Lec6 5th stage

Organic Pharmaceutical Chemistry IV

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Macrmolecular prodrugs(polymeric prodrugs):- is a conjugation of a drug with a polymer.

The main advantages of polymeric prodrugs include:-

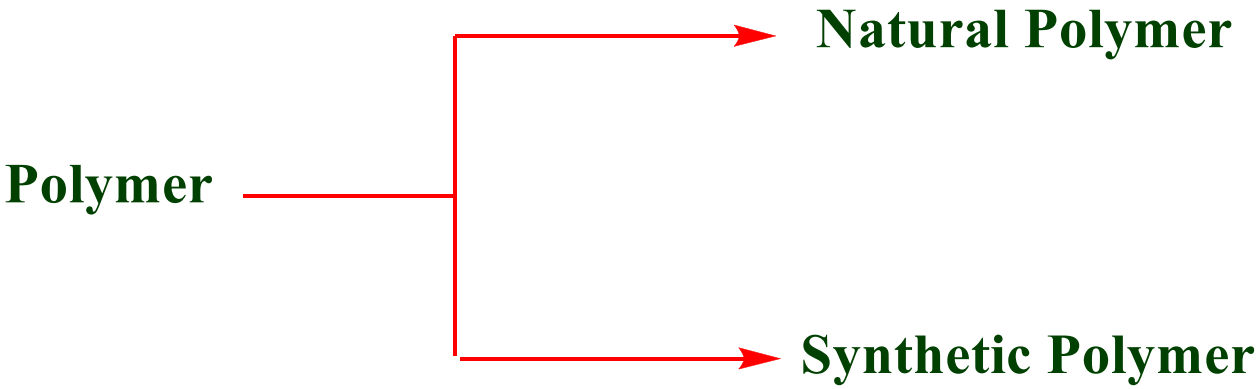
1. An increase in water solubility of low soluble or insoluble drugs, and therefore, enhancement of drug bioavailability
2. Protection of drug from deactivation and preservation of its activity during circulation, transport to targeted organ or tissue.
3. Increase stability.
4. Delayed action (sustained release) large duration of action.
5. An improvement in pharmacokinetics.
6. A reduction in antigenic activity of the drug leading to a less pronounced immunological body response.
7. The ability to provide passive or active targeting of the drug specifically to the site of its action.

Properties of polymer (Macromolecule)

1. Water soluble
2. Safe (non toxic),non immunogenic, non carcinogenic, not induce allergic reaction.
3. Biocompatible with blood components or other component in the body.
4. Don’t form complication reactions with blood component.
5. Should be elimination from the body within reasonable time (not accumulative).
6. Biodegradable.
7. Molecular weight not exceed 7500 unit.

Along with the polymer, the physico-chemical properties of the drug or Biomolecule to be conjugated are equally important. The following properties of the drug molecules make it suitable as an ideal candidate to form the polymeric conjugate:

1. Lower aqueous solubility.
2. Instability at varied physiological pHs.
3. Higher systemic toxicity.
4. Reduced cellular entry.



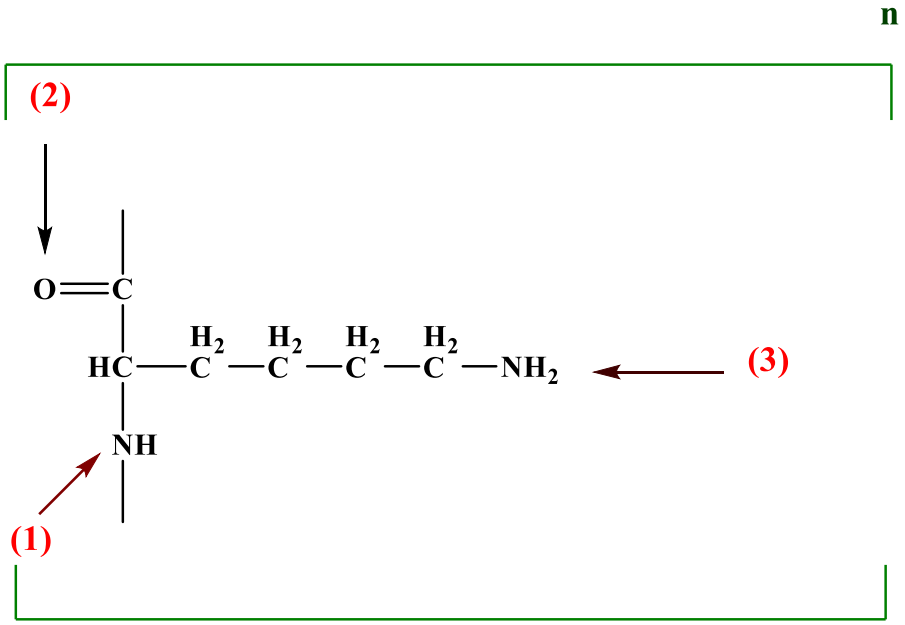
Natural polymers

•Proteins (enzyme, antibody, Immnuglobin G" IgG") molecular weight 7000-7500.

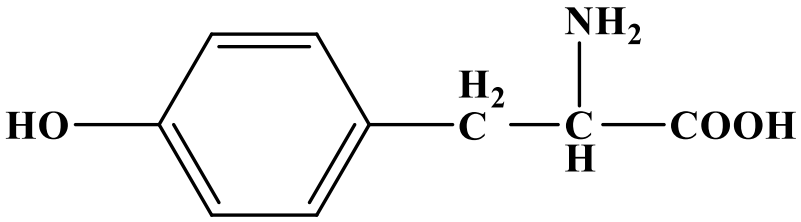
•Poly amino acids ,such as poly lysine, poly glutamine, poly aspartic acic.....etc. Molecular weight 7000-7500.Ingeneral poly (L- amino acids) are biocompatible and biodegradable.

•Poly lysine

So lysine has three functional groups, and act as homo type Through {NH_2 (1) , NH_2 (3) },while act as hetero type Through {NH_2 (1), C=O (2)}.One molecule of lysine contain three functional group, while 10 molecule of lysine contain 11 functional groups of NH_2 .

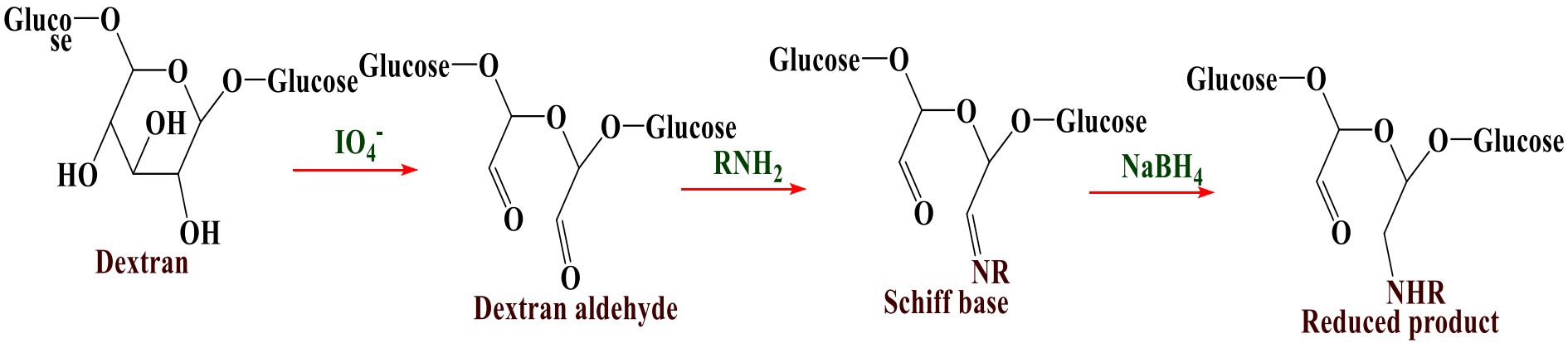


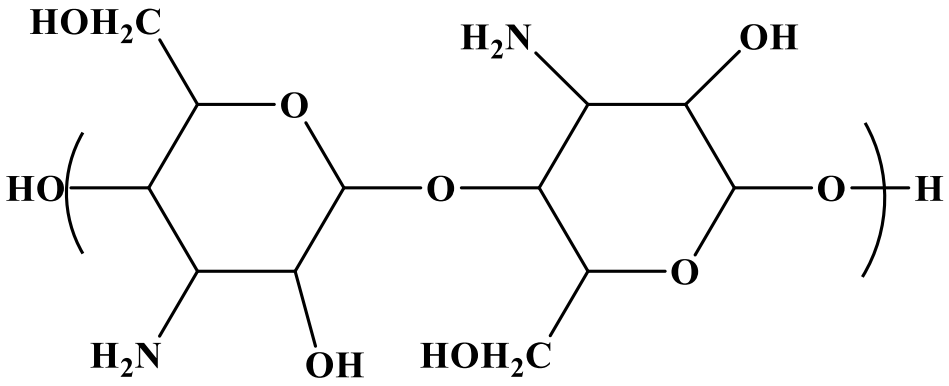
Note:- Tyrosine, serine, cysteine , glutamine all are amino acid that are multifunctional (contain three functional groups)



Tyrosine
more desirable molecule, because its natural

Carbohydrats:_ contain OH group like dextran [1](multifunctional • OH group), and may also contain NH group like Glucosamine {Chitosan; (poly(glucos amine)}.

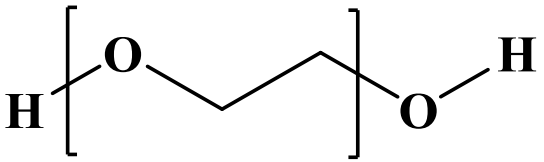




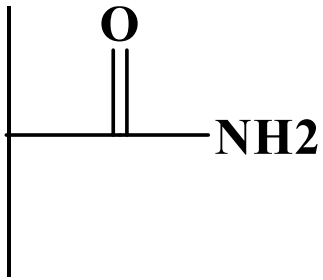
Chitosan

Synthetic polymers

1) Poly (ethylen glycol)



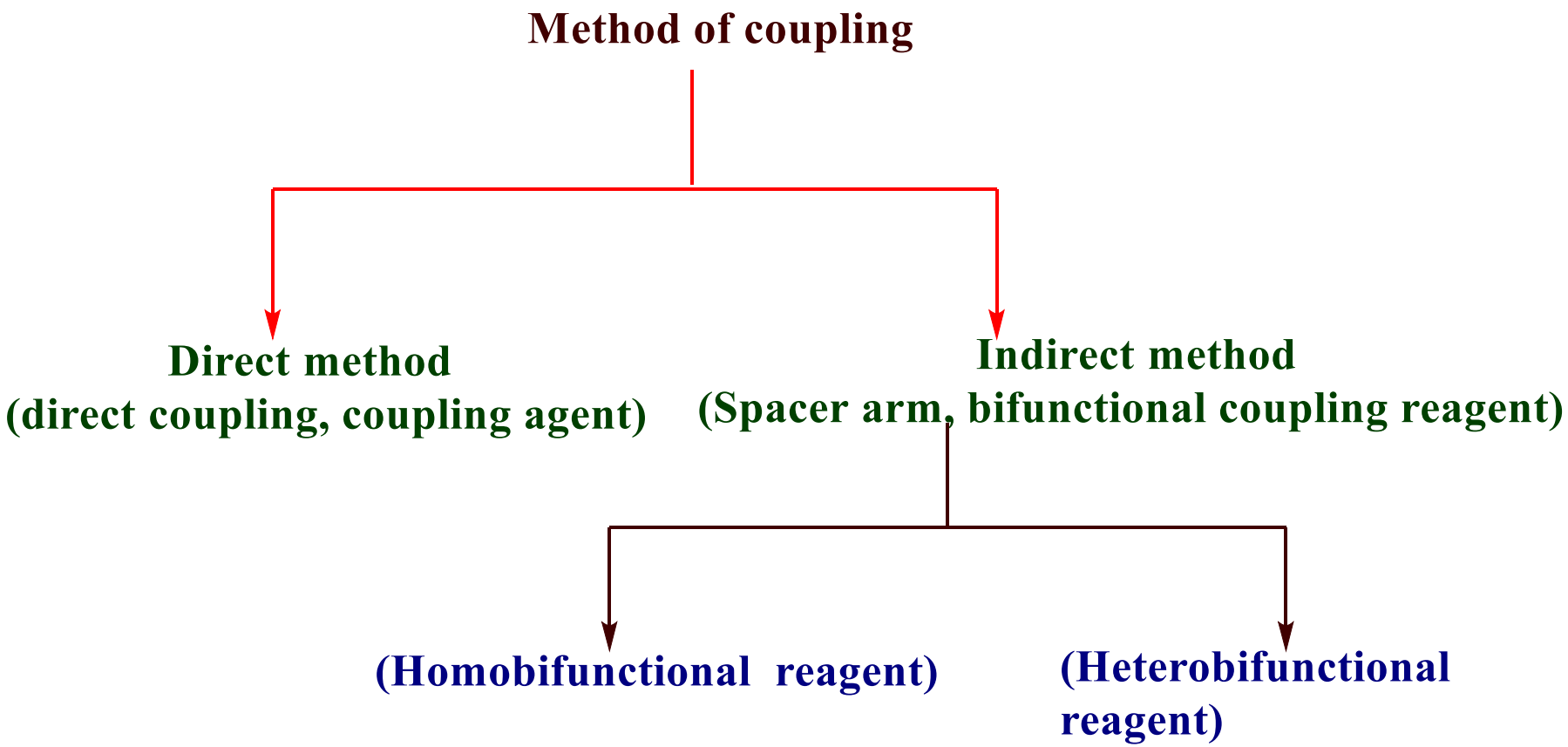
2) Poly acryl amide



Modification of a polymer to form a conjugate with a drug molecules depend on two factors:-

1- Reactive functional groups present in the polymer

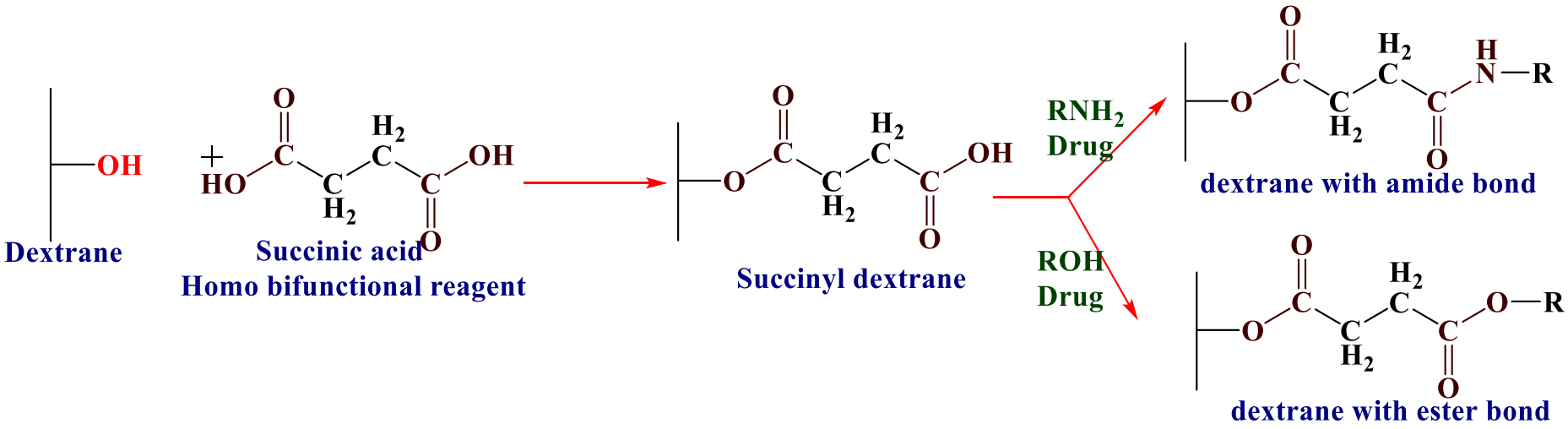
2- Functional groups present on the drug.



1- Spacer arm (bifunctional coupling reagent)

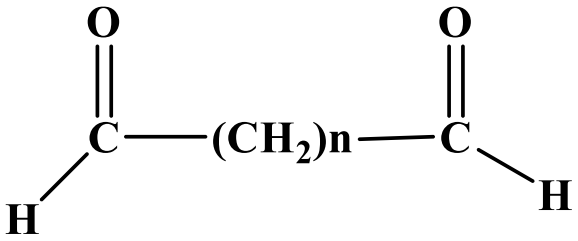
a- Homobifuctional coupling reagent X−X

1- Succinic acid with dextrane



Succinic acid with PEG (Homework)

2-



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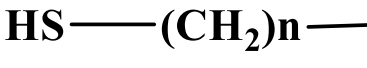
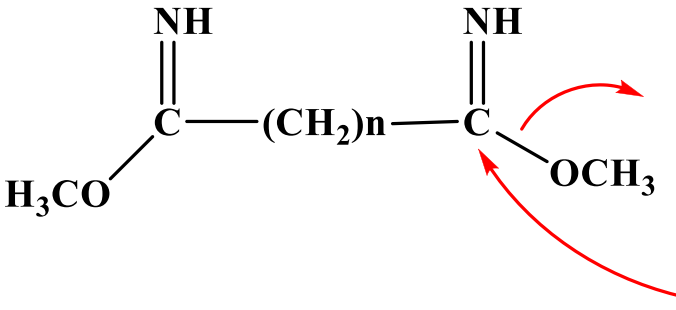
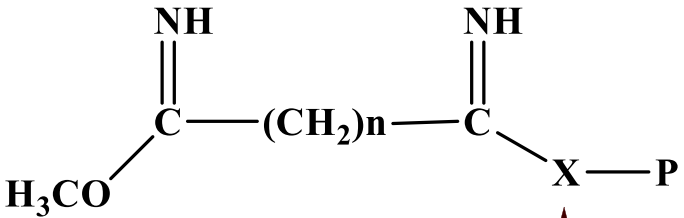
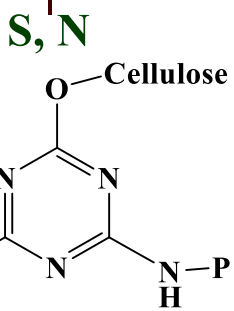
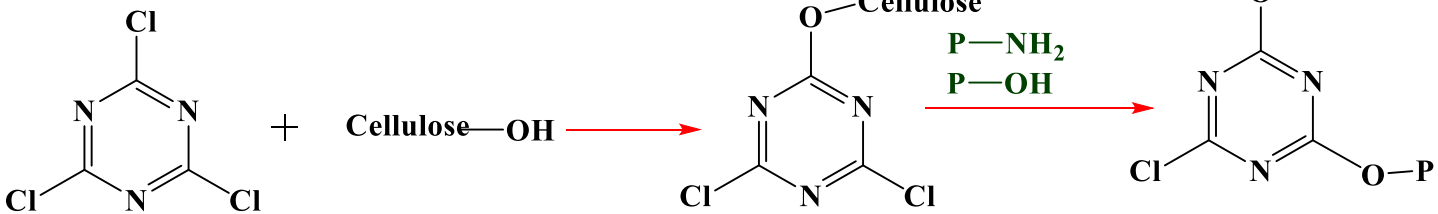








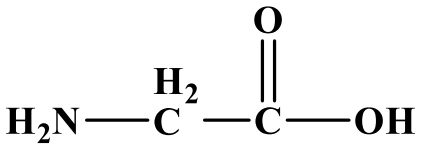


2,4,6-trichloro-1,3,5-triazine

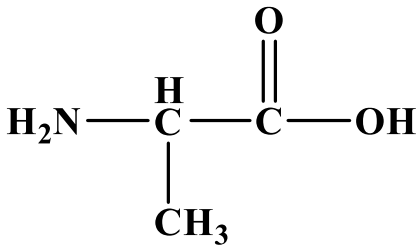
Heterobifunctional coupling reagents X ∿∿ Y

•**Amino acid spacers** such as glycine, alanine, and small peptides are preferred due to their chemical versatility for covalent conjugation and biodegradability.

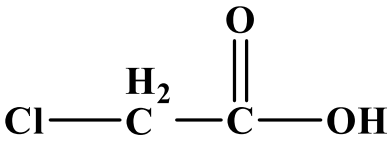
a- Glycine (Gly)



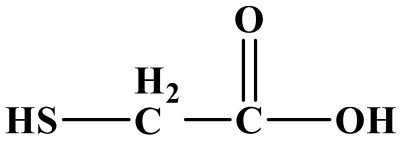
b- Alanine



2- Chloroacetic acid

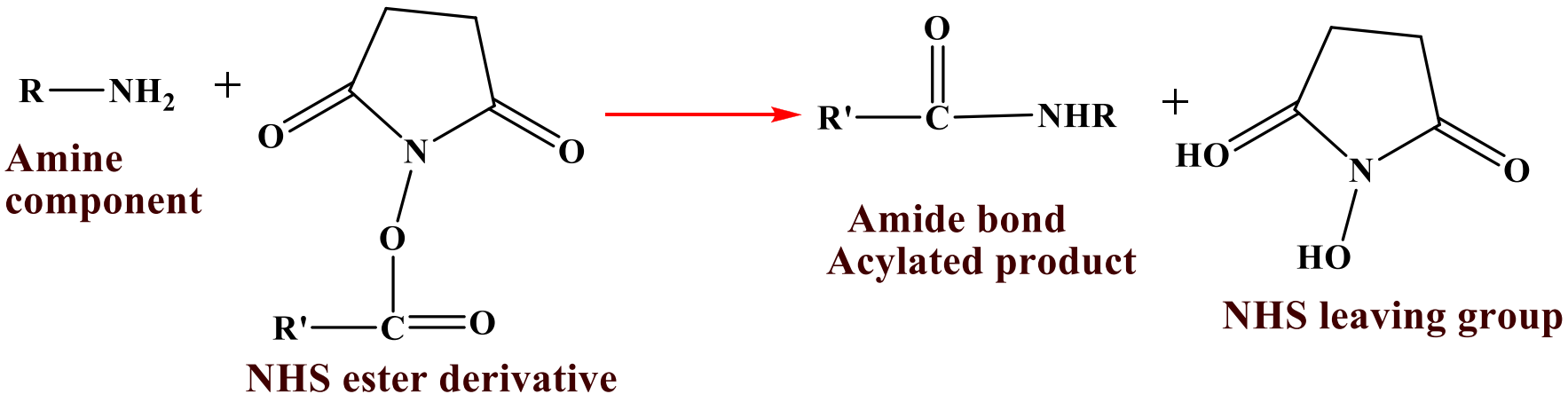


3- Mercapto acetic acid

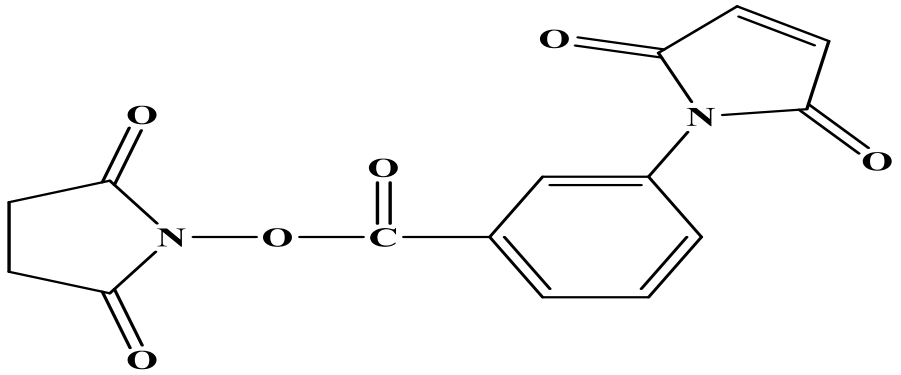


N-hydroxysuccinimidyl (NHS) ester and coupling methods•

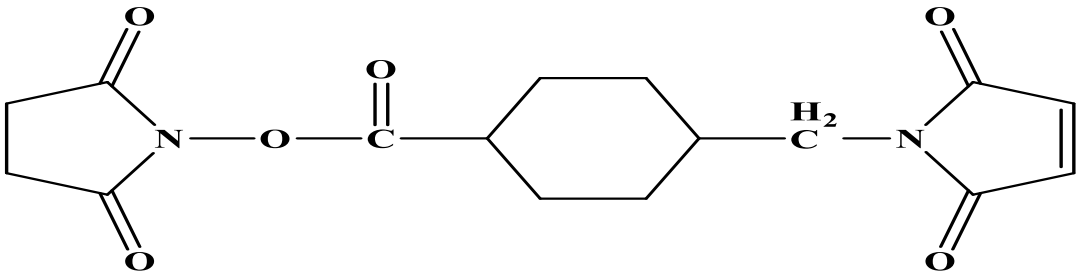
NHS is widely used as an acylating agent and is preferred for conjugation with amine terminal compounds. NHS ester compounds react with nucleophiles to release the NHS leaving group and form an acylated product.



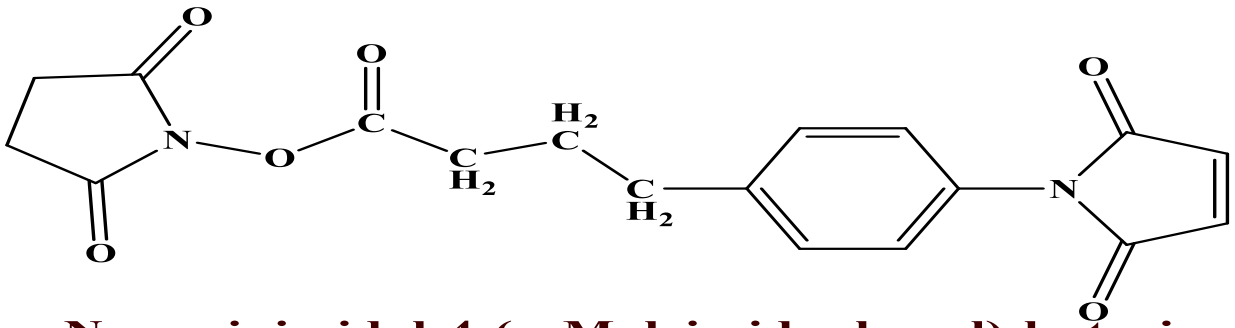
Examples of NHS



N-maleimidobenzoyl-N-hydroxysuccinimide
(MBS)

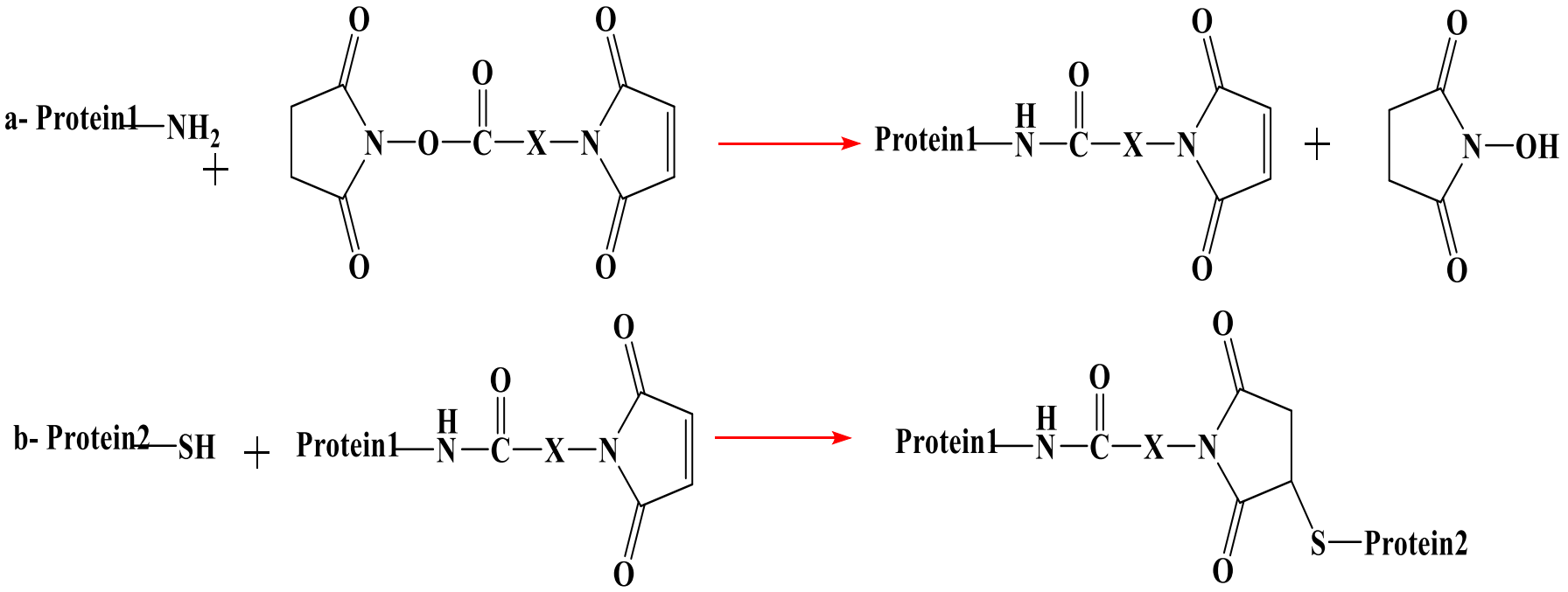


N-succinimidyl-4-(N-Maleimidomethyl)-cyclohexane-1-carboxylate
(SMCC)



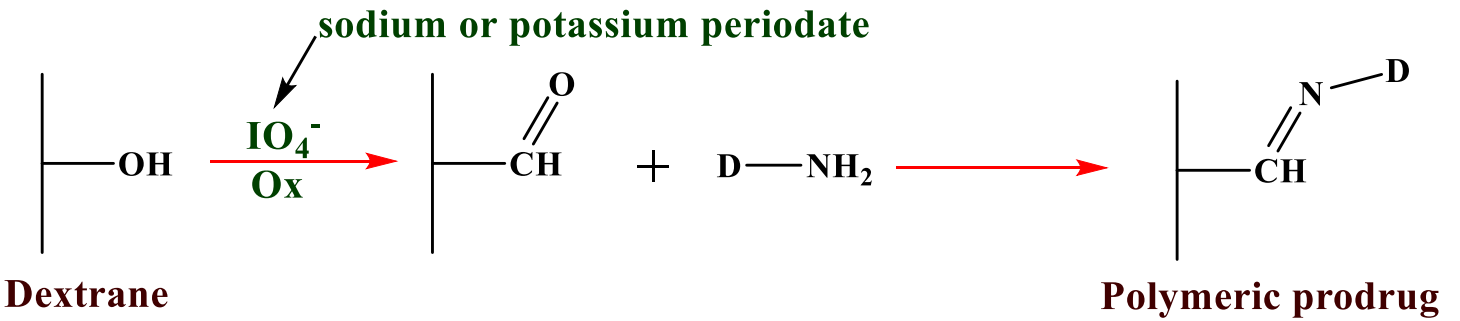
N-succinimidyl-4-(p-Maleimidophenyl)-butyric acid
(SMPB)

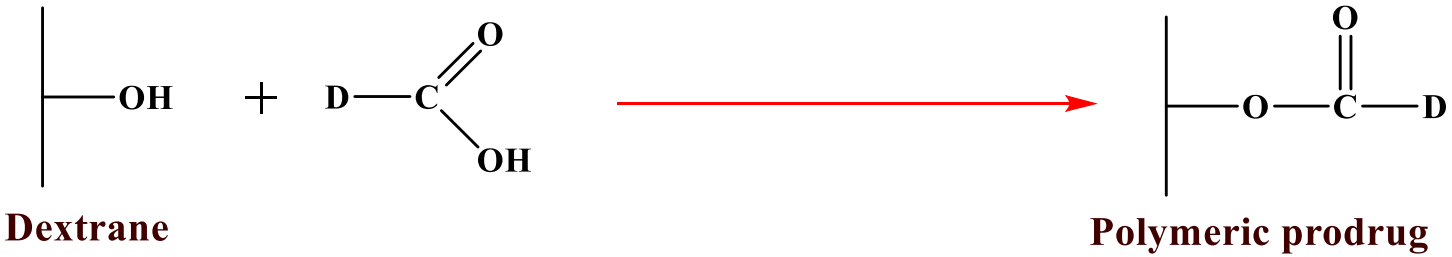
In most of the bioconjugates, the NHS ester anhydride is reacted with primary $-NH_2$ of the peptide at slightly higher pH (7.5) to form an amide bond which links the maleimide group to the protein and releases NHS. Thereafter, the maleimide group can be further reacted with the thiol containing moieties or proteins to form a thioether bond in the presence of a slightly acidic or neutral pH.



Scheme for protein coupling using N-hydroxysuccinimide ester/maleimide heterobifunctional agents. X represents the spacer groups of varying chain lengths

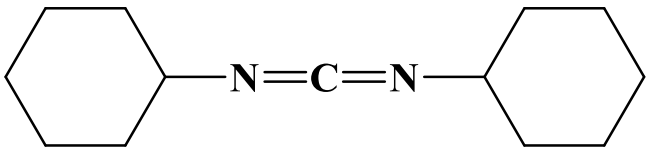
Direct coupling (no spacer) :-



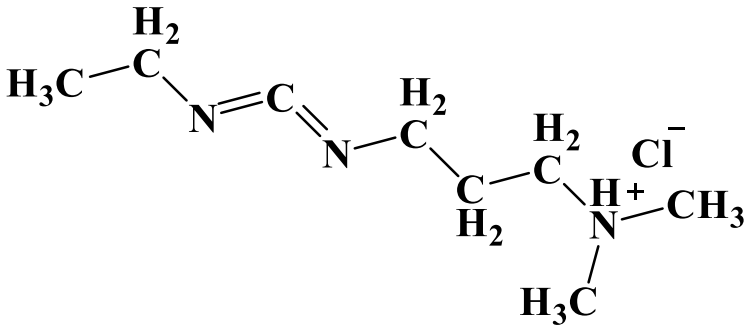


***Zero lengths cross- linkers*:- Coupling agents mediate the conjugation of the two molecules by forming a bond with no additional spacer atom. Therefore, one atom of the molecule is covalently linked to an atom of the second molecule with no additional linker or spacer needed.**

a) Carbodiimides

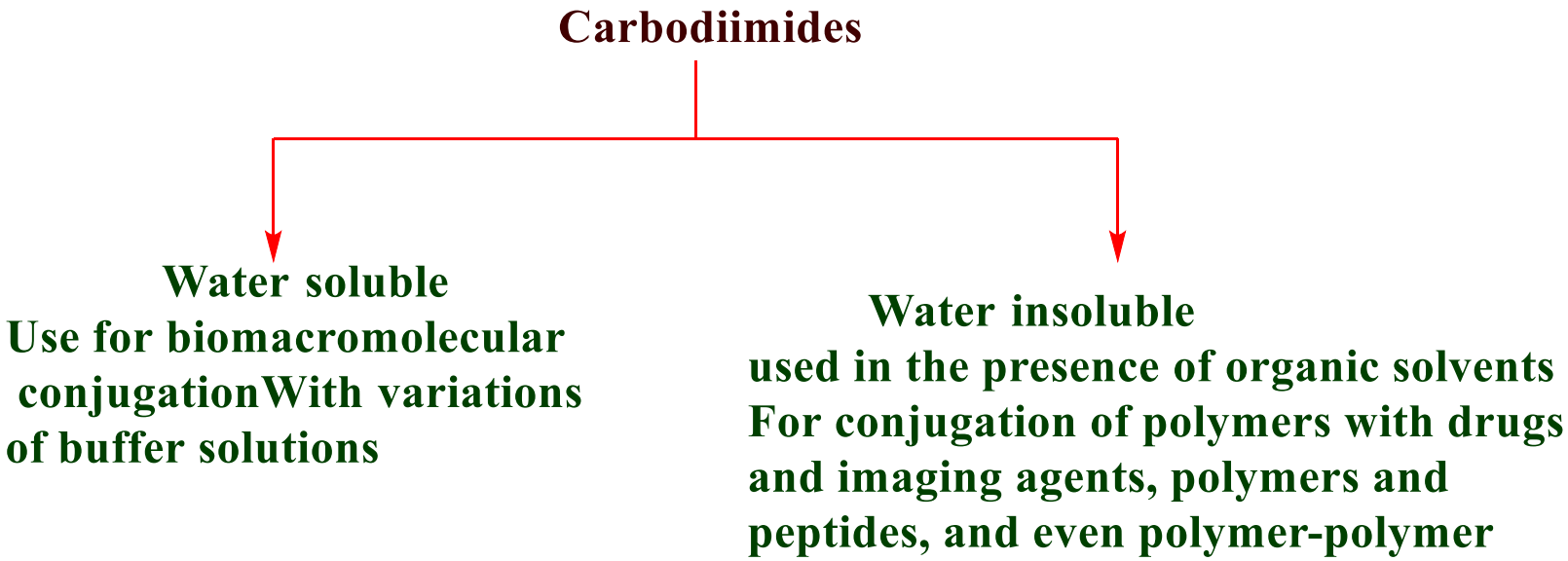


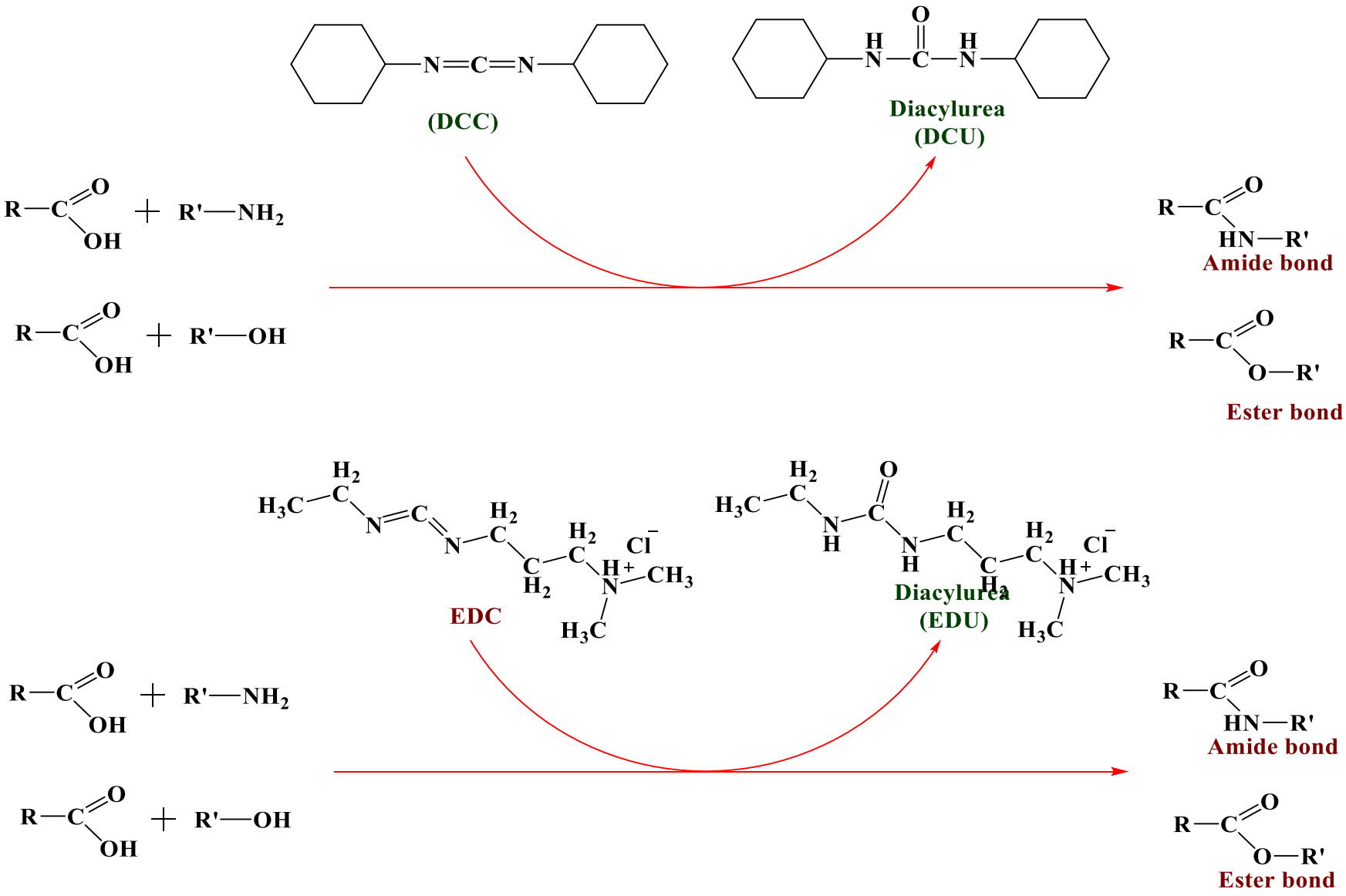
Dicyclohexyl carbodiimide (DCC)
soluble in organic solvent



1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)
Soluble in water

They are most commonly used as coupling reagents to obtain amide linkage between a carboxylate and an amine or phosphoramidate linkage between a phosphate and an amine. They are unique due to their efficiency and versatility to form a conjugate between two polymers, between protein molecules, between a peptide and a drug molecule, or between a peptide and a protein plus any combination of these small molecules.





Mechanism of action of DCC and EDC→ Homework

Carbodiimide activates the phosphate to an intermediate phosphate ester, identical to its reaction with carboxylates. Further, in the presence of an amine on a polymer containing – NH_2 terminal groups, carbodiimide can be conjugated to form a stable phosphoramidate bond.