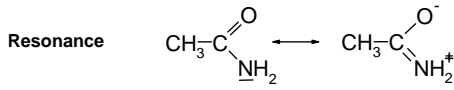


## Peptides

### Properties-Synthesis-Hydrolysis



Properties:

*Neutral* (free electron pair of N: delocalized)

*Planar unit* ( $\text{sp}^2$ -hybridisation of C=N), C-N bond is shortened

Restricted rotation – partial double bond character!

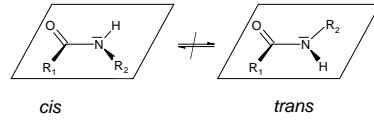
*Stable* (loss of positive character on carbonyl atom - nucleophilic addition less likely)

The amide linkage forms the basis of stability and three-dimensional structure of peptides and proteins

Hydrolysis of peptides: 6 M HCl, 105°

## Peptides

### Properties-Synthesis-Hydrolysis



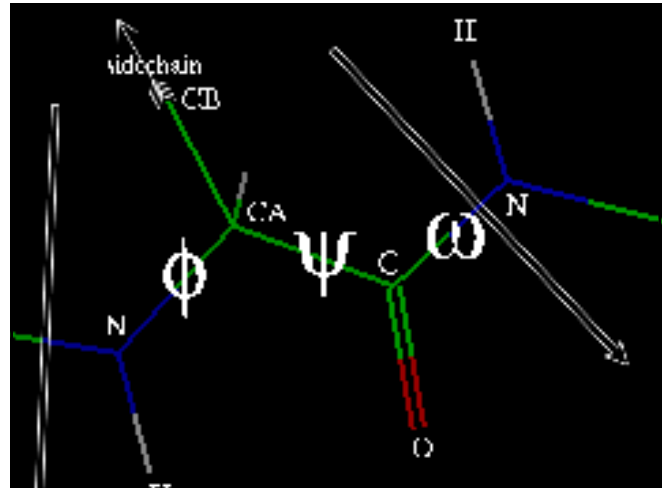
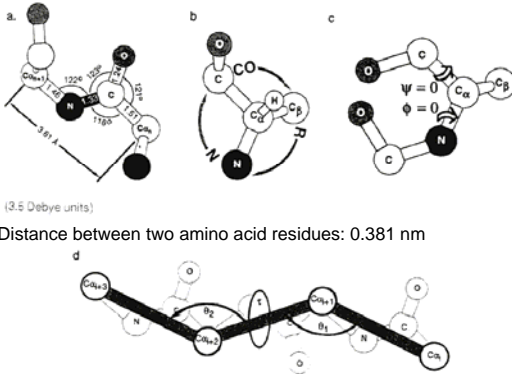
Rotational barrier: 18.8 kcal/mol (41.8 kJ/mol)

Rate of isomerisation at 40° :  $\sim 0.15 \text{ s}^{-1}$

*Trans*-form more stable (factor 10<sup>3</sup>)

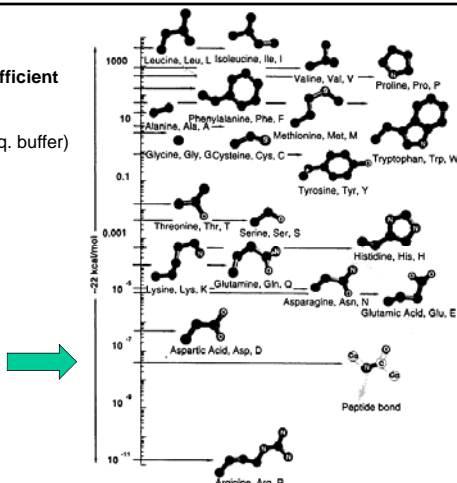
Exception: proline (factor 4)

## Geometry of peptide bond



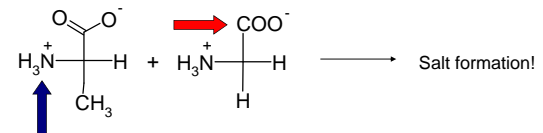
## Distribution coefficient of amino acids

(Cyclohexane / aq. buffer)

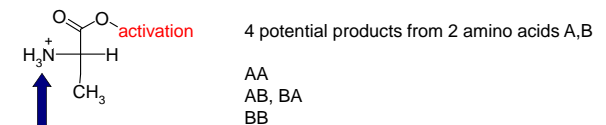


## Principles of peptide synthesis

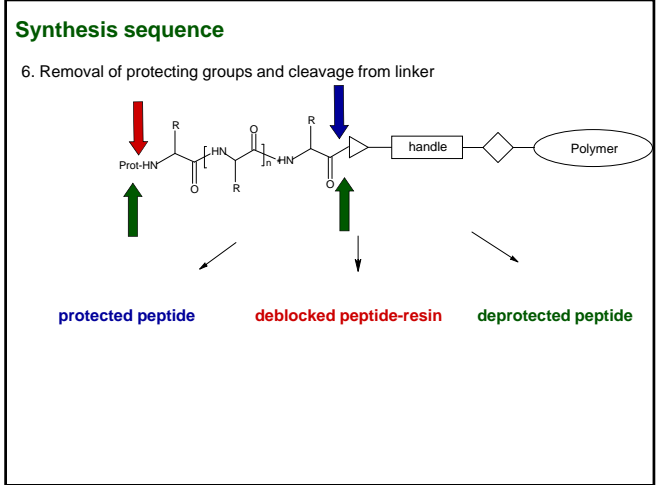
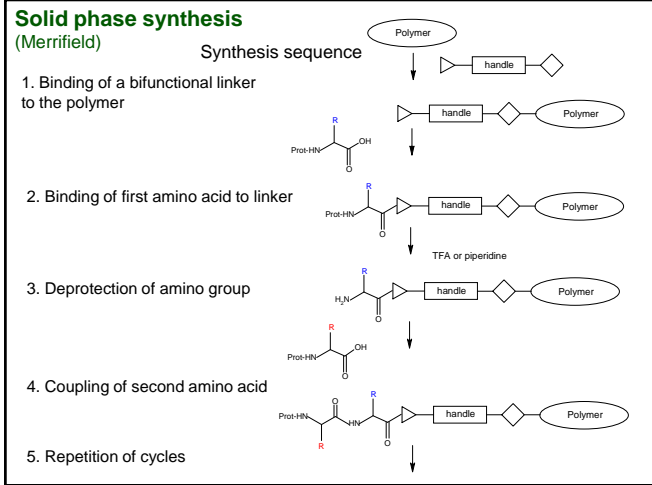
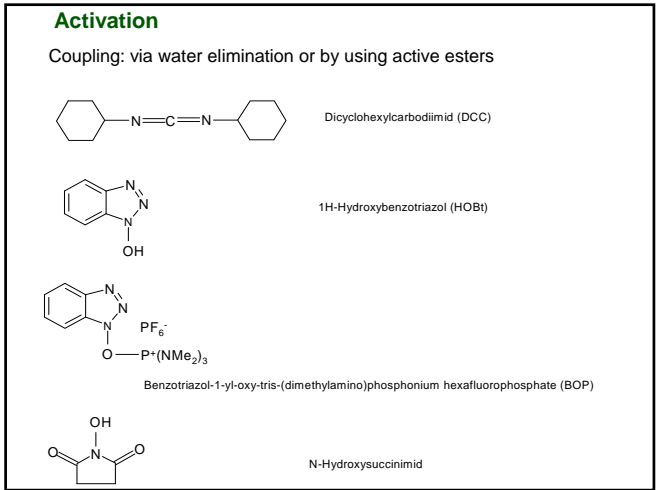
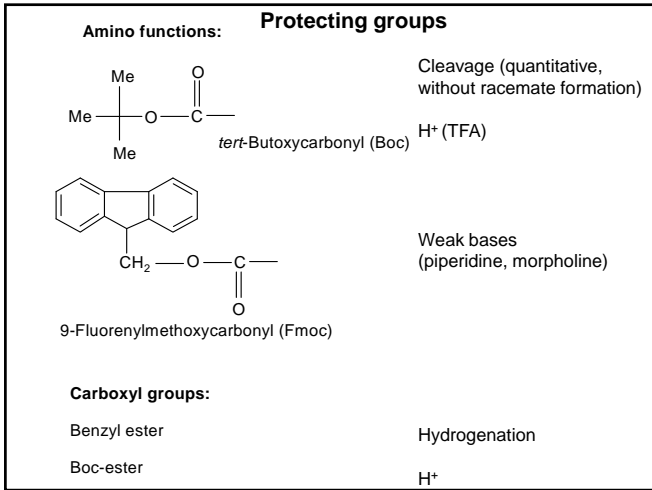
1. Reaction of the  $\alpha$ -amino group with an activated carboxylic group



2. Protection needed for amino and carboxylic groups



3. Protecting groups for side chain residues (-SH, -OH, -COOH, -NH<sub>2</sub>)



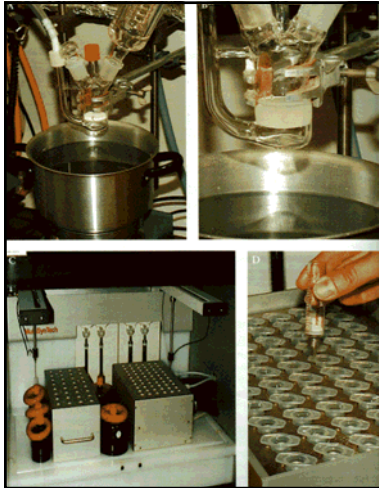
TentaGel beads (crosslinked polystyrene, 130  $\mu\text{m}$  grafted with polyethyleneglycol)

Capacity: 0.2-0.8 mmol / g  
 15 mg product (M: 500) ~ 40-150 mg resin

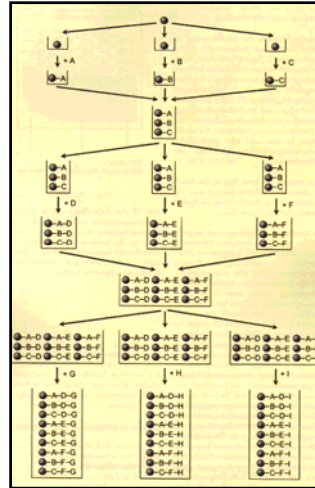
Scheme for solid phase synthesis

Chiuz 1996 (30) 270-285.

Linker type	Attachment	Cleavage	Resin	Reagent	Prod.
<b>Hydroxy-Resin</b>			Wang, TGA, Tentagel Rink Acid	TFA 10% HOAc/DCM 5% TFA/DCM	RCOH RCH RCOOH RCH2OH RCOOH RCH2OH RCOOH RCH2OH RCOOH RCH2OH
<b>Amino-Resin</b>			Rink Amide, Rink Amide MBHA, TGA, Tentagel, Ester	TFA 1% TFA/DCM	RCOHN RCOHN
<b>Tityl-Resin</b>				TFA/DCM	RCOOH RCH RCH



Combinatorial synthesis  
(Compound libraries)



Combinatorial synthesis  
(Compound libraries)

„Mix and Split“

9 Reactions yield 27 compounds  
(3 groups of 9 components)

**Examples:**  
Chymotrypsin, Trypsin, Elastase, Subtilisin

**Serin Proteases**

1 245 Chymotrypsinogen (Inactive)  
↓ Trypsin  
1 15 16 245 π-Chymotrypsinogen (active)  
Arg Ile

1 13 16 146 149 245 α-Chymotrypsin (active)  
Leu Ile Tyr Ala

A-chain B-chain C-chain

Disulfide bridges

**Mechanism of Serin Protease-hydrolysis of peptides**

1. Enzyme-substrate complex      2. Tetrahedral intermediate

3. Acyl enzyme-intermediate      4. Hydrolysis of acyl enzyme

5. Tetrahedral intermediate      6. Enzyme-product complex

Mechanism  
catalytic triade, proton shuttle