PHARM.D • YEAR 1

Pharmaceutical Organic Chemistry

CHAPTER 11

Nucleophilic Addition Reaction

PPT CHAPTER COVER



CARBONYL POLARITY AND NUCLEOPHILIC ADDITION

DEFINITION

- Nucleophilic addition is a reaction in which a nucleophile adds to an electron-deficient carbon atom, typically the carbonyl carbon (C=O).
- Most common in aldehydes and ketones due to their polar carbonyl group.

WHY IT HAPPENS

- Oxygen is more electronegative than carbon.
- It pulls electron density toward itself, making the carbonyl carbon partially positive (δ+).
- A nucleophile (e^--rich; e.g., OH^-, CN^-, R^-, H_2O) is attracted to this δ+ center.

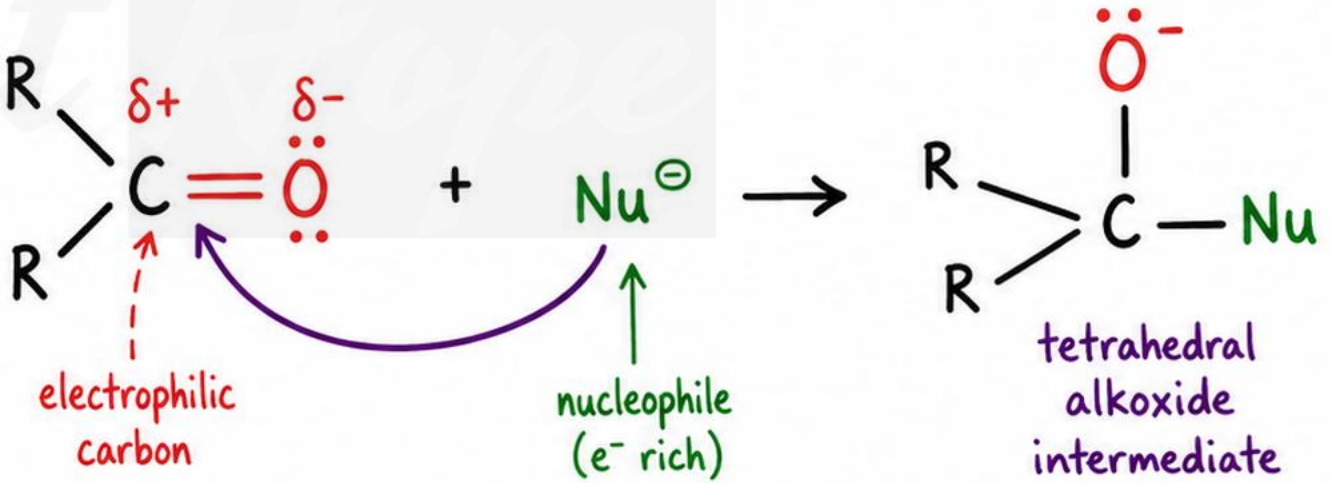
KEY TAKEAWAY

Polar C=O → C(δ+) attracts Nu^- → π bond breaks → tetrahedral alkoxide intermediate forms.

STEP-BY-STEP MECHANISM

1 NUCLEOPHILIC ATTACK ON THE CARBONYL CARBON

- A nucleophile (electron-rich species) attacks the electrophilic carbonyl carbon.
- This breaks the π bond of the carbonyl, forming a tetrahedral alkoxide intermediate.



$$R_2C{=}O + Nu^{\ominus} \longrightarrow R_2C(O^-)(Nu)$$

BASE-CATALYSED NUCLEOPHILIC ADDITION

DEFINITION:

- A nucleophilic addition reaction is a type of reaction in which a nucleophile adds to an electron-deficient carbon atom, typically the carbonyl carbon (C=O) of aldehydes or ketones.

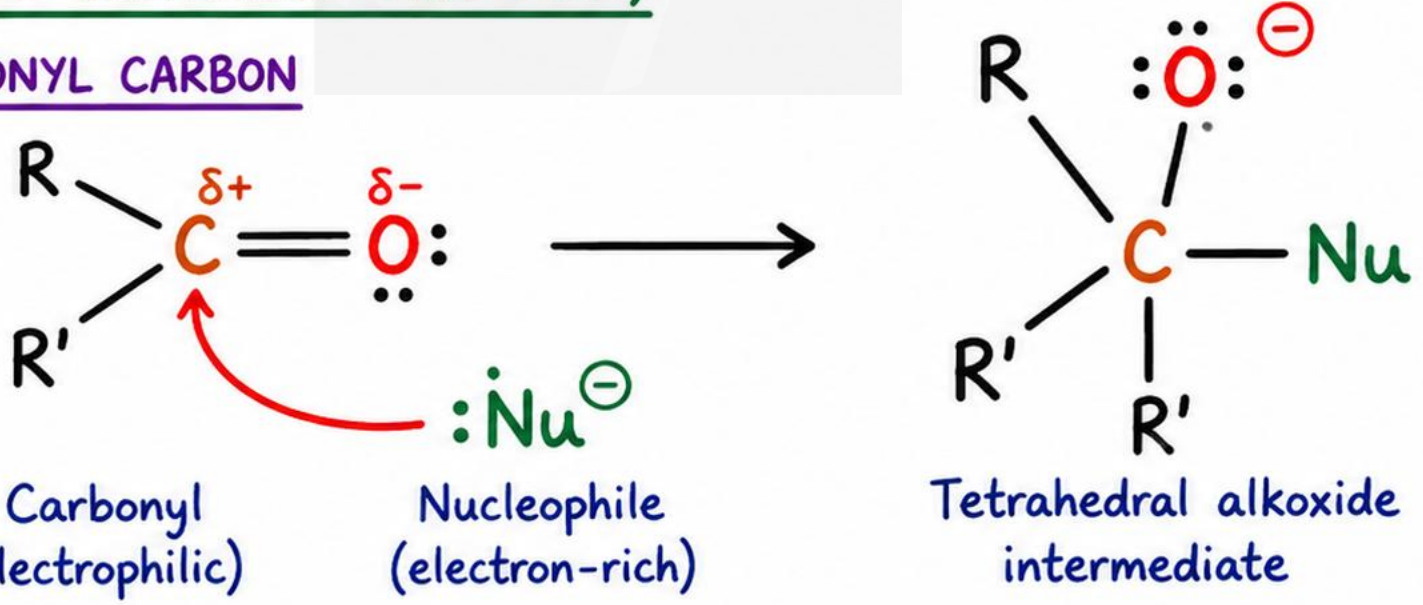
WHY IT HAPPENS:

- In a carbonyl group, oxygen is more electronegative and pulls electron density toward itself, making the carbonyl carbon partially positive (δ+).
- Electron-rich nucleophiles (e.g., OH^-, CN^-, R^-, H_2O) are attracted to this δ+ carbon.

STEP-BY-STEP MECHANISM (BASE-CATALYSED ADDITION)

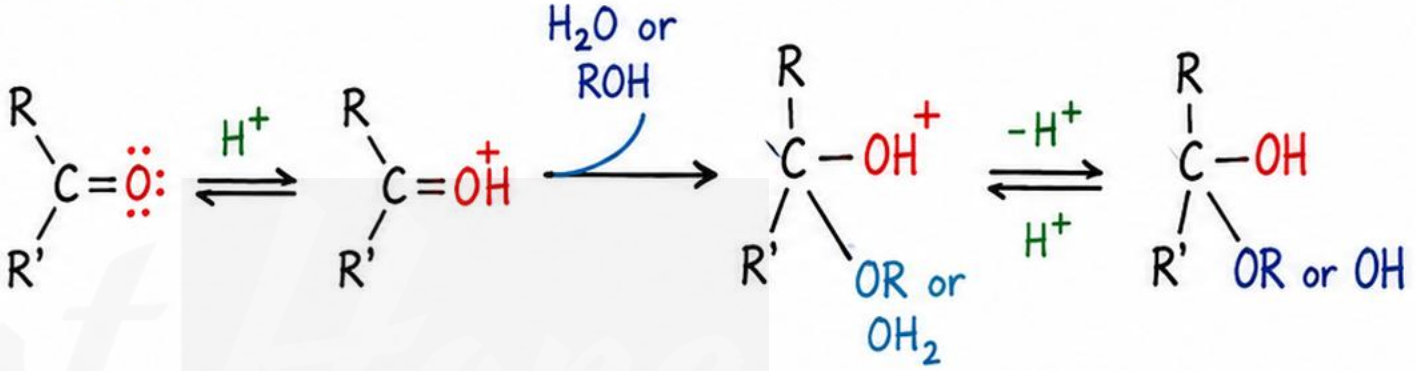
① NUCLEOPHILIC ATTACK ON THE CARBONYL CARBON

- A nucleophile (Nu^-) attacks the electrophilic carbonyl carbon.
- The π bond of the C=O breaks, and the electrons move to oxygen.
- A tetrahedral alkoxide intermediate is formed.

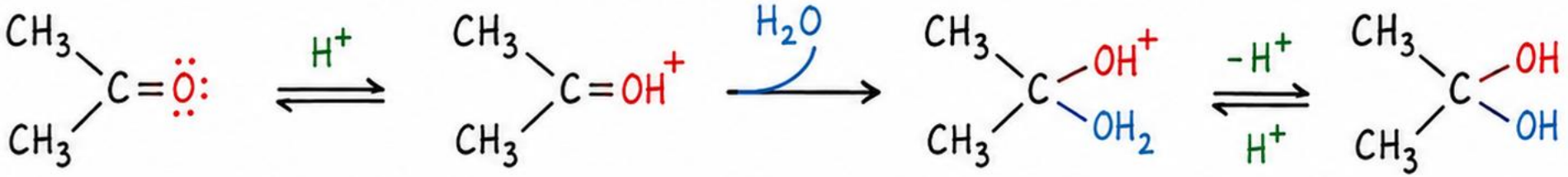


ACID-CATALYSED ADDITION OF WEAK NUCLEOPHILES

- Aldehydes and ketones react with weak nucleophiles such as water (H_2O) or alcohols (ROH) in the presence of a strong acid catalyst.
- Acid protonates the carbonyl oxygen, increasing the electrophilicity of the carbonyl carbon.
- H_2O or ROH attacks the carbonyl carbon to form a tetrahedral oxonium intermediate.
- Deprotonation gives the neutral addition product and regenerates H^+.



EXAMPLE: acetone + H_2O ⇌ acetone hydrate (gem-diol), acid catalysed

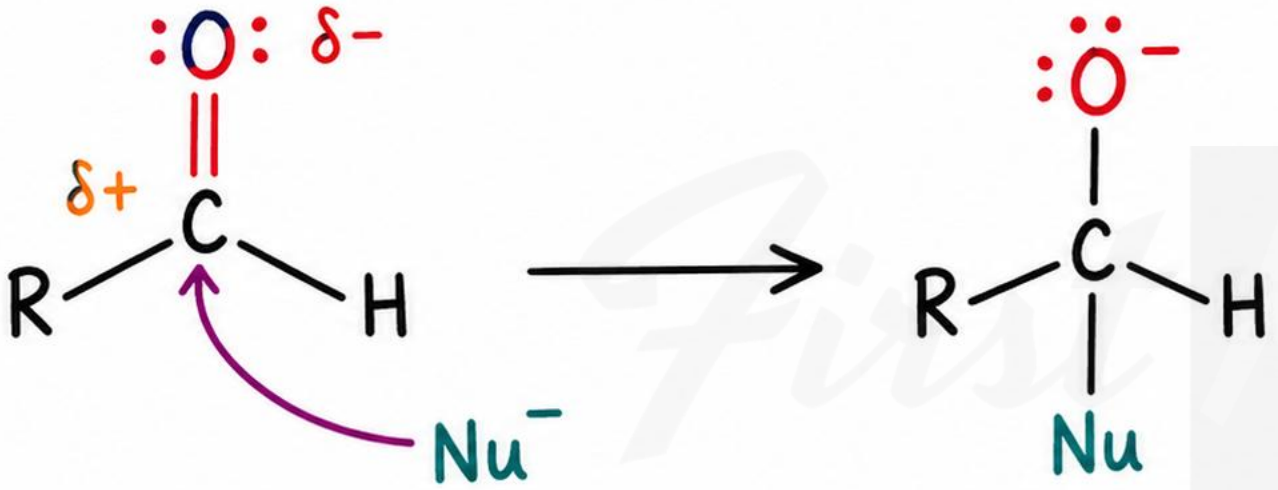


acetone hydrate (gem-diol)
$(CH_3)_2C(OH)_2$

★ NOTE: With an alcohol (ROH), the initial addition gives a hemiacetal. Further acid-catalysed reaction with ROH can convert the hemiacetal into an acetal.

WHY ALDEHYDES ARE USUALLY MORE REACTIVE THAN KETONES

NUCLEOPHILIC ADDITION TO CARBONYL



ALDEHYDE
(LESS HINDERED)

TETRAHEDRAL
ALKOXIDE INTERMEDIATE

- Aldehydes are less sterically hindered than ketones because they have one alkyl group and one hydrogen.
- Less steric hindrance allows the nucleophile easier approach to the carbonyl carbon.
- Aldehydes have less electron-donating alkyl substitution (only one alkyl), so the carbonyl carbon is more δ^+ (more electrophilic).
- Therefore, nucleophilic addition occurs faster and more readily with aldehydes than with ketones.

TAKEAWAY: Aldehydes are more reactive toward nucleophilic addition because they are less sterically hindered and have less alkyl electron donation.

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