Lec 7 5th stage

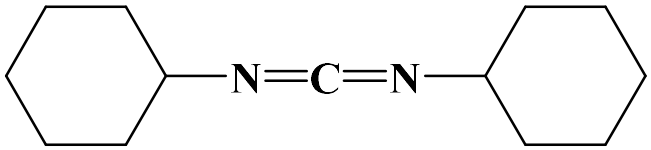
Organic Pharmaceutical Chemistry IV

2018-2019

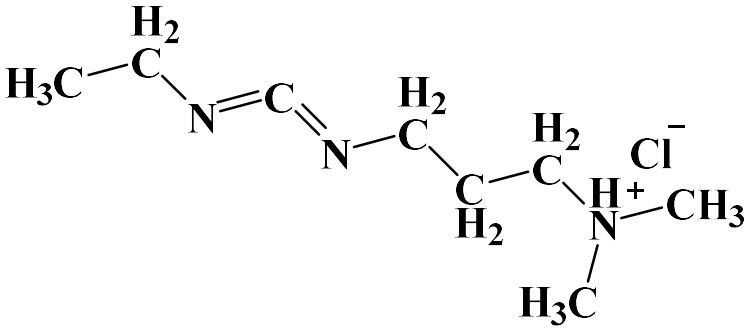
Assist prof. Dr.Rita Sabah Elias
College of Pharmacy, university of Basrah

***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

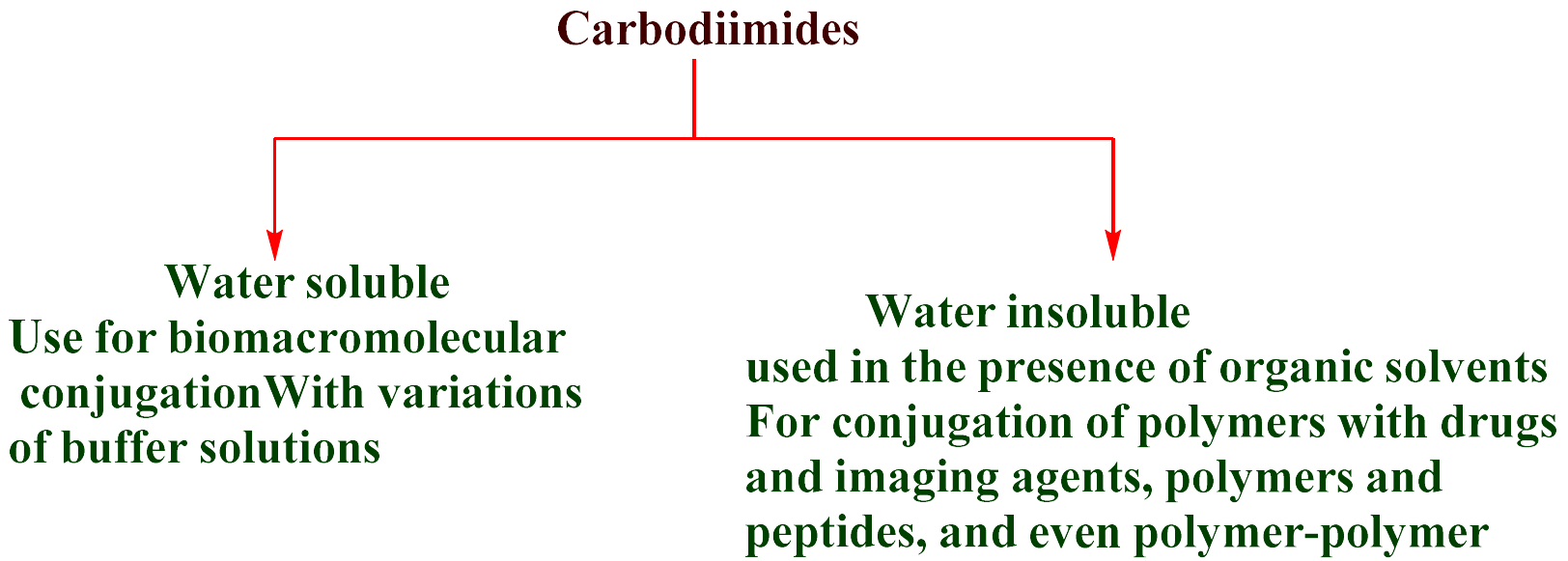


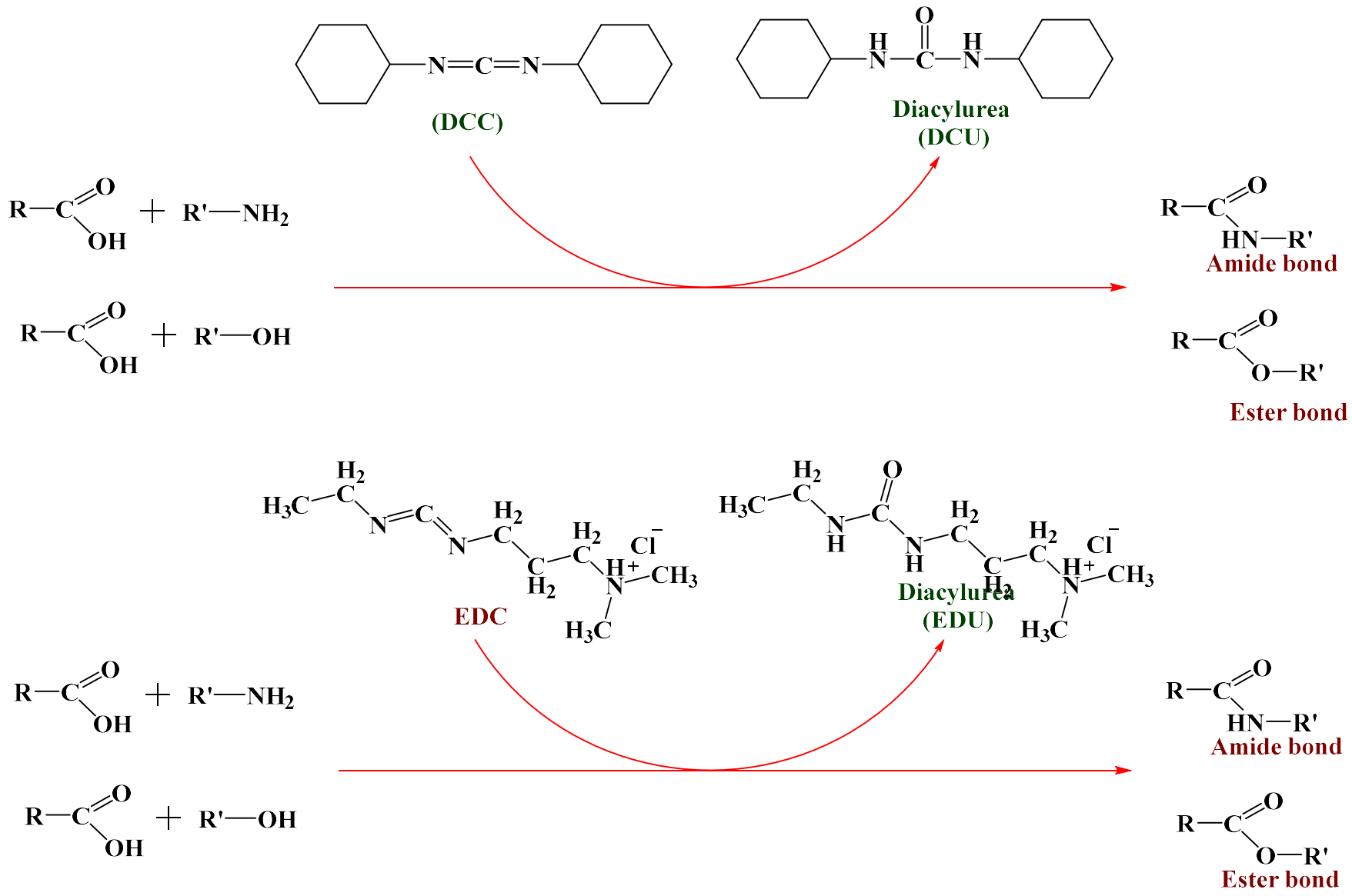
Dicyclohexyl carbodiimide (DCC)
soluble in organic solvent



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

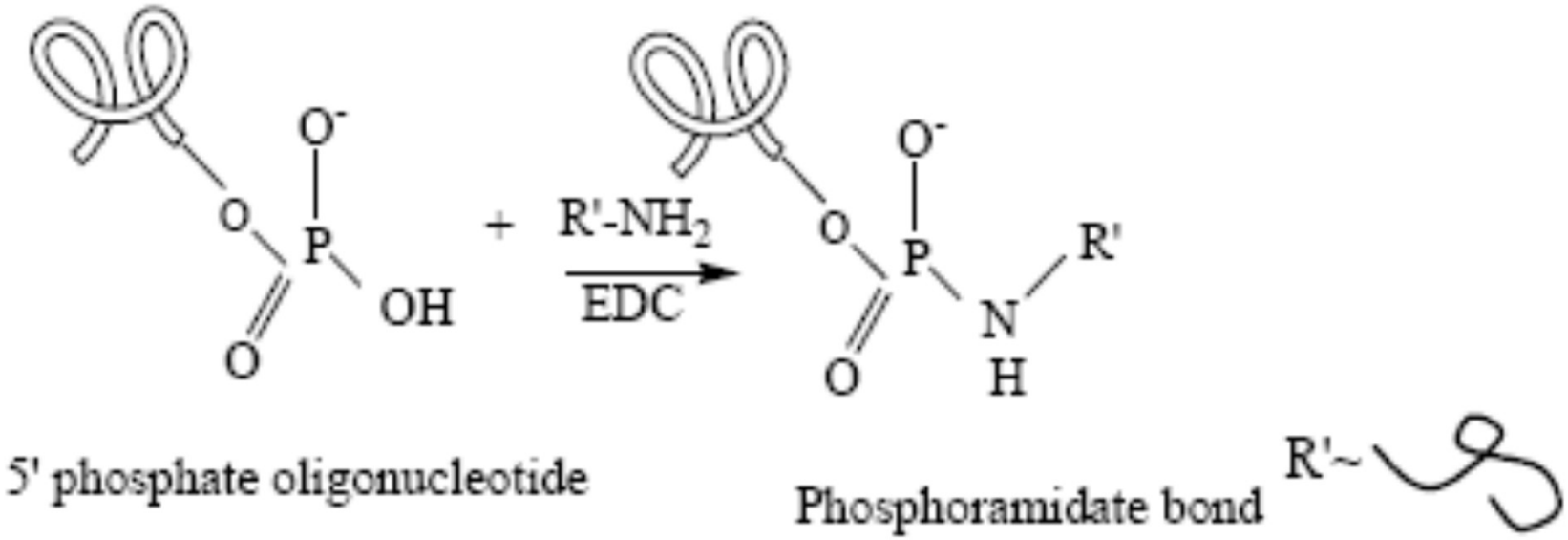
They are most commonly used as coupling reagents to obtain amide linkage between a carboxylate and an amine or phosphoramidate linkage between a phosphate and an amine. They are unique due to their efficiency and versatility to form a conjugate between two polymers, between protein molecules, between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





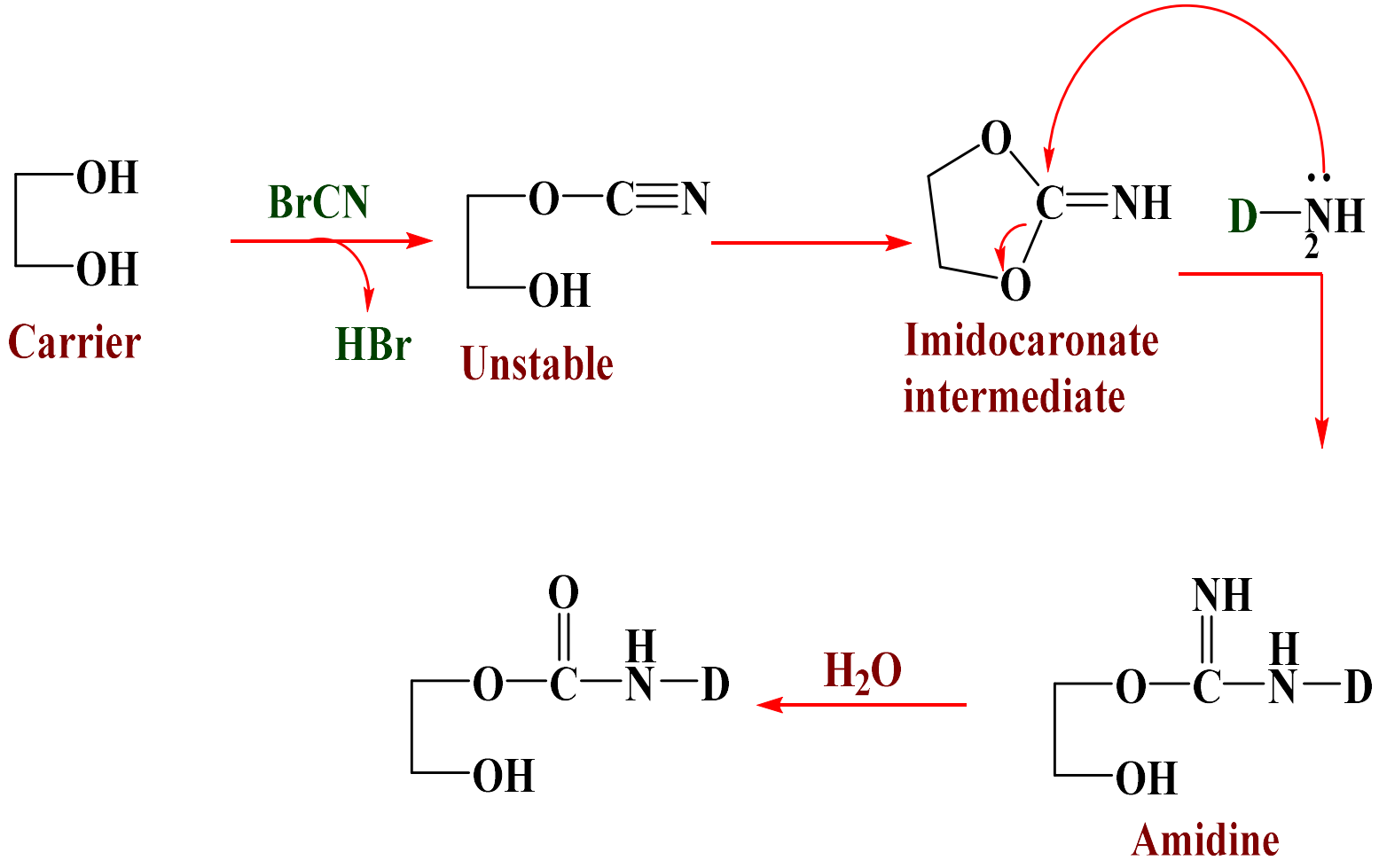
Mechanism of action of DCC and EDC→ Homework

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.

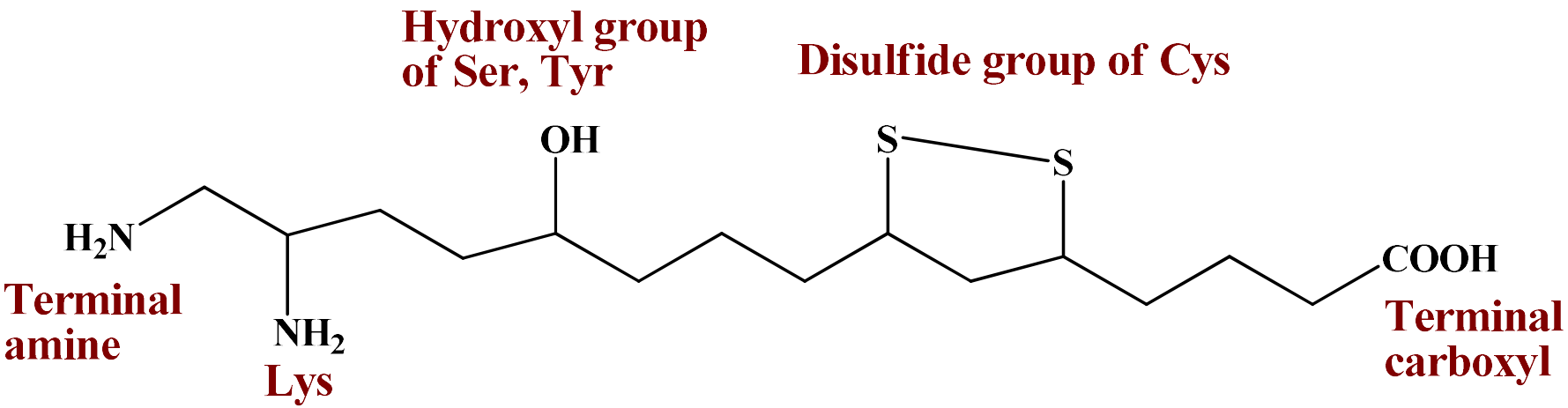


Mechanism of DCC and EDC→ Homework

Cyanogens bromide (BrCN) → (activation to OH group)

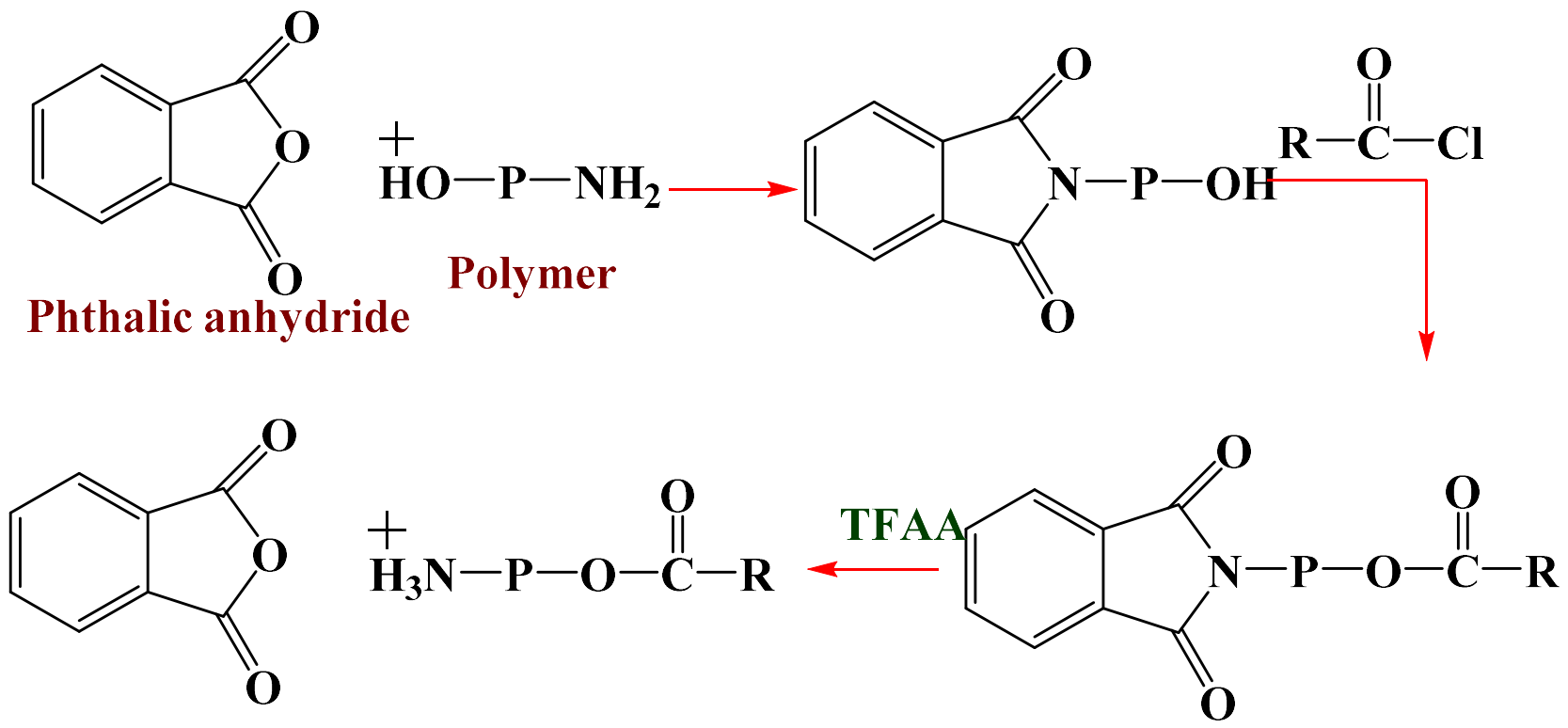


Chemistry of proteins

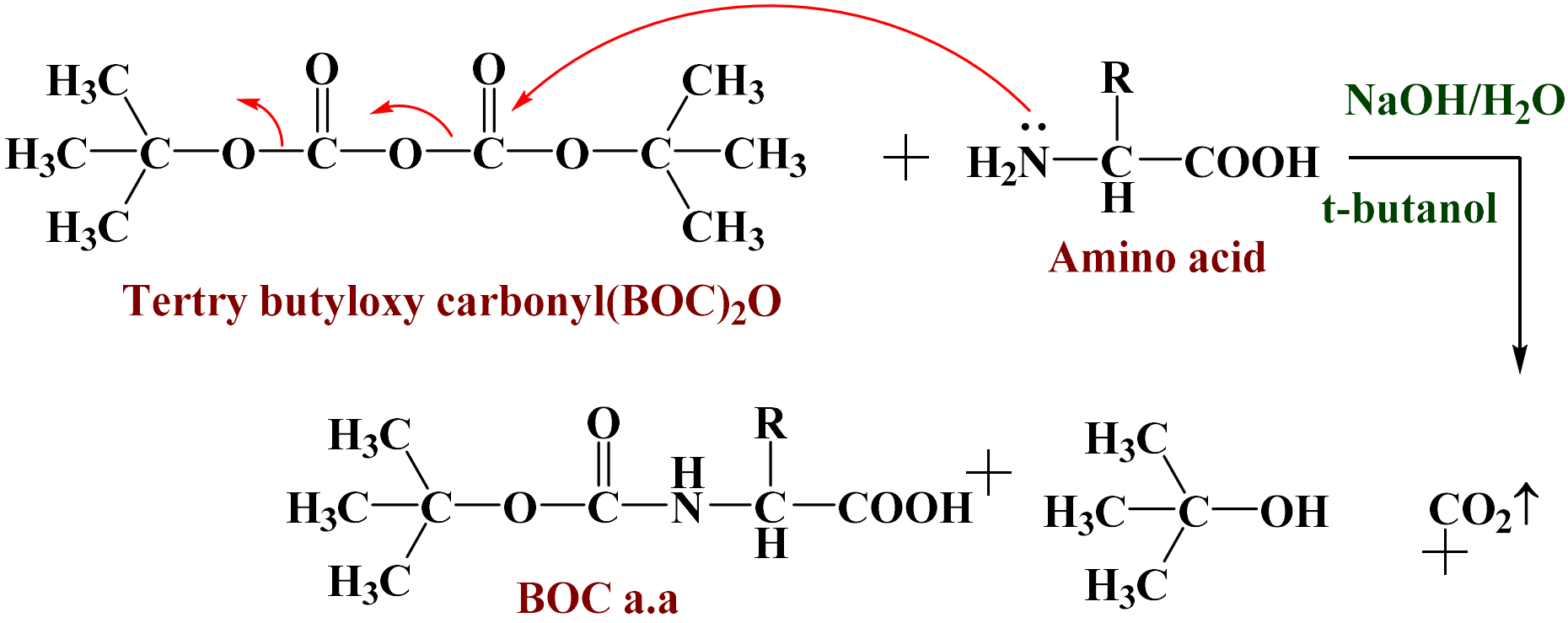


N- protection

- **Phthalic anhydride**



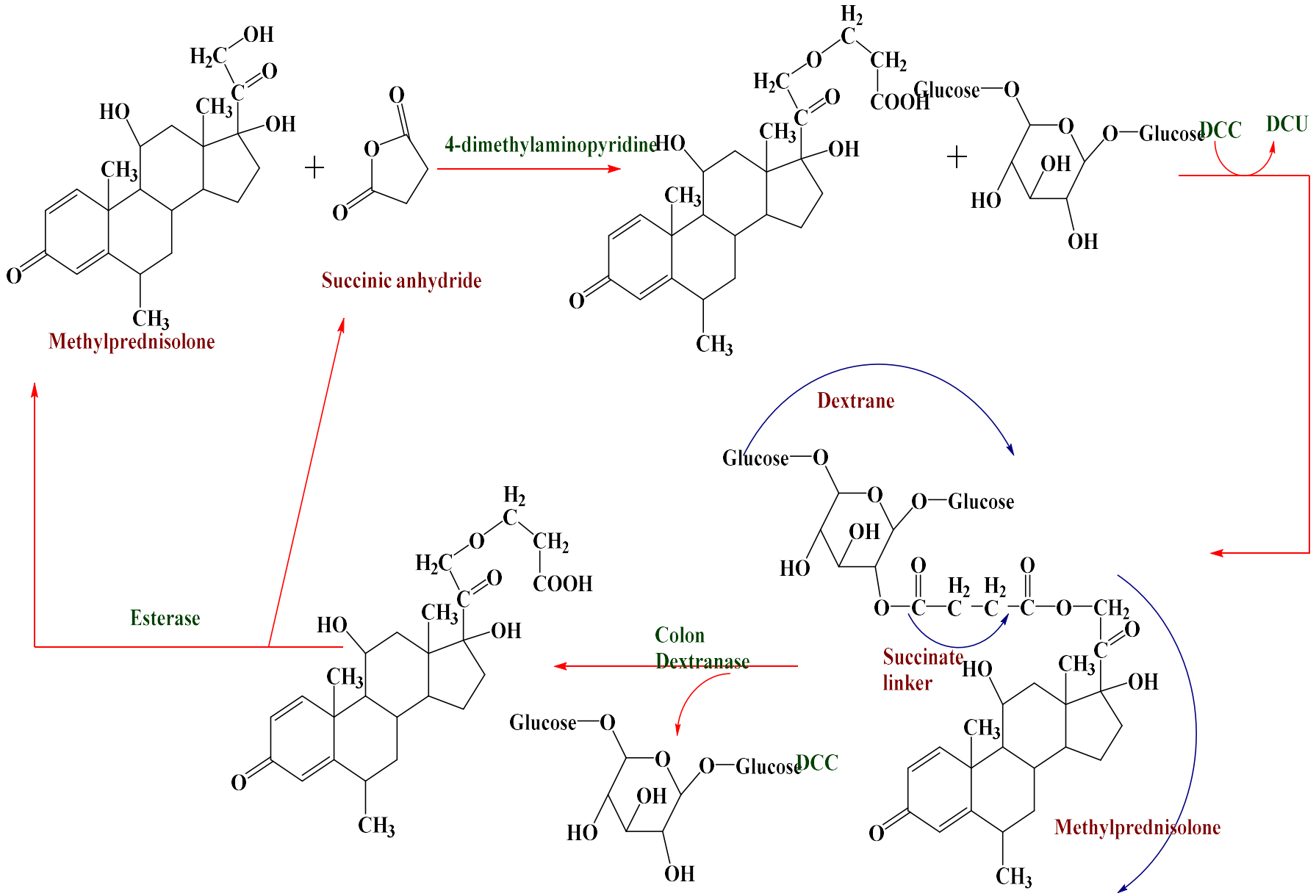
Tertry butyloxy carbonyl$(BOC)_2O$•



Example of polymeric prodrug

Dextran possesses multiple hydroxyl groups and therefore can be easily conjugated with drugs and proteins with reactive groups either by direct conjugation or by incorporation of a spacer arm. After oral administration, the polymer is not significantly absorbed. Therefore, most of the effective applications of dextran as polymeric carriers are through injections.

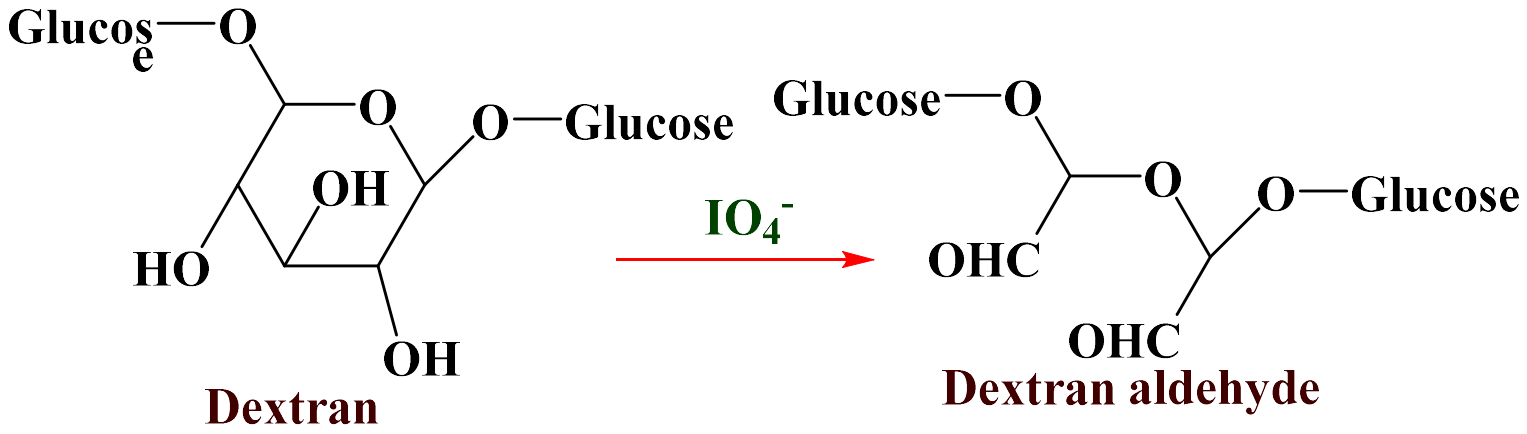
Conjugates of dextrans with corticosteroids have been evaluated previously for the local delivery of steroids in colon as anti-inflammatory agents.


Methylprednisolone
Succinic anhydride
4-dimethylaminopyridine
DCC
DCU
Dextrane
Succinate linker
Colon Dextranase
DCC
Esterase
Methylprednisolone

methylprednisolone -succinate-dextran conjugate is more hydrophilic and has a larger molecular
weight, which may decrease its possibility of being absorbed into the systemic circulation through the small intestinal epithelial cells. When it arrives to the colon, the dextran structure is hydrolyzed quickly by endogenous dextranase and then the esterase breaks the ester bond to release the methylprednisolone.

Naproxen-Dextran prodrug (long duration of action and reduced ulcerogeneicity)

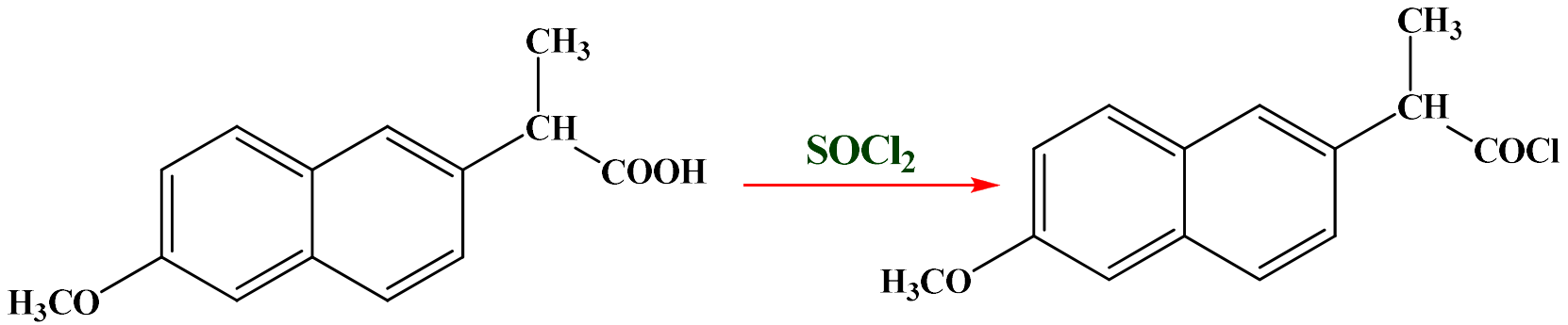
1) Activate the hydroxyl groups of dextran (periodate oxidation)



Dextran

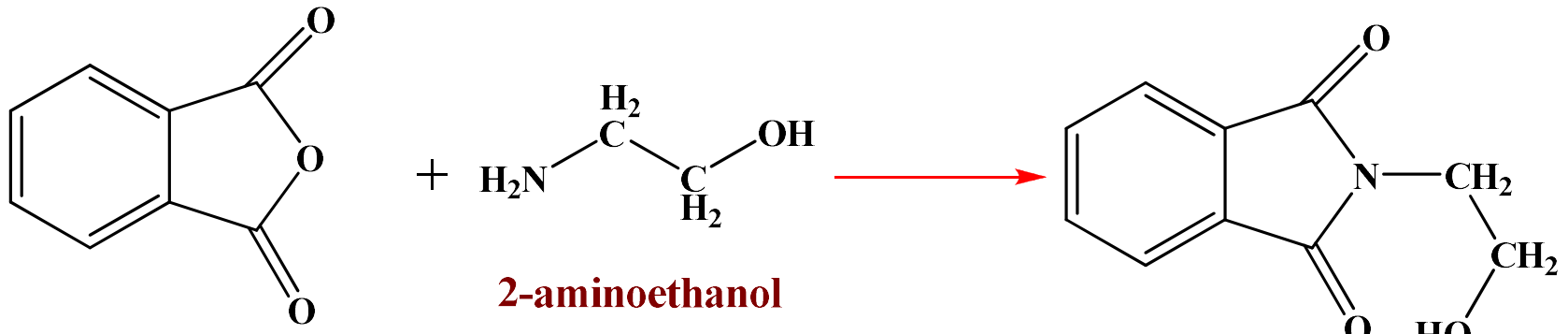
Dextran aldehyde

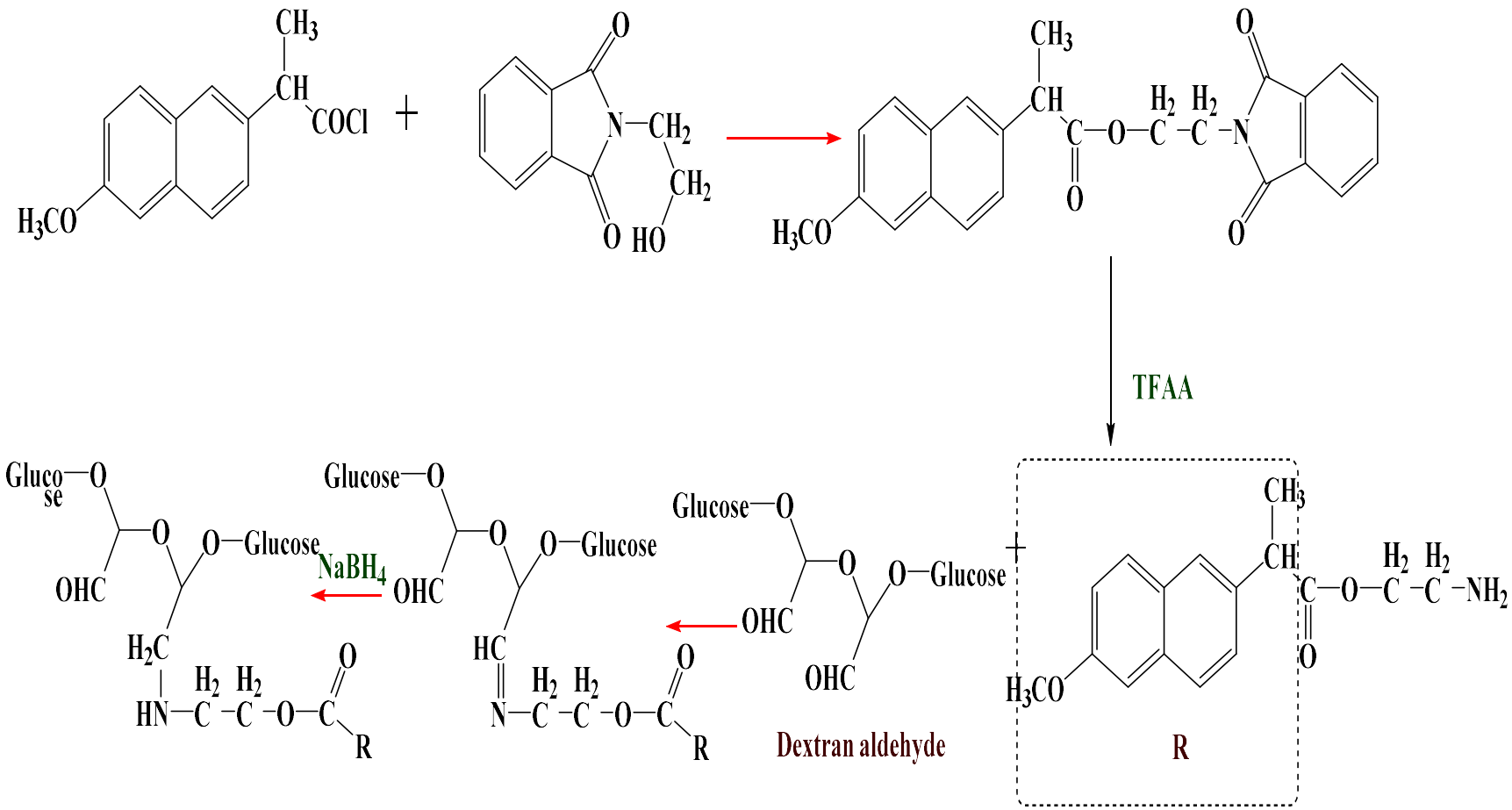
2) Carboxyl group of the active ingredient Naproxen was used for coupling.



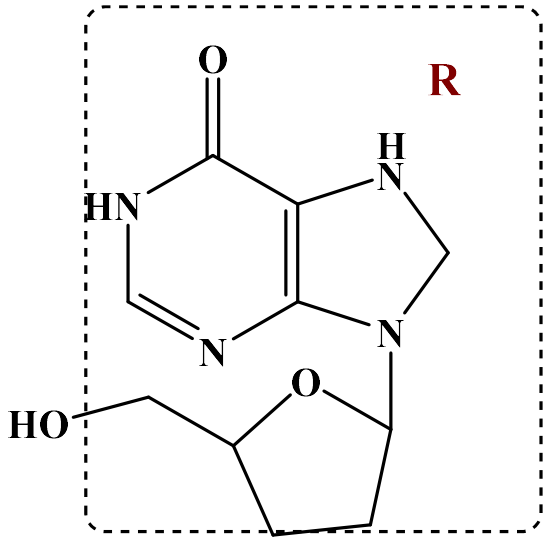
Naproxen

3) Spacer arm Ethanol amine (N-protection)




TFAA
NaBH4
Dextran aldehyde
R

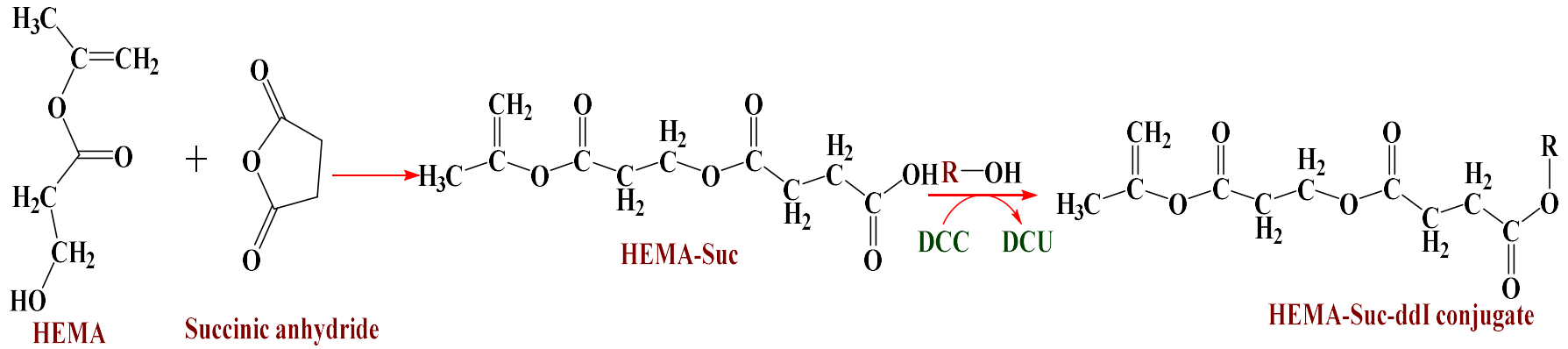
Synthesis, of a macromolecular prodrug of Didanosine(ddI)



Didanosine (ddI) is effective against HIV

Didanosine is associated with several limitations like short plasma half life (1-1.5 h), relatively low bioavailability (42 %) and severe dose dependent cellular toxicities.Didanosine is a highly acid labile compound which is quite stable in alkaline environment

It is easily damaged by stomach acid which is the major reason for its low bioavailability. It was proposed therefore, to synthesize a macromolecular prodrug of ddI for oral administration by coupling the drug to Poly (2-hydroxy ethyl methacrylate, HEMA) through a succinic spacer by ester linkages which would undergo pH dependent hydrolysis to cleave the parent drug in a sustained manner in the alkaline environment of the lower GI tract rather than the acidic environment of the stomach. This pH dependent and sustained release of ddI may result in increasing the bioavailability, t1/2 and maintaining the plasma drug level within the therapeutic range.

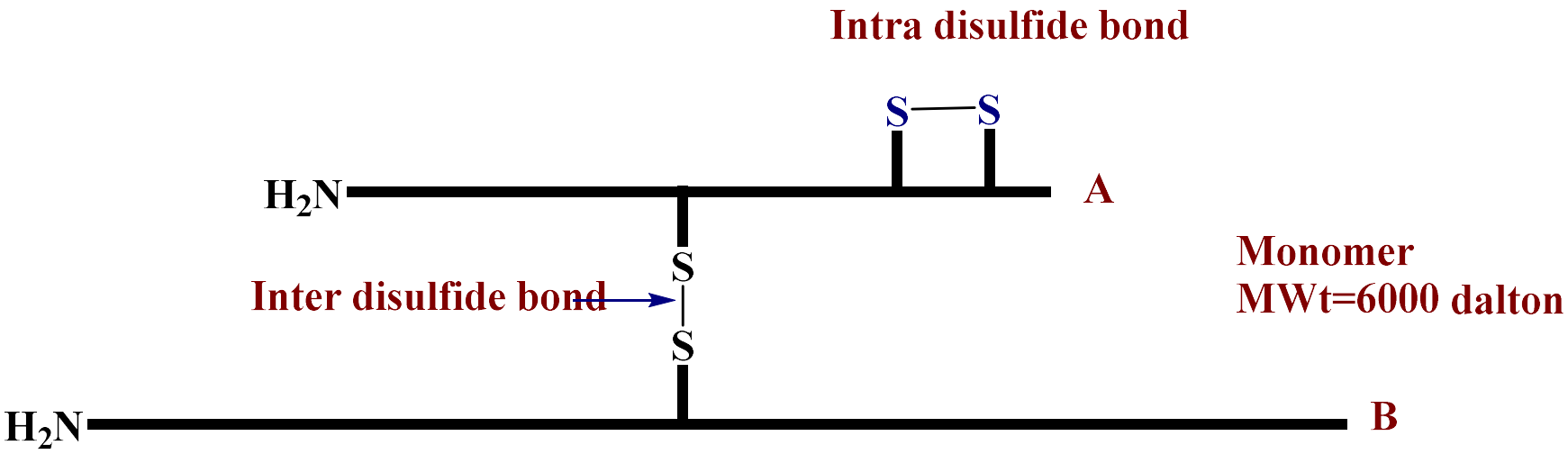


Synthesis of Macromolecular prodrug of Didanosine

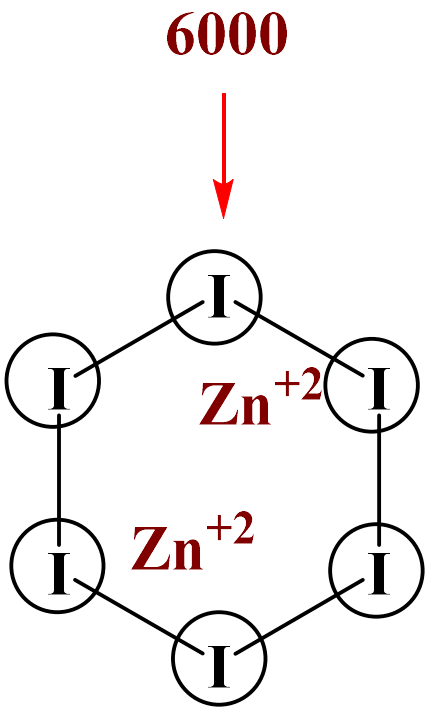
result 100% dgree of substitution which is requir for higher yeilds of dug release

Insulin example for chemical modification.

Insulin molecule consist of two chains A and B, with 21 and 31 amino acid residues respectively. These two chains are connected by two disulfide linkages, with an additional disulfide linkage within chain A.



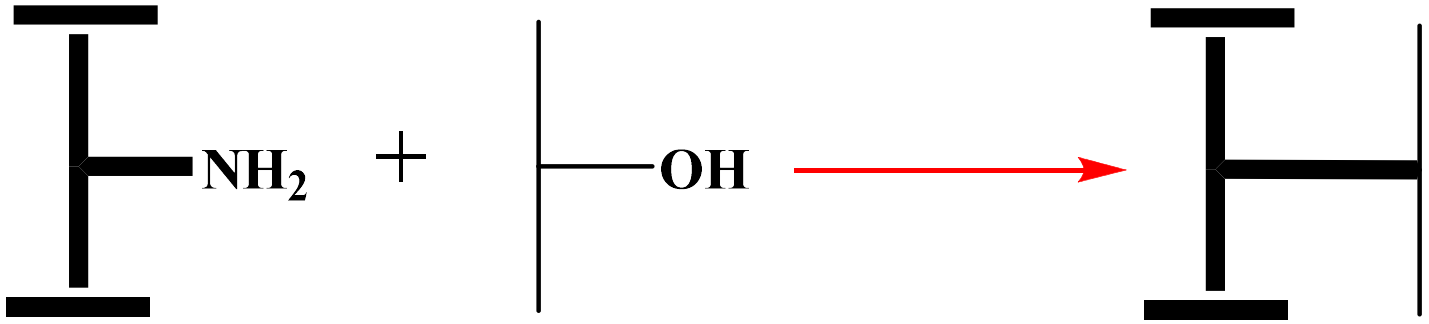
Insulin exist as hexoses "hexane form" physiologically attached to the Zn^{+2} to provide large duration of action.



Hexamer of insulin

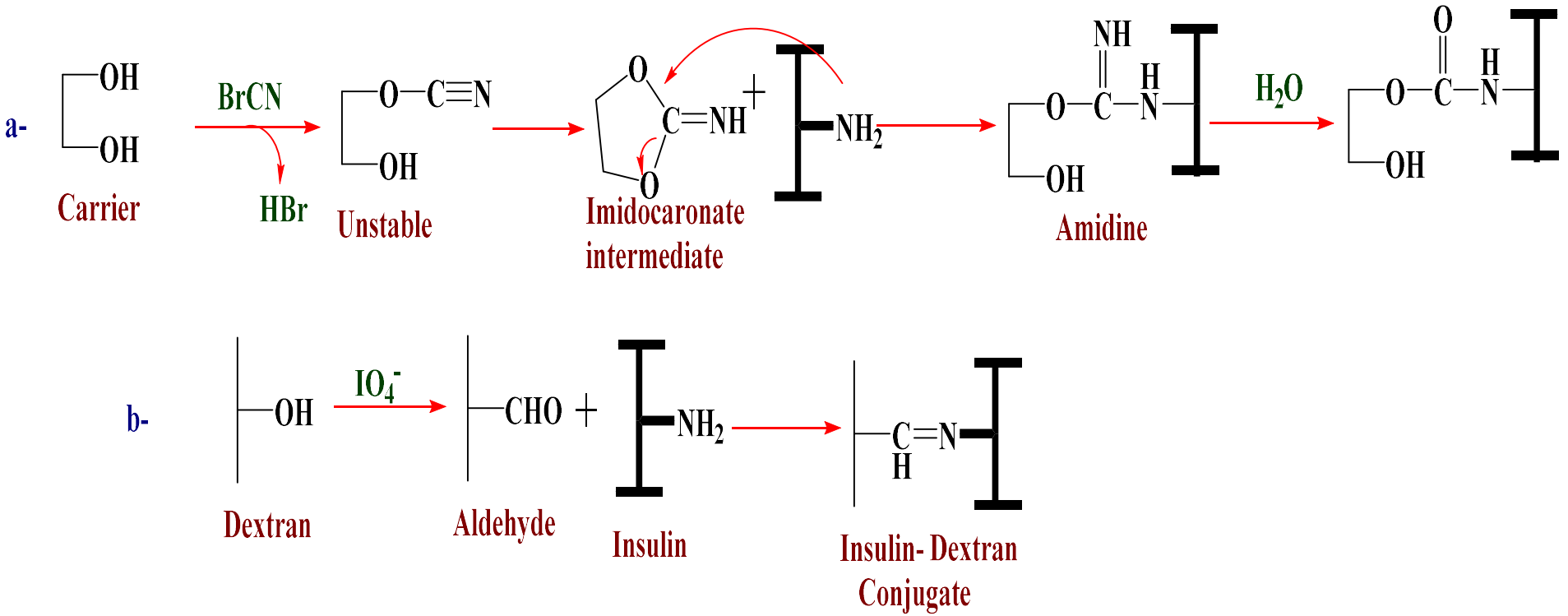
MWt: 6 * 6000 =36000 dalton

Chemical modification of insulin → gives long acting insulin

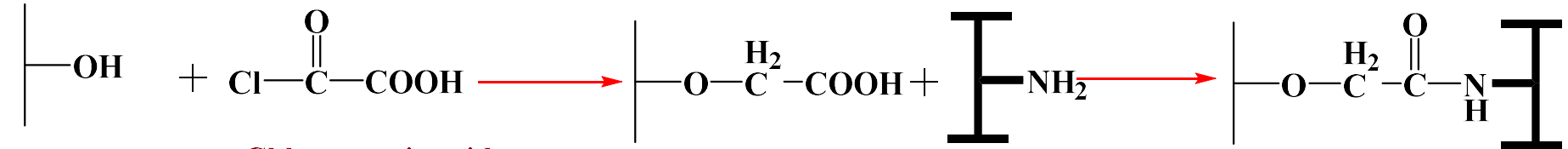


Insulin **Dextran** **Insulin-Dextran conjugate**

Direct reaction•



Indirect method (Spacer arm, chloroacetic acid)•



Dextran

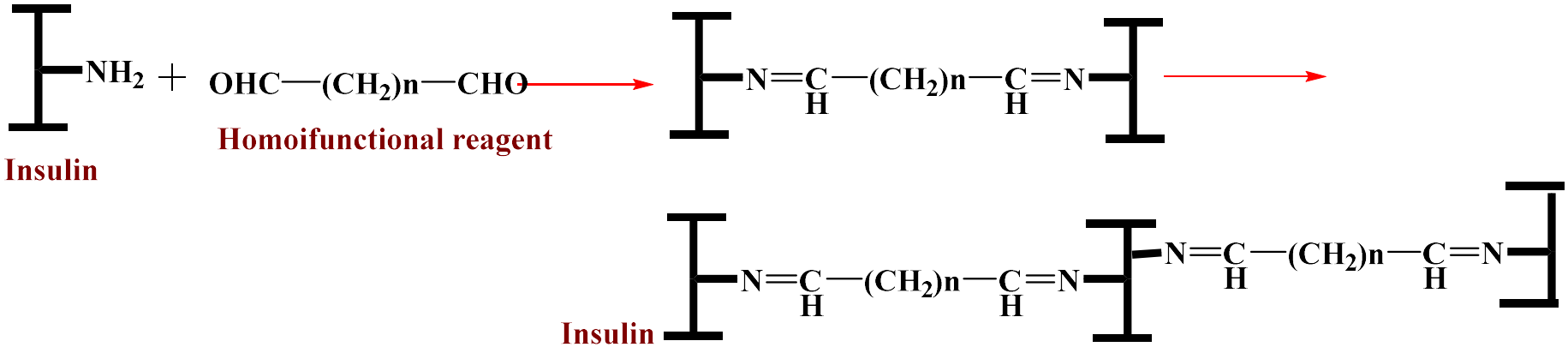
Chloro acetic acid

Insulin

Insulin- Dextran Conjugate

Polymerization of insulin (I-I-I-I)

- Homo bifunctional



If the reaction persists for long time → ppt will occur because of high MWt. In this case all the NH_2 group will react which lead to loss activity and solubility. So we must determine the:-

- **Degree of modification.**
- **Limitation 50%.**

Heterobifunctional•