We will revisit amides in Lecture 7

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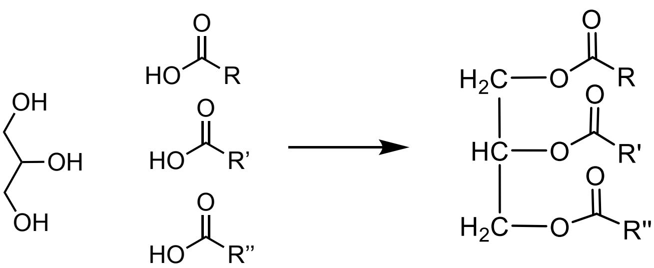
Fatty acids and fatty acid derivatives

- Fatty acids are **carboxylic acid derivatives**
- The ‘free’ carboxylic acid is usually found in very low amounts in dietary fats, but are incorporated into **triglycerides** and **phospholipids** as **esters**

Triglycerides, are made up of

R, R’, R’’ are long alkyl chains



glycerol — 3 x long chain carboxylic acids — A **triglyceride** *a type of lipid*

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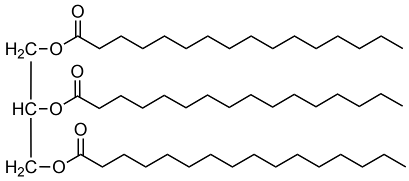
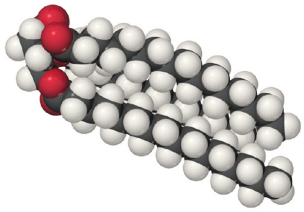
Triglycerides

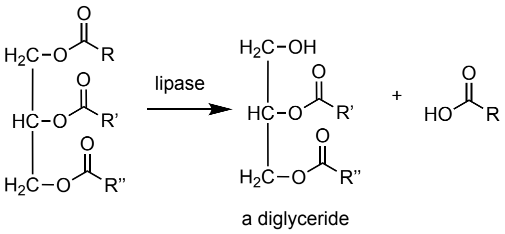
- The R, R', R'' can all be different, can be saturated or unsaturated





glyceryl tripalmitate, a **saturated triglyceride**

- Triglycerides are broken down in our body by enzymes called **lipases**



….. Further lipase reactions cleave the other fatty acids…..

Washing powder contains **lipase**, to breakdown triglycerides on clothing …. More on **enzymes** in Lecture 8

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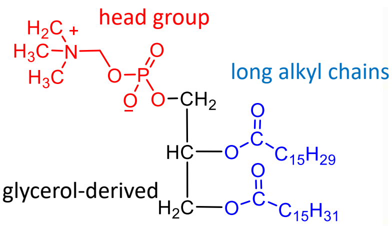
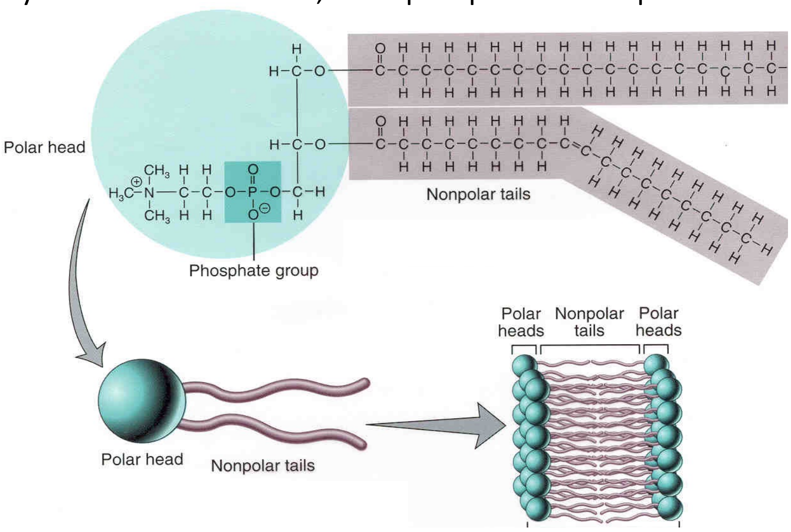
Phospholipids

- Phospholipids are also carboxylic acid-derived esters, but a phosphate is also present





- In the above example, at physiological pH, the ionised phosphate and amine forms the 'polar head' group
- These charges help reduce ester breakdown

CELL MEMBRANE

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Fatty acids and fatty acid derivatives

- Kuku | Green lipped mussel
- Kuku are a taonga species
- Economically, ecologically, and culturally important species in Aotearoa

- Farming of kuku in Aotearoa is primarily for human consumption, **petfood ingredients** and **human supplements**.

Powder and oil, in various forms

What are some of the fatty acids in kuku thought to have beneficial biological activity?

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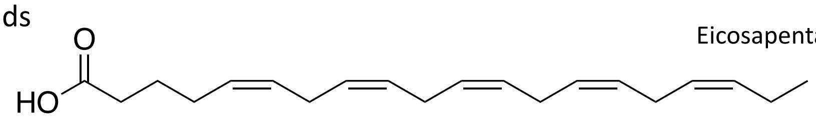
Fatty acids and fatty acid derivatives

- Lipids from kuku are thought to have health benefits, due to certain omega 3 unsaturated fatty acids



Eicosapentaenoic acid (EPA)

- Only a small % of the EPA in kuku is in the above form. Most are present as phospholipids and triglycerides

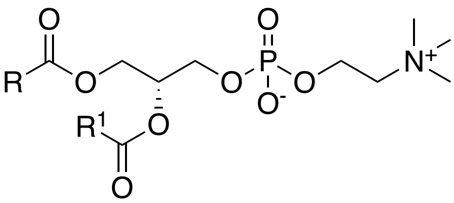
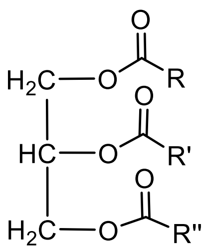


image credit: Alan Dove



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* Homework *

Draw out a full mechanism for **acid catalysed ester hydrolysis**, i.e. the reverse of slide 11, i.e. showing the mechanistic arrow starting from an ester to form a carboxylic acid and alcohol

Page 1329, exercise 28.40

Page 1368, exercise 29.50