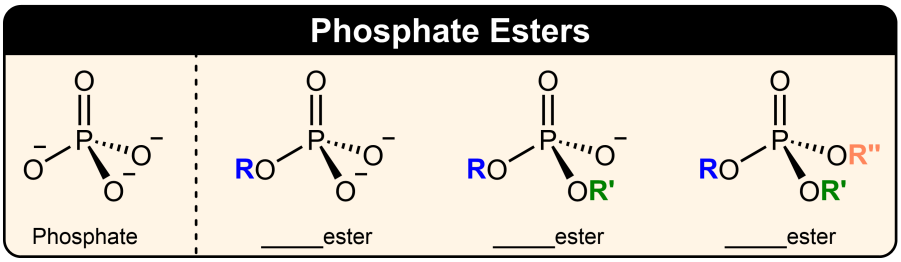
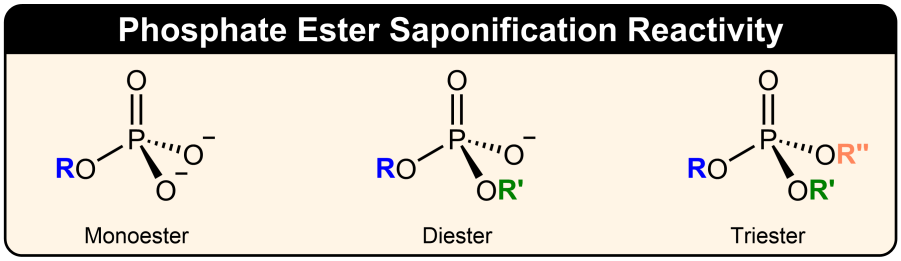
CONCEPT: HYDROLYSIS OF PHOSPHATE ESTERS

Intro to Phosphate Esters

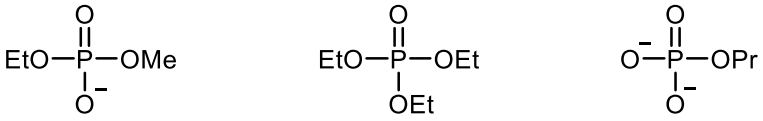
- Depending on the number of alkyl groups, phosphate esters can be of ____ types.



- The reactivity of phosphate esters towards hydrolysis ___ as the charge on the molecule ___.



EXAMPLE: Arrange the following compounds from least reactive to most reactive in a saponification reaction.



I II III

a) I < II < III

b) III < II < I

c) II < I < III

d) III < I < II

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Phosphate Triester Saponification

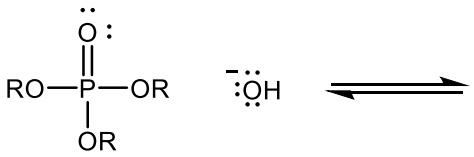
- Basic hydrolysis of phosphate triesters can proceed through _____ possible mechanisms.
  1. **P–O Bond Cleavage:** nucleophilic acyl substitution at the P atom.
  2. **C–O Bond Cleavage:** S_N2 substitution at the C atom.

1 P–O Bond Cleavage

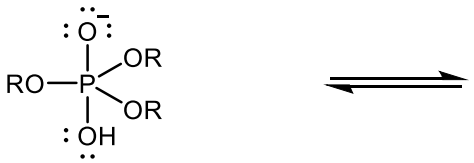
- Similar to the attack on the carbonyl C, a nucleophile attacks the P atom in the P–O bond cleavage mechanism.

Step 1	Step 2	Step 3
Nucleophilic Attack	Leaving Group	Proton Transfer

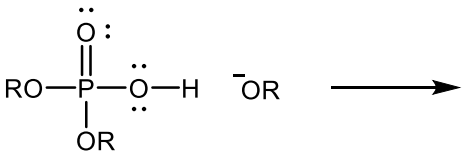
STEP 1: Hydroxide ion attacks the ___ atom, forming a trigonal bipyramidal intermediate (_____-coordinated).



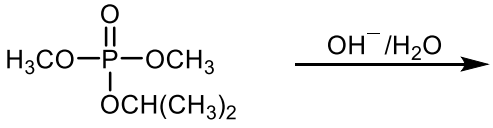
STEP 2: The intermediate collapses and an alkoxide is kicked out.



STEP 3: The alkoxide anion deprotonates the protonated dialkyl phosphate.



EXAMPLE: What products are formed when the following ester undergoes complete saponification:



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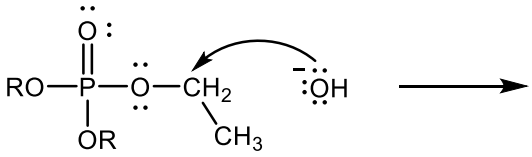
(2) C–O Bond Cleavage

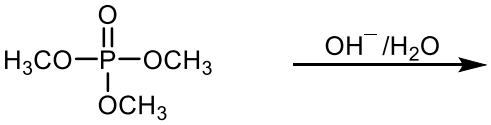
- The OH^- ion can attack the ___-carbon of an alkyl group to give products via the S_N2 mechanism.
  - □ A dialkyl phosphate and an _____ are formed in a single step.

Step 1
Nucleophilic Attack



- Phosphate esters with _____, ___ alkyl groups prefer the C–O bond cleavage mechanism.

EXAMPLE: Write a mechanism for the basic hydrolysis of trimethyl phosphate. (For one alkyl group only.)



PRACTICE: Draw the mechanism for the hydrolysis of the benzyl group in benzyl dimethyl phosphate.