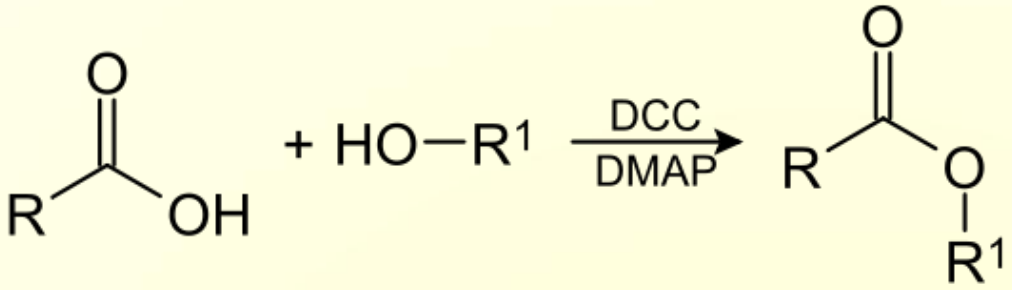
Coupling Reagents (part 2.)

2015-7-14

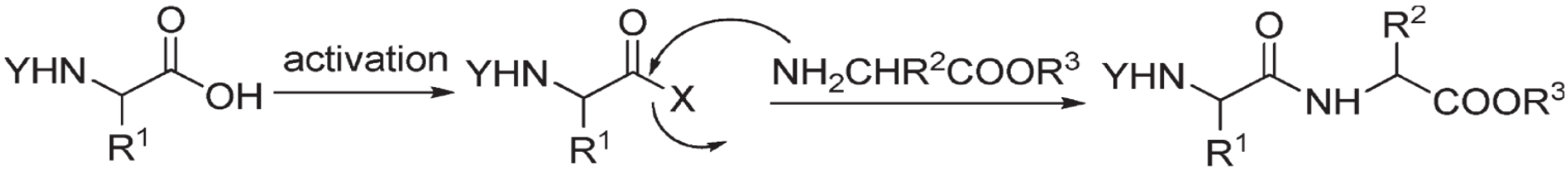
WZQ

Applycations

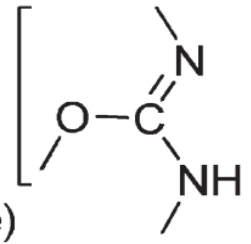
Esterification



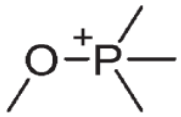
Peptide Bond Formation



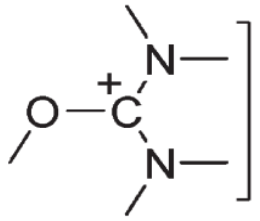
X = halide, N_3,
OR (active ester),
OCOR (mixed or
symmetris anhydride)



(O-acyl urea)

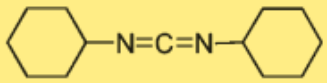
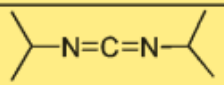
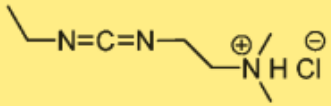
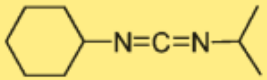
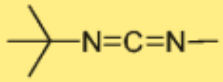
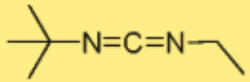
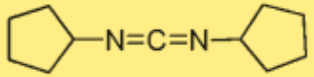
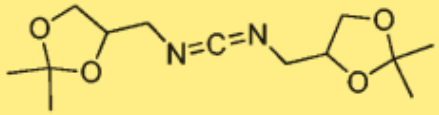
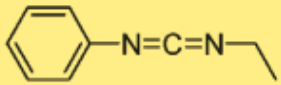


(acyl phosphonium)

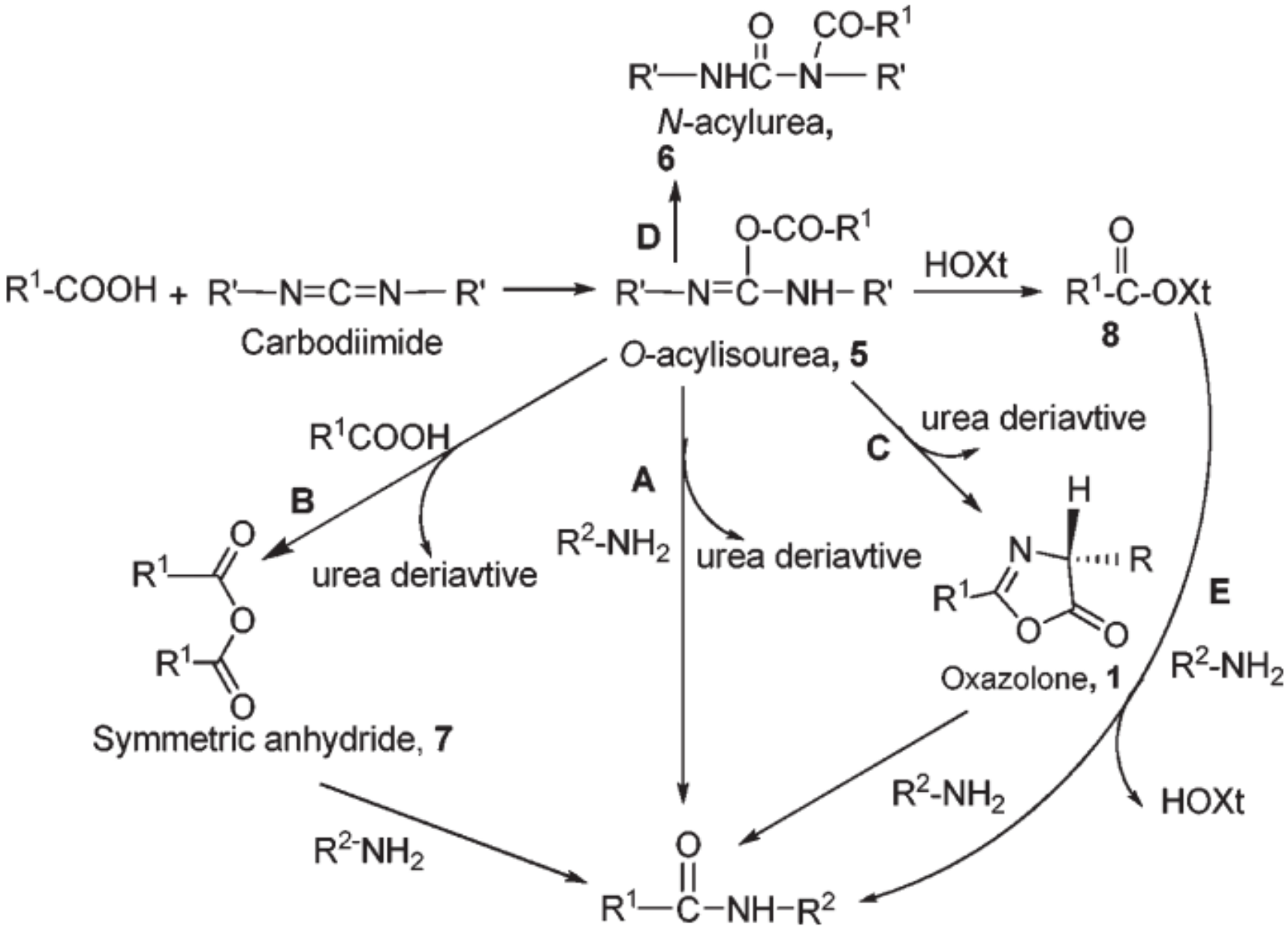


(acyl uronium)

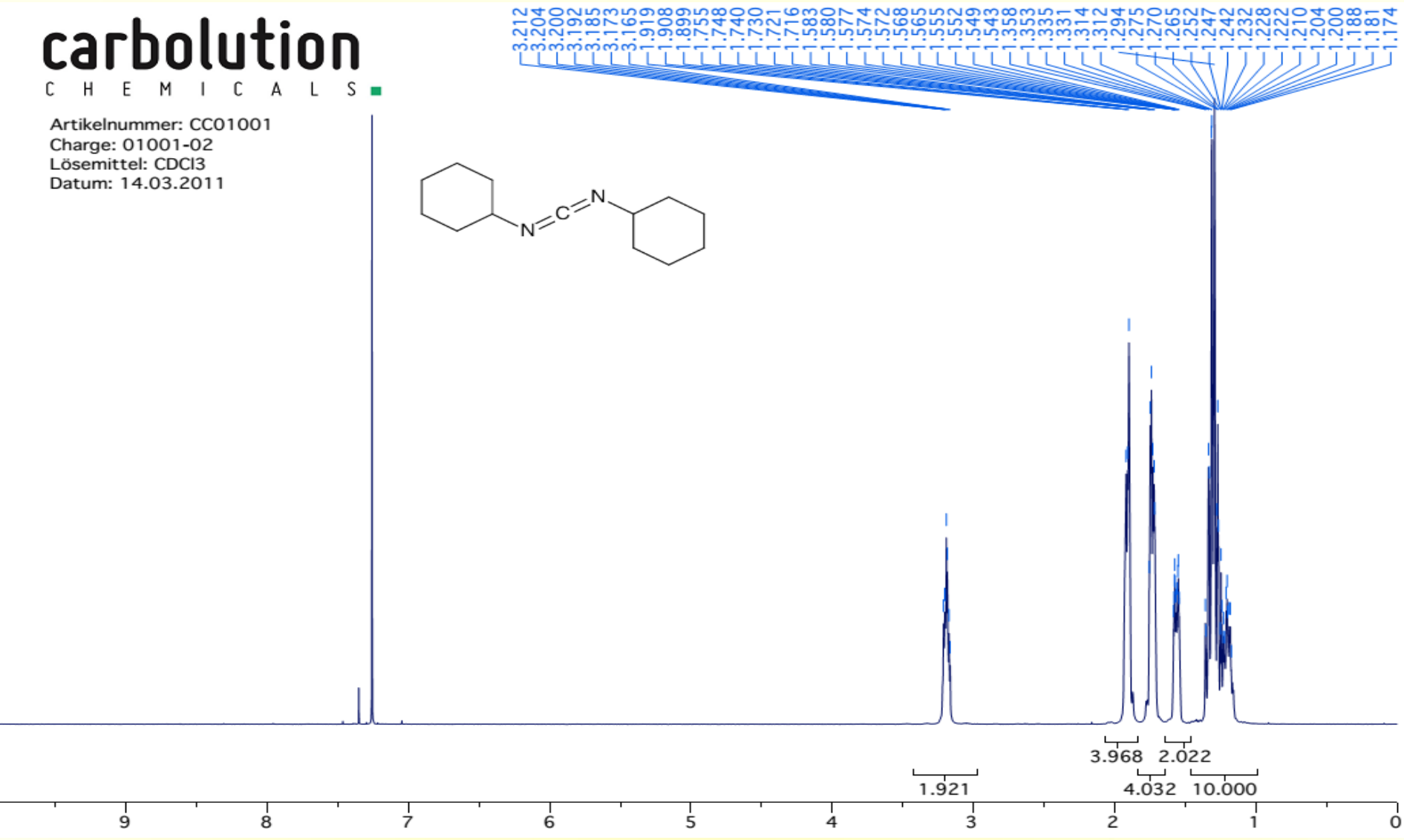
Carbodiimides

Abbreviation	Name and Structure
DCC	*N,N'*-dicyclohexylcarbodimide 
DIPCDI, DIC	*N,N'*-diisopropylcarbodimide 
EDC, WSC	*N*-ethyl-*N'*(3-dimethylaminopropyl)carbodimidehydrochloride 
CIC	*N*-cyclohexyl, *N'*-isopropylcarbodiimide 
BMC	*N-tert*-butyl, *N'*-methylcarbodiimide 
BEC	*N-tert*-butyl, *N'*-ethylcarbodiimide 
CPC	*N,N'*-dicyclopentylcarbodiimide 
BDDC	*bis*[[4-(2,2-dimethyl-1,3-dioxolyl)]methyl]carbodiimide 
PEC	*N*-ethyl, *N*-phenylcarbodiimide 

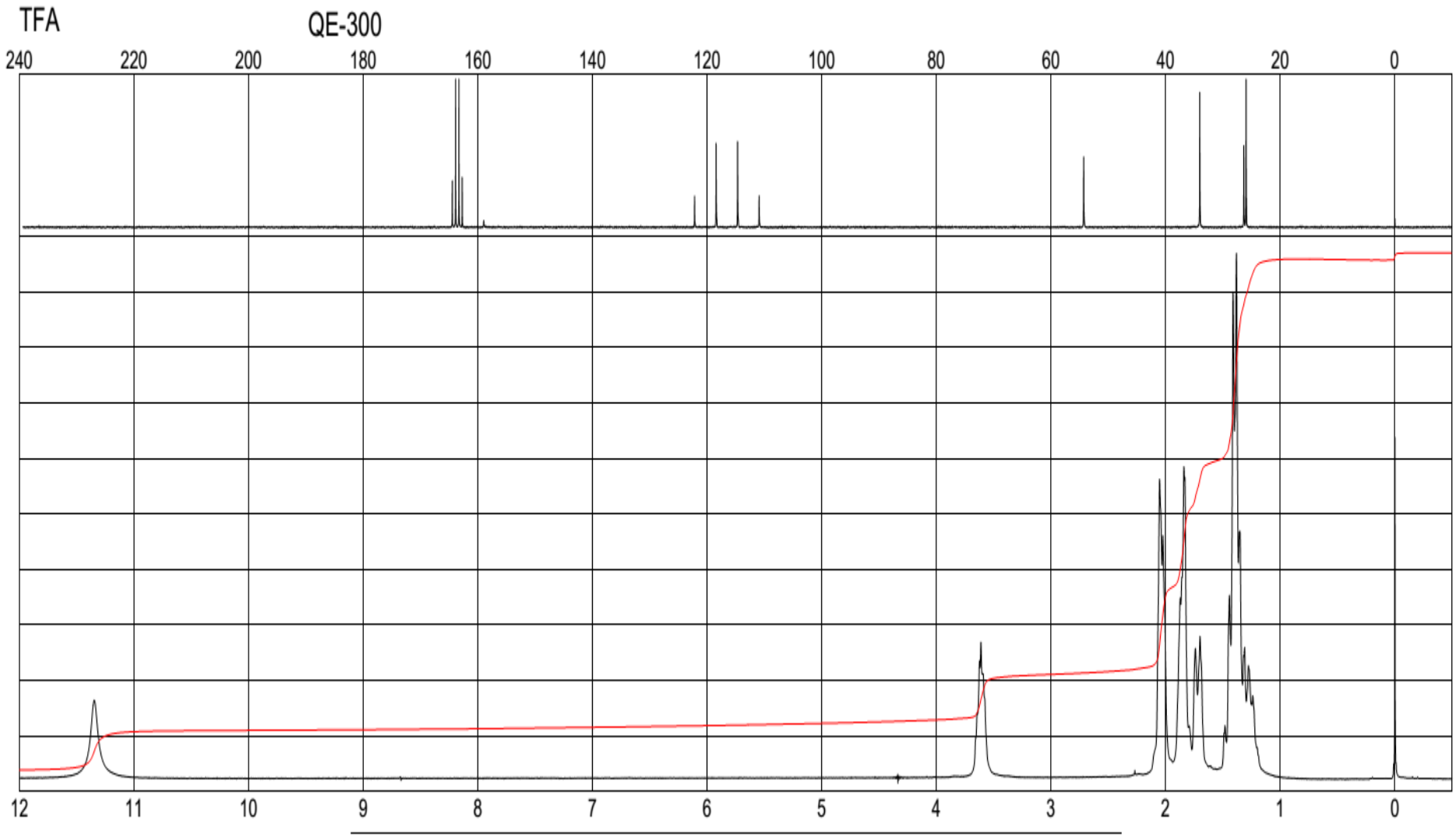
Mechanism


R'—NHC(=O)—N(CO-R1)—R'
N-acylurea,
6
D
R1-COOH + R'—N=C=N—R'
Carbodiimide
R'—N=C(O-CO-R1)—NH—R'
O-acylisourea, 5
HOXt
R1-C(=O)-OXt
8
R1COOH
B
urea deriavtive
A
R2-NH2
urea deriavtive
C
urea deriavtive
Symmetric anhydride, 7
Oxazolone, 1
E
R2-NH2
R2-NH2
HOXt
R2-NH2
R1—C(=O)—NH—R2

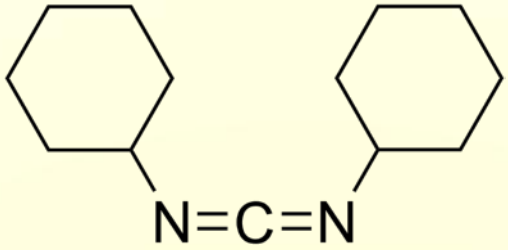
Dicyclohexylcarbodiimide（DCC）



Dicyclohexylcarbodiimide（DCC）



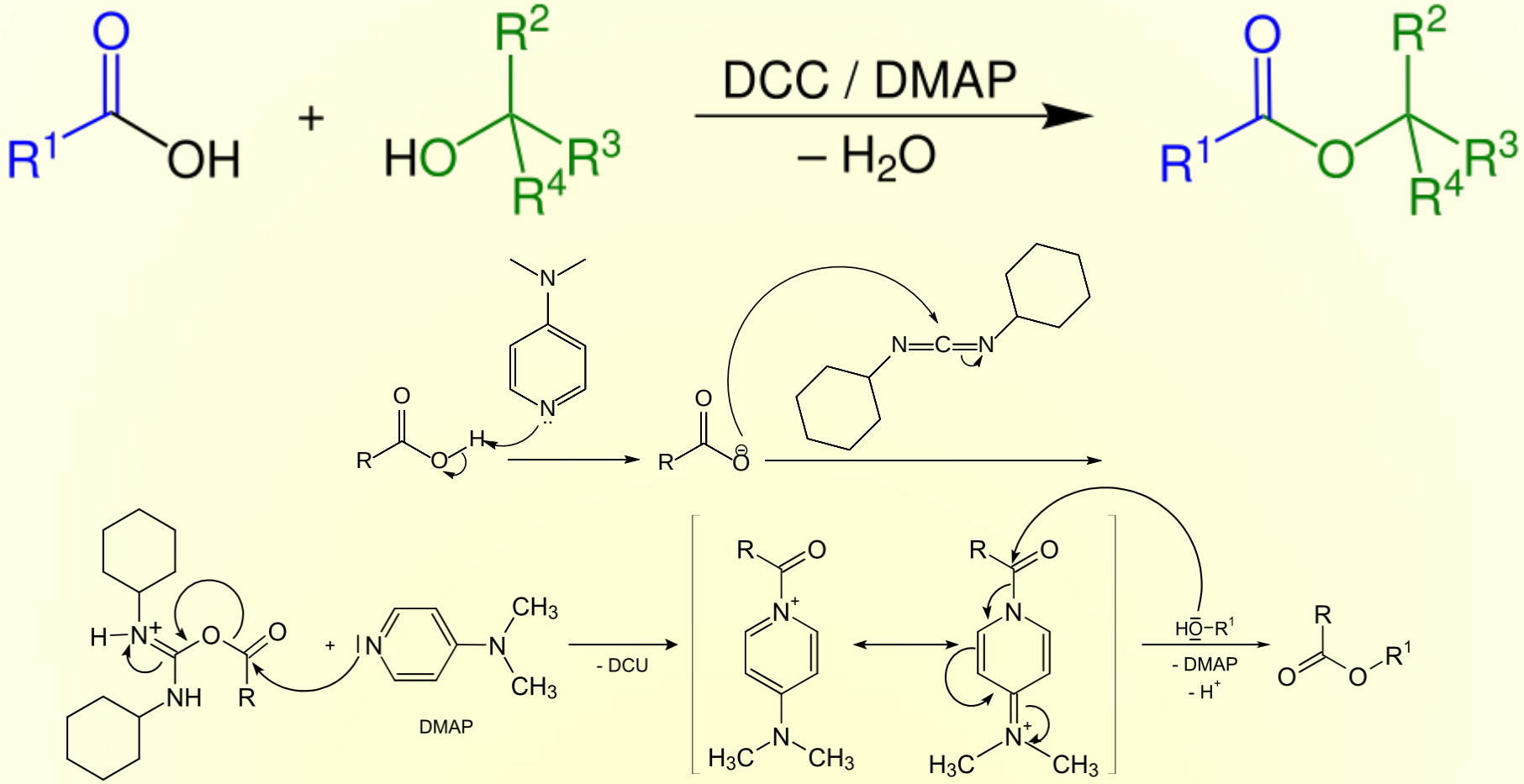
Dicyclohexylcarbodiimide（DCC）



1. Applied for coupling since 1955 and is still much in use today.
2. The reaction does not require additional base, so that racemization can be kept minimal.
3. Additives such as HOBt or HOSu is needed inorder to reduce epimerization in the case of peptides or racemization in the case of amino acids.
4. N,N'-dicyclohexylurea (DCU) is soluble only in TFA， thus DCC is compatible with solid-phase synthesis only –Boc chemistry， not –Fmoc chemistry。
5. NOT compatible with DMSO!(Pfitzner-Moffatt oxidation).

applications（DCC）

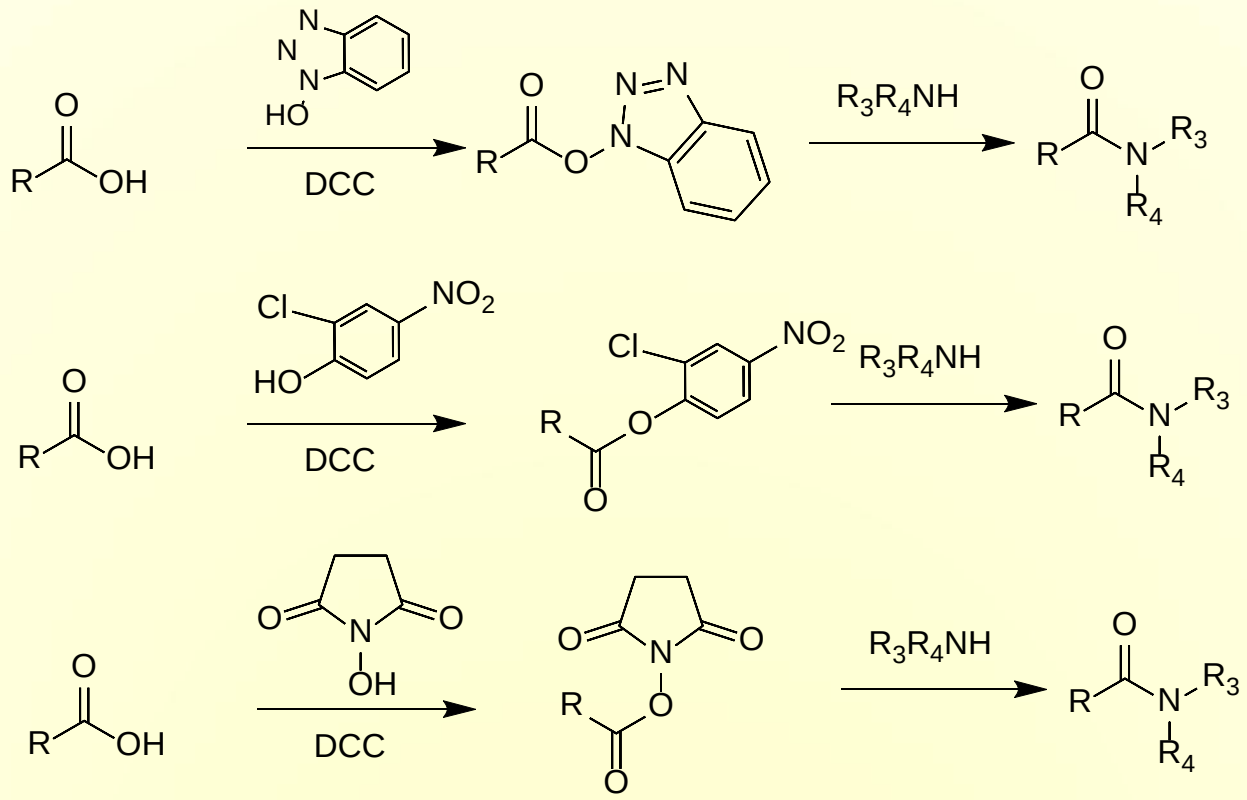
Steglich esterification



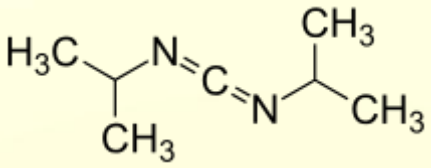
applications（DCC）

Manufacture of active esters---

The low solubility of DCU turns into an advantage of this activation method.



N,N'-Diisopropylcarbodiimide（DIC）



DIC (acronym for N,N'-diisopropylcarbodiimide) was developed as an alternative to DCC. DIC is identical to DCC in nearly every way except:

1.As a liquid, DIC is easier to handle than DCC (which is a waxy solid).

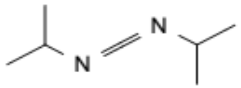
2.The product, N,N'-diisopropylurea, is soluble in organic solvents and is easily removed by extraction. Hence, DIC is more often used in solid-phase synthesis.

3.DIC is far less likely than DCC to cause an allergic reaction.

N,N'-Diisopropylcarbodiimide（DIC）

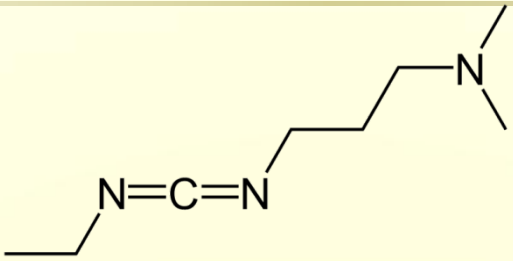
carbolution
CHEMICALS

Artikelnummer: CC01002
Charge: 01002-01
Lösemittel: CDCl3
Datum: 23.11.2010

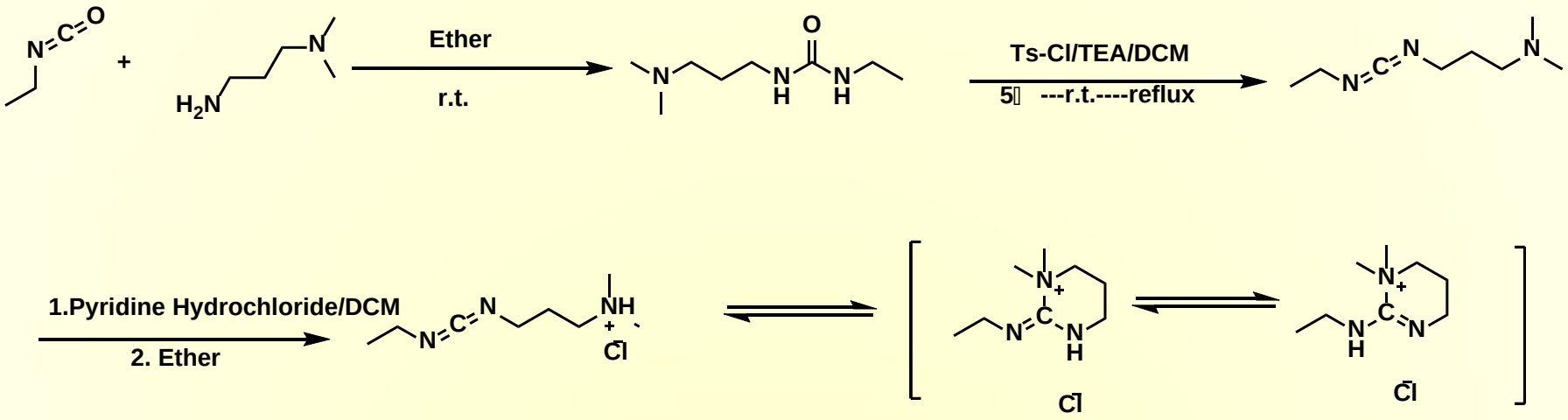


1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

(EDC/EDCI/WSC)



Preparation



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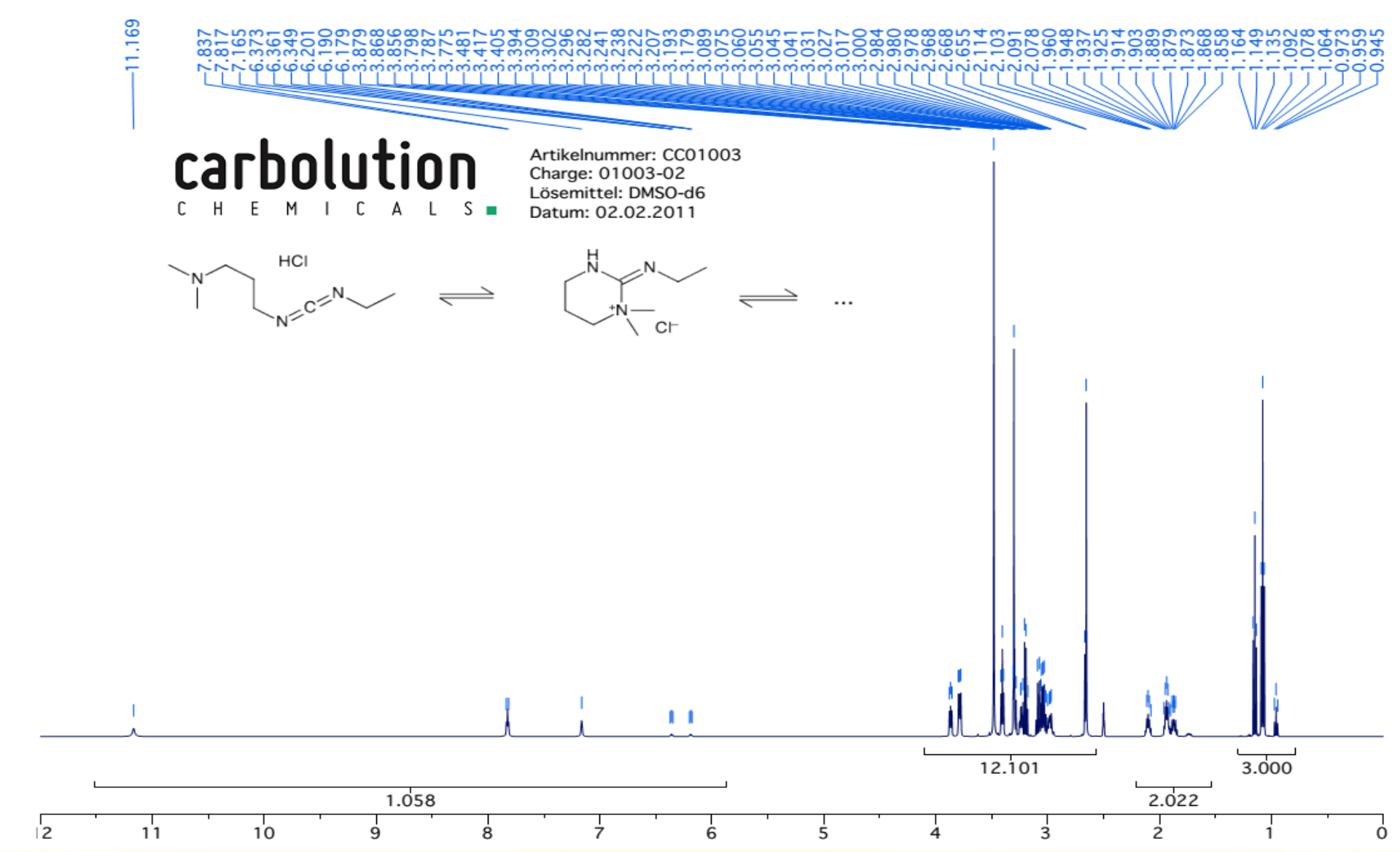
1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

(EDC/EDCI/WSC)



1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

(EDC/EDCI/WSC)

Stability of Carbodiimide in Aqueous Media.

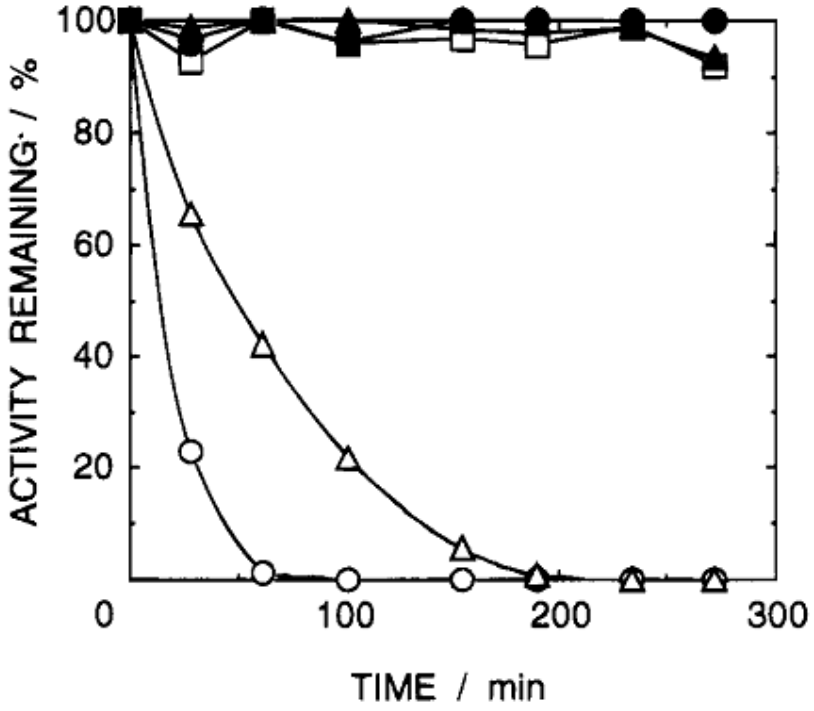


Figure 1. pH dependence of EDC stability at 25 °C. A 0.1 mL portion of 10 mg/mL of aqueous EDC solution kept at different pHs was taken out from the aliquot at given time intervals and added to 3.0 mL of pyridine buffer solution. The relative activity was evaluated from the absorbance measurement. pH: (○) = 2.52, (△) = 3.95, (□) = 6.54, (●) = 8.75, and (▲) = 9.84.

Reaction of EDC with Carboxyl Groups

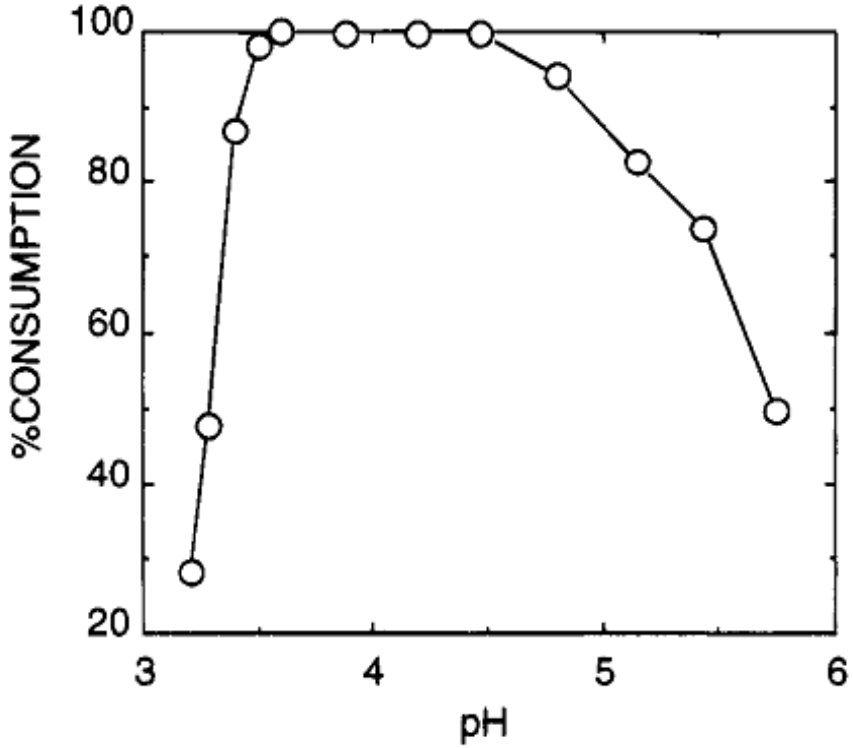


Figure 2. pH dependence of the consumption of carboxyl groups in Gel-A in the presence of EDC. Three pieces of swollen gels were placed in 20 mL of 10 mg/mL of EDC aqueous solution of different pHs without acetic acid at 25 °C for 2 h. Data are the average of three readings.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

(EDC/EDCI/WSC)

The pH dependence of the stability of product yieldedfrom the carboxyl groups and EDC

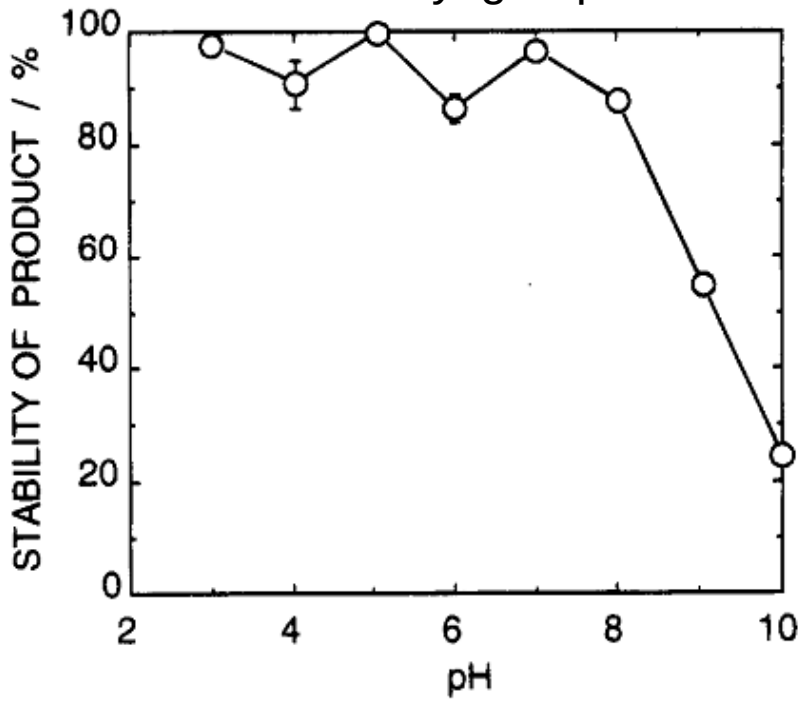


Figure 3. pH dependence of stability of the product formed between carboxyl groups in Gel-A and EDC. Thirty pieces of Gel-A were placed in 100 mL of 10 mg/mL of EDC aqueous solution of pH 4.5 at 25 °C for 2 h. Then, three pieces were taken out and treated with 30 mL of 5 v/v % acetic acid aqueous solution of various pHs at 25 °C for 16 h. Data are the average of three readings.

one-step method the optimal **pH** for amide formation was observed around **5**

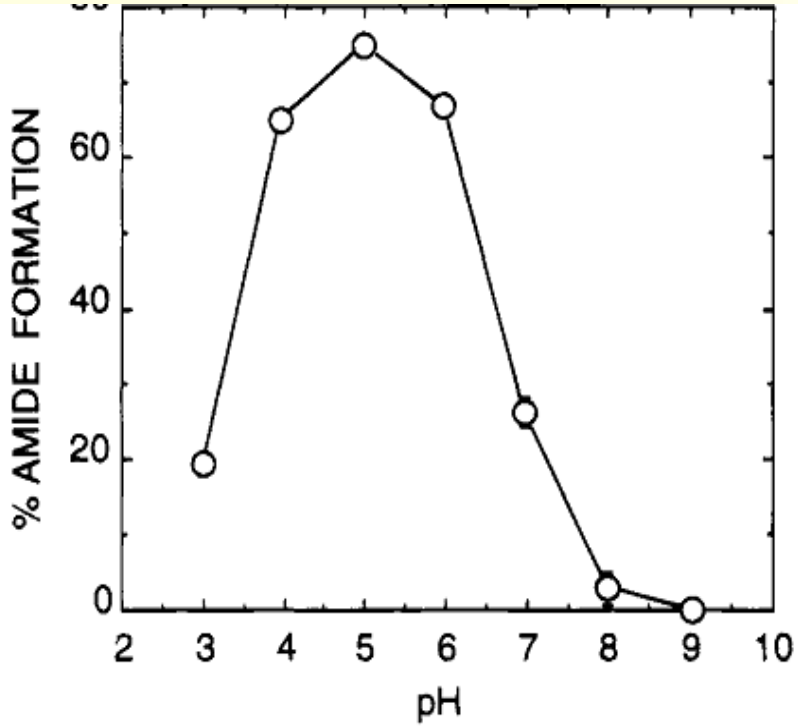
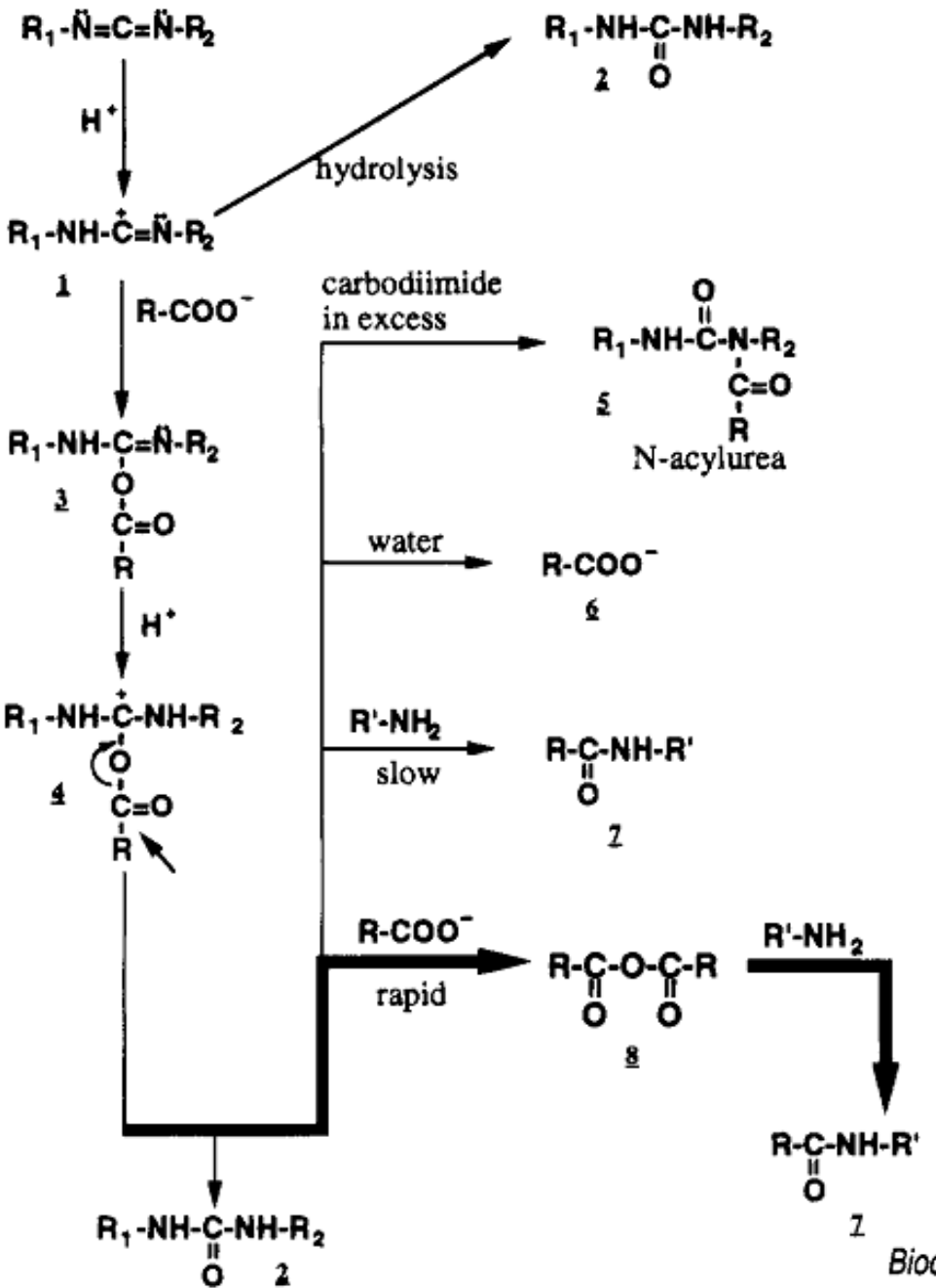


Figure 7. Amide formation from Gel-B and ethylenediamine with the one-step method. Three pieces of Gel-B were placed in 30 mL of mixture of 0.1 M ethylenediamine, 0.1 M NaH_2PO_4, and 0.01 M acetic acid at various pHs and allowed to react at 25 °C for 30 min after an addition of 0.72 mL of 40 mg/mL of EDC aqueous solution. Data are the average of three readings.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC/EDCI/WSC)

Amide Formation by Carbodiimide in Aqueous Media



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To be continued