CHEM 191
Module 4
Structures and reactions of biological molecules

Lecture 2
Reactions of Carbonyl Compounds

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Module 4 Lecture 2
Learning objectives

Learning Objectives:

- Understand the structure and reactivity of carbonyl compounds
- Draw mechanisms for the reactions of nucleophiles (weak and strong) with carbonyl compounds
- Understand the chemistry of vision
- Draw mechanisms for the formation of hemiacetals, acetals and imines

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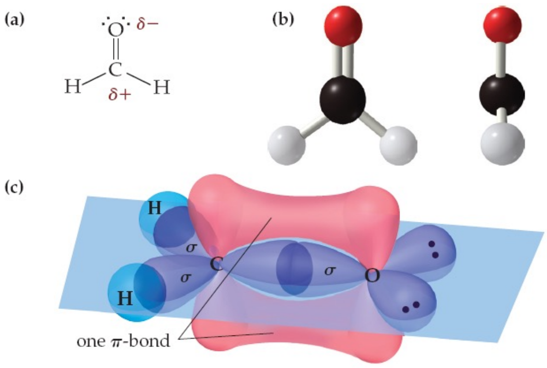
Carbonyl compounds

Aldehydes and ketones are examples of carbonyl compounds

Fig 28.1 page 1293



- contain a carbonyl (C=O) functional group
- Carbon and oxygen are sp^2, planar
- The C=O bond is *polarised*

- Compare back to the π-bond in an alkene, module 3

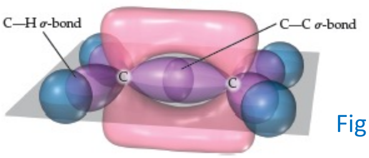


Fig 26.5 page 1213

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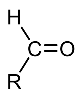
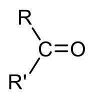
Aldehydes and Ketones



R = H or alkyl group

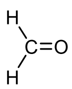


R, R' = alkyl group

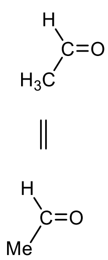
Aldehyde

Ketone

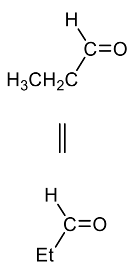
For example



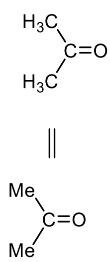
methanal



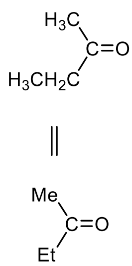
ethanal



propanal



propanone



butanone

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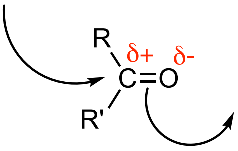
Reactivity of aldehydes and ketones

Pages 1304-1305

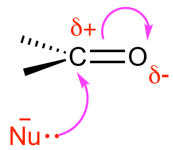
- Aldehydes and ketones most commonly undergo addition reactions

Attack by a nucleophile (Nu)

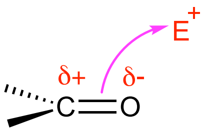


Compare back to addition reactions of alkenes in module 3, some similar concepts

- The mechanism is different depending on if the **nucleophile (Nu)** is
  - strong (i.e. a good base), e.g. amine (R-NH_2)
    nucleophile attacks in first step



OR



  - weak (i.e. a weaker or poor base), e.g. water (H-OH), alcohol (R-OH)
    carbonyl reacts with an electrophile in first step

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Addition reactions of aldehydes/ketones with a <u>stronger</u> Nu

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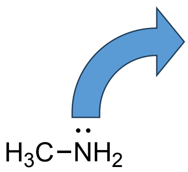
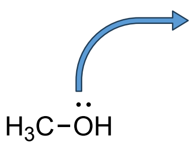
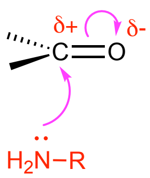
- An amine (R-NH_2) is a stronger nucleophile than an alcohol (ROH), as the lone pair of electrons on nitrogen are more loosely held and more easily shared.





- An amine is a **strong** enough **nucleophile** to directly attack the carbonyl carbon



So what happens next?

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Addition reactions of aldehydes/ketones with a <u>stronger</u> Nu

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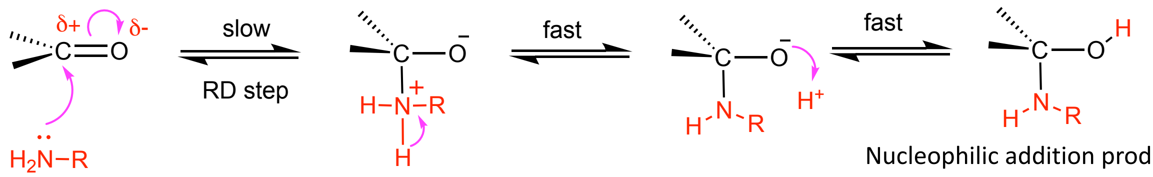

Nucleophilic addition product
(in this case unstable
… see next slide)

1. Nucleophile attacks - rate determining (RD) step, slow
2. Deprotonation
3. O^- attacks the electrophile (H^+)

Compare back to addition reactions of alkenes in module 3, some similar concepts

We have **added** a nucleophile (R-NH_2) and electrophile (H^+) across the C=O

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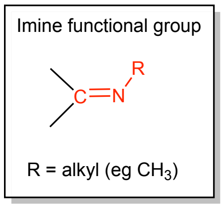
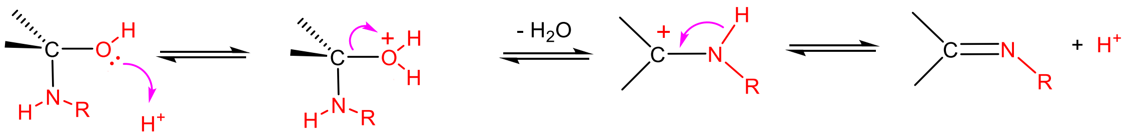
After addition of an amine to an aldehyde/ketone – something else happens

- Under the same reaction conditions, the unstable addition product forms an **imine** via the loss of water



Nucleophilic addition product
(from previous slide)



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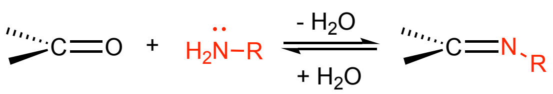
- An aldehyde/ketone reacting with an amine to form an imine is an important covalent, reversible bond used in the body



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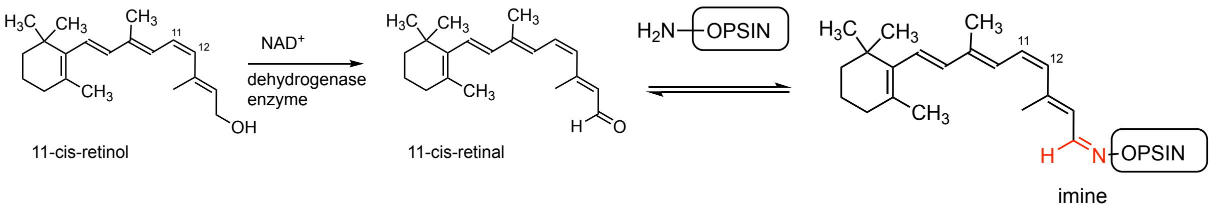
The chemistry of vision

Page 1223, 1406

- Reversible imine formation is a key part of vision



Retin**ol** is oxidized to retin**al**

The **aldehyde** of retinal reacts with an **amine** of the protein (the opsin)

Figure 31.3

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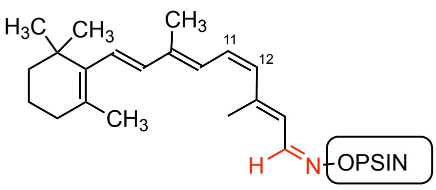
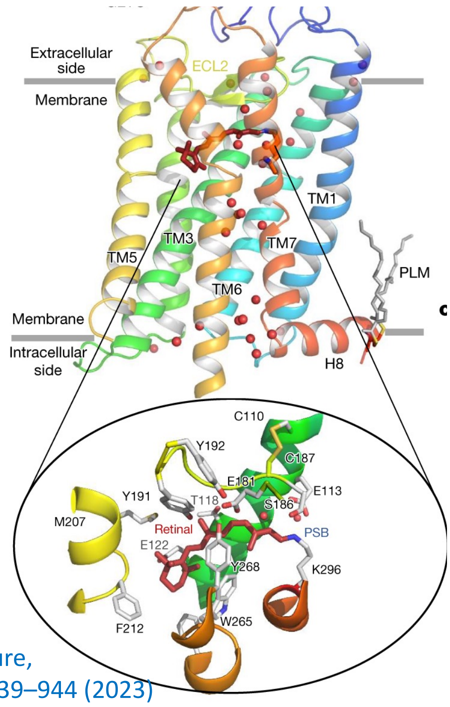
The chemistry of vision

- From lecture 1 - appreciate the importance of molecular shape for biological activity
  - The comparatively small 11-cis-retinal ‘fits well’ and is ‘recognised’ by the much larger protein





Different opsins are optimized for different colours, which gives colour vision.

Fig 1, from Nature, volume 615, p939–944 (2023)

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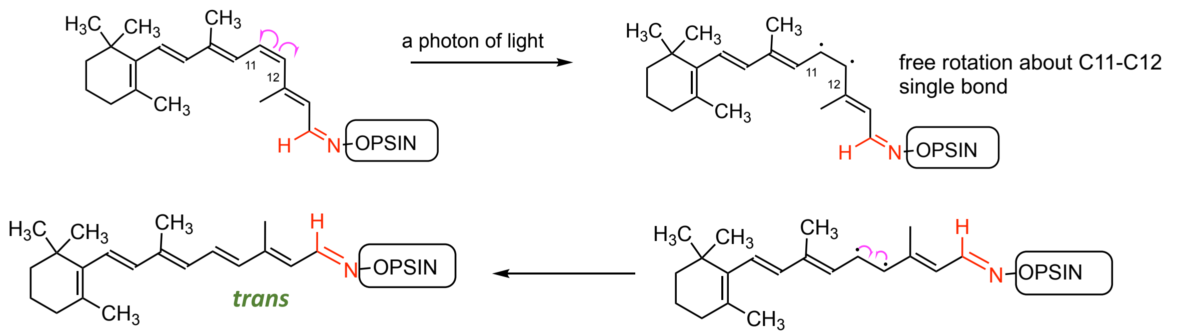
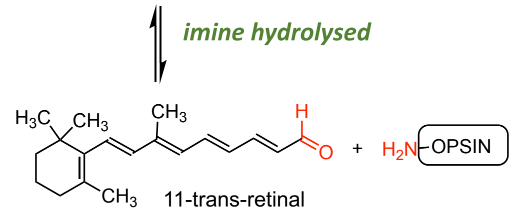
The chemistry of vision

- What happens once the retinal forms an imine with the opsin protein?





- Formation of the **trans** alkene changes the **shape** of the bound retinal, which change the **shape** of the protein, which sends a signal from the eye to the brain.
- 11-trans-retinal is isomerized by enzymes and recycled back into the 11-cis isomer.

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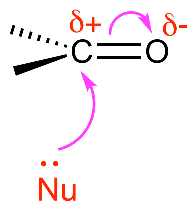
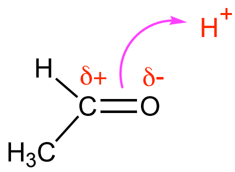
Addition reactions of aldehydes/ketones with a <u>weaker</u> Nu

For weaker nucleophiles (e.g. H-OH, R-OH)

- The nucleophile is too weak to *effectively* attack a C=O directly/in the first step



- The reactivity of the carbonyl carbon can first be increased for better reactivity



So what happens next?

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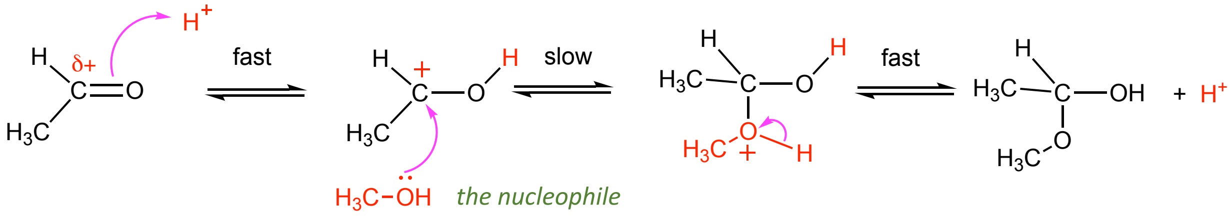
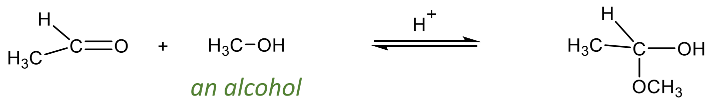
Addition reactions of aldehydes/ketones with a weaker Nu



1. The π-bond reacts with an electrophile, ‘E^+’ is often H^+, i.e. ‘acid catalysed’
2. The nucleophile attacks - rate determining step, slow
3. Deprotonation

We have **added** a nucleophile (R-OH) and electrophile (H^+) across the C=O

acid catalysed



an alcohol
weak nucleophile

a hemiacetal

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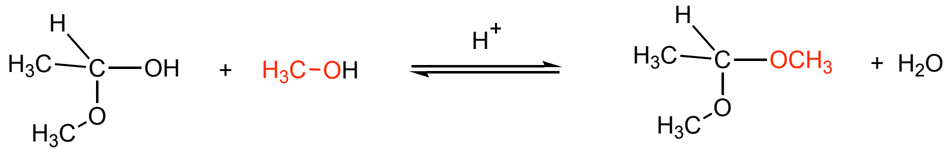
Hemiacetal reacts further to form an acetal



hemiacetal *alcohol* *acetal*

Acetals have two O-alkyl bonds, and no O-H bonds

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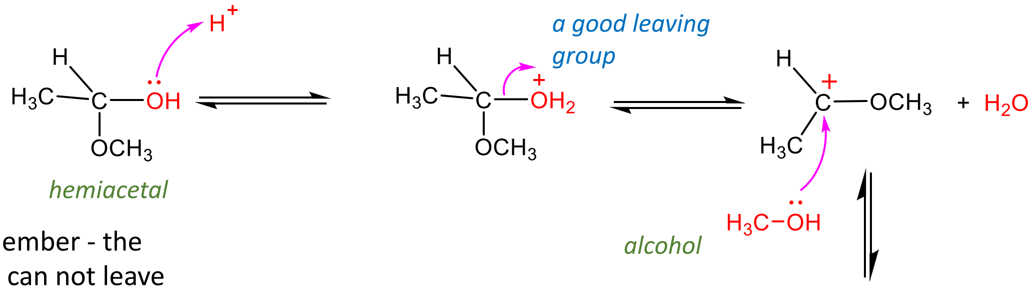
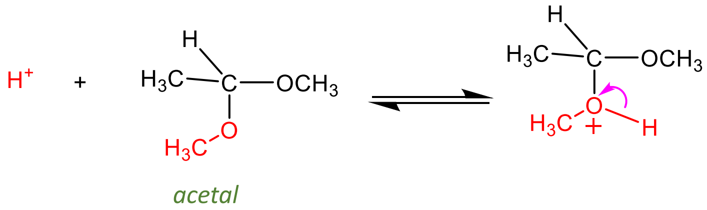
Hemiacetal reacts further to form an acetal



Remember - the 'OH' can not leave directly as a hydroxide ion as hydroxide is a bad leaving group (*module 3, lecture 8*)



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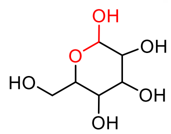
Hemiacetals and acetals dominate the chemistry of carbohydrates

Lectures 3 and 4

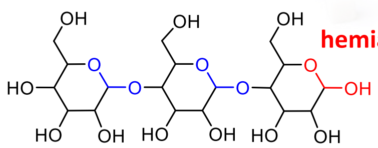
hemiacetal



Carbohydrates
E.g. glucose, galactose

acetals

hemiacetal



complex carbohydrates
Starch, cellulose

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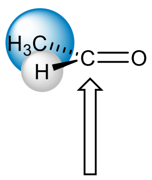
Aldehydes versus ketones

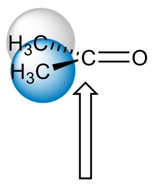
- Both can undergo addition reactions with strong and weak nucleophiles…. but
- **Aldehydes are more reactive than ketones**
- The carbonyl carbon of aldehydes is **more** attractive to nucleophiles for **2 reasons**

Sterics

- Aldehyde is less sterically hindered, one substituent is 'H' and small



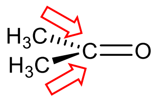
less steric hinderance
easier for Nu to attack

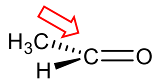


greater steric hinderance
harder for Nu to attack

Electronics

- Electron donating alkyl groups reduce δ^+ on C of C=O





Some concept as Module 3, lecture 7, S_N2 reactions

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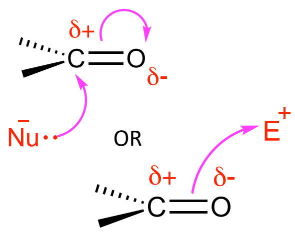
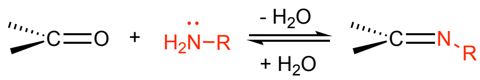
Summary

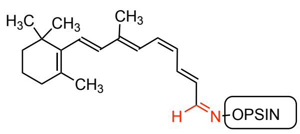


- Aldehydes and ketones most commonly undergo addition reactions
  - The mechanism is different depending on if a **stronger** (e.g. R-NH_2) or **weaker** (e.g. R-OH) nucleophile is present.

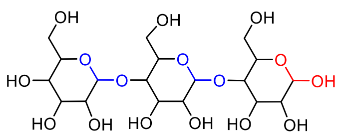
- An aldehyde/ketone + amine undergo an addition reaction and then a dehydration reaction to form an **imine**.



- Imines are widely used in the body as reversible, covalent bonds, e.g. in the chemistry of vision.



- An aldehyde/ketone + alcohol undergo an addition reaction to form a **hemiacetal**, which can then react with another equivalent of alcohol to form a **acetal**.



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* Homework *

Sample Exercise 28.4, page 1306

Page 1330, exercise 28.45 (imines, some harder examples), 28.46

Page 1368, exercise 29.48

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