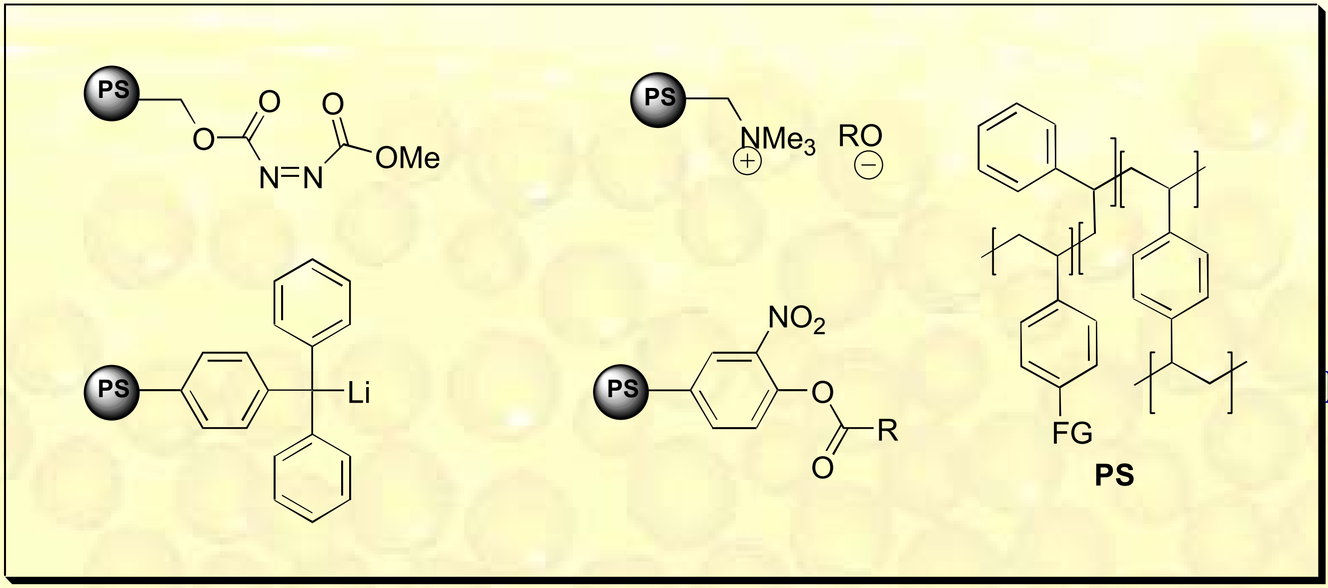
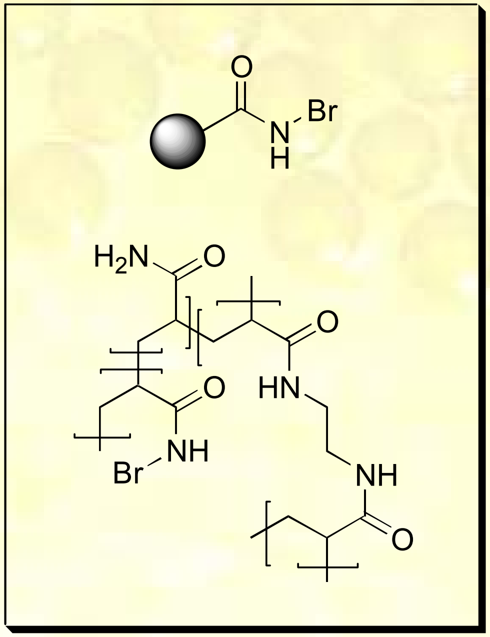
Polymers as reagents

Other polymer supported reagents



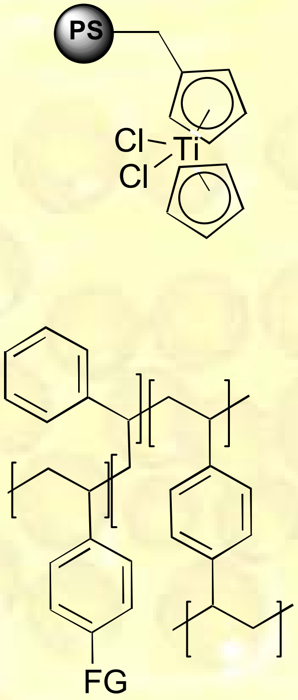


Substitutions:
Mitsunobu reactions
etherification
esterifications
acylations
halogenations

Additions

Polymers as catalysts

Catalysts for reductions



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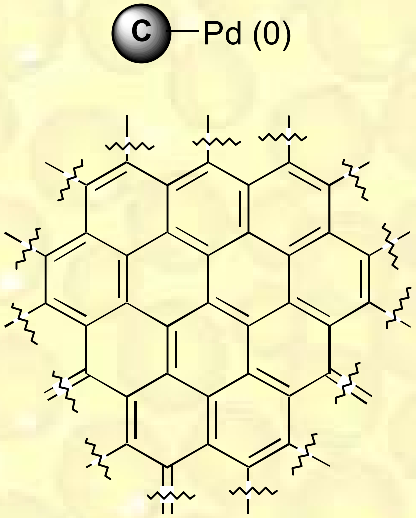

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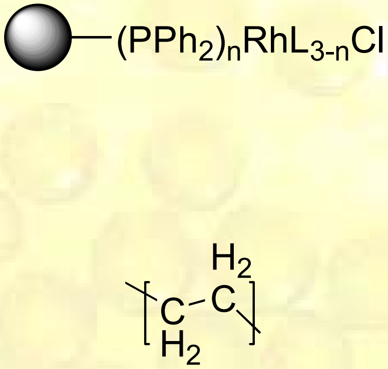
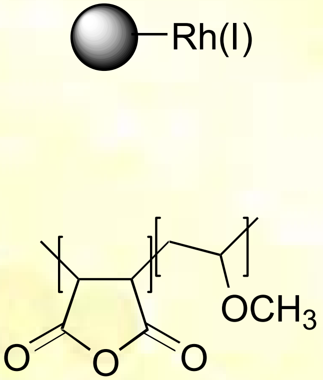
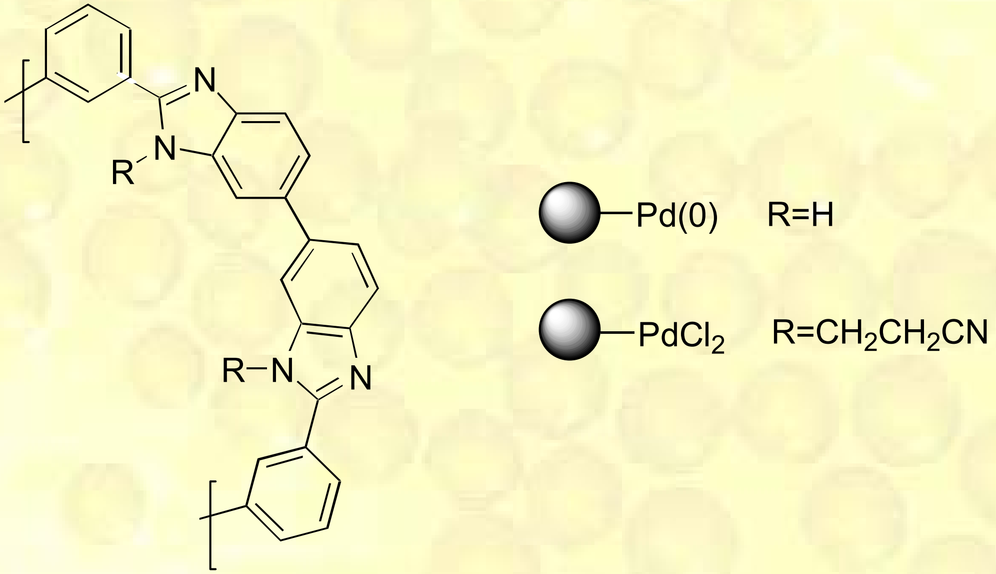
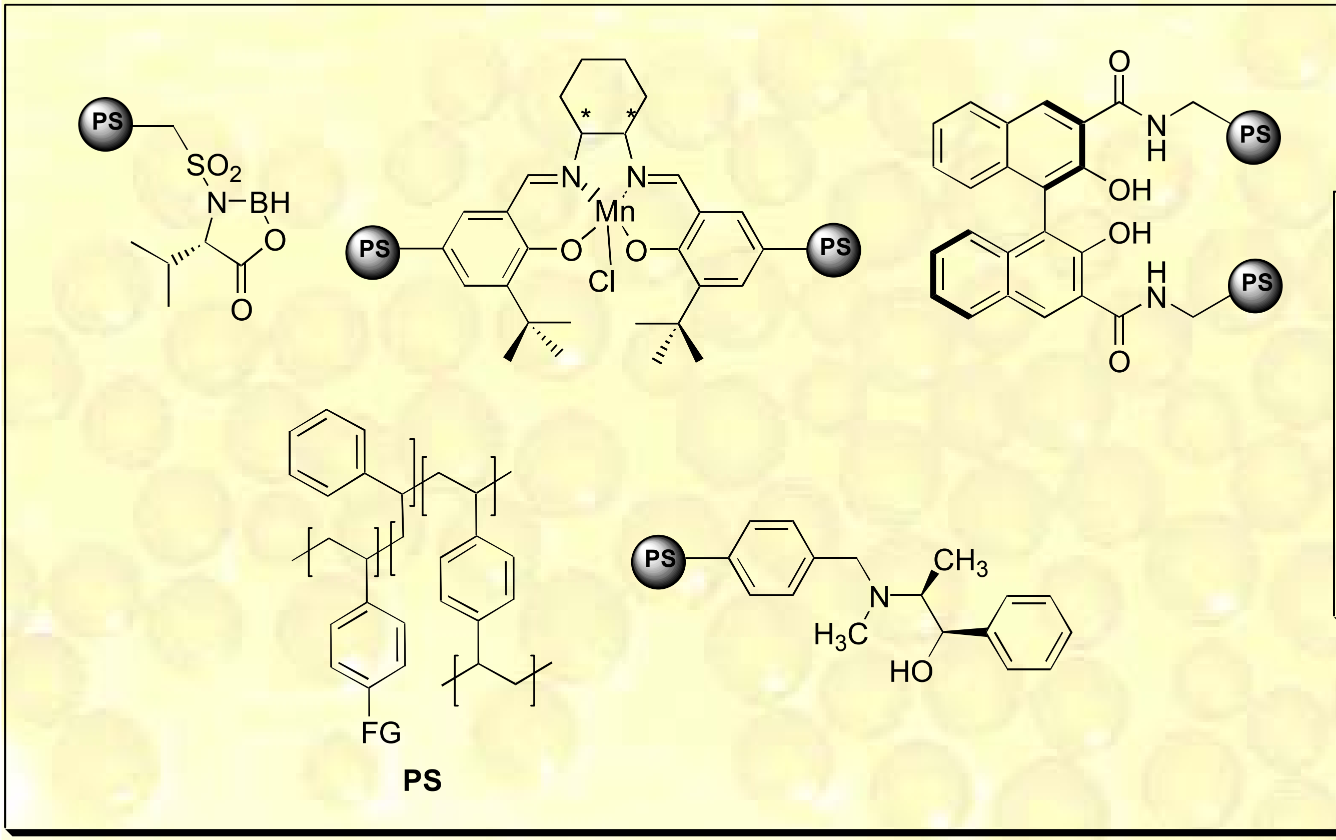


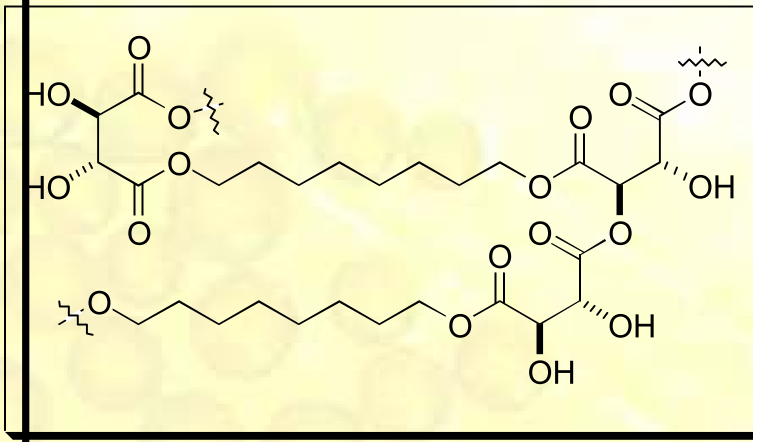




Polymers as catalysts

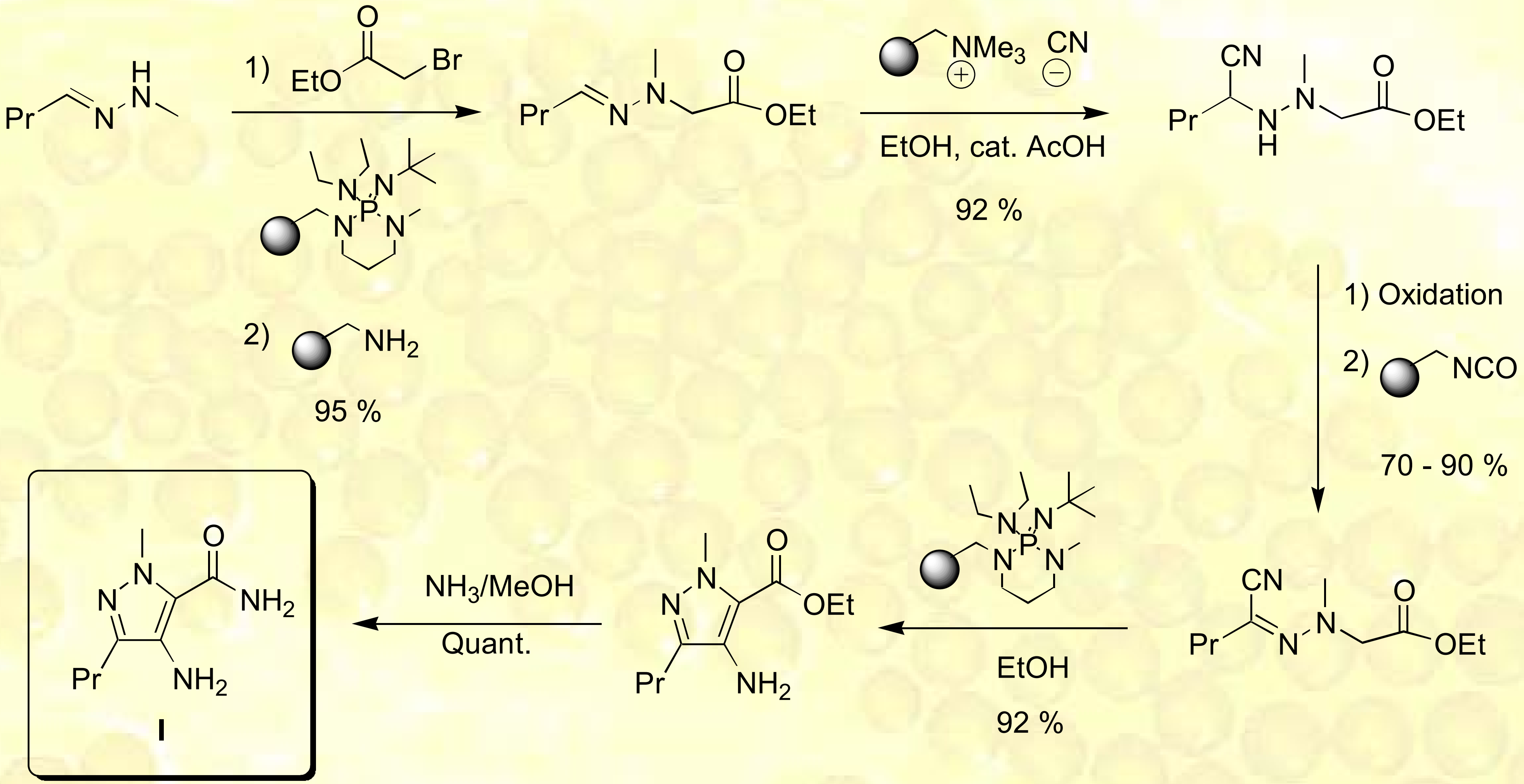
Asymmetric catalysts





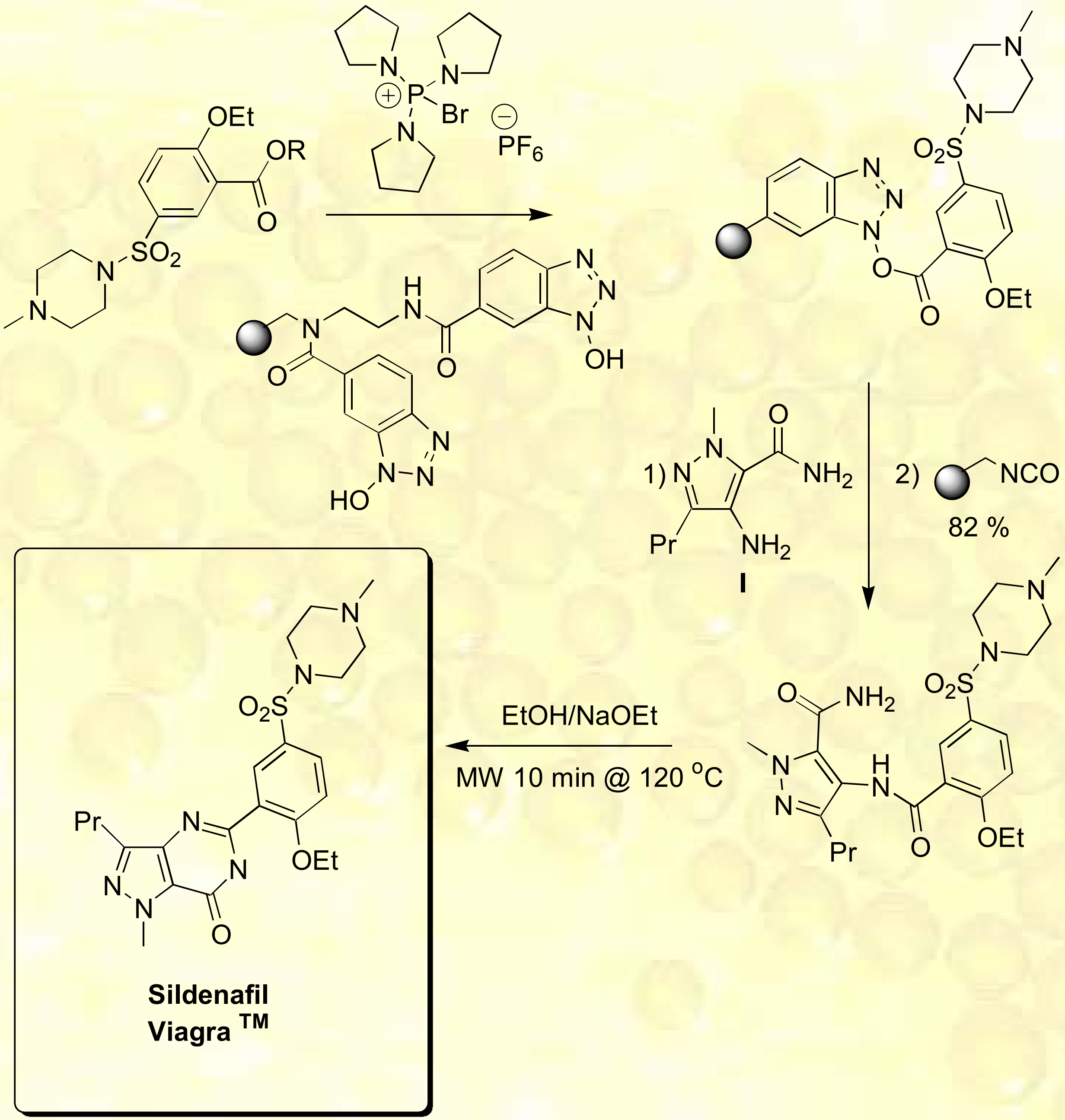
Polymer as reagents and catalysts

Total synthesis



Polymer as reagents and catalysts

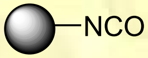
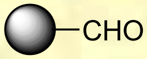
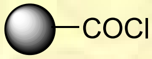
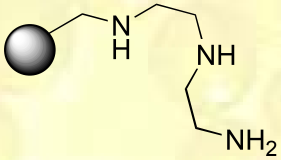
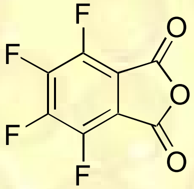
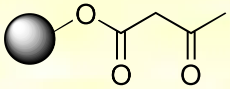
Total synthesis



Sildenafil
Viagra ™

Polymer supported reagents for purification

Scavengers for nucleophiles

Entry	Resin	Co-reagent	Reagent type quenched
1			1° and 2° amines
2			1° amines
3			1° and 2° amines
4			1° and 2° amines Anilines
5			1° amines selectively in the presence of 2° amines

Polymer supported reagents for purification

Scavengers for electrophiles

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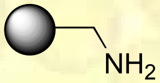
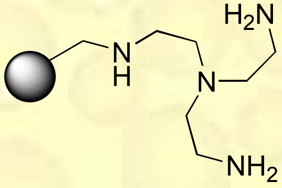
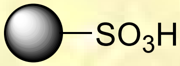
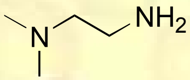
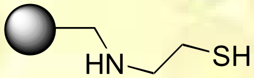
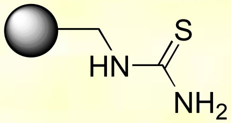
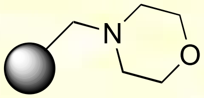
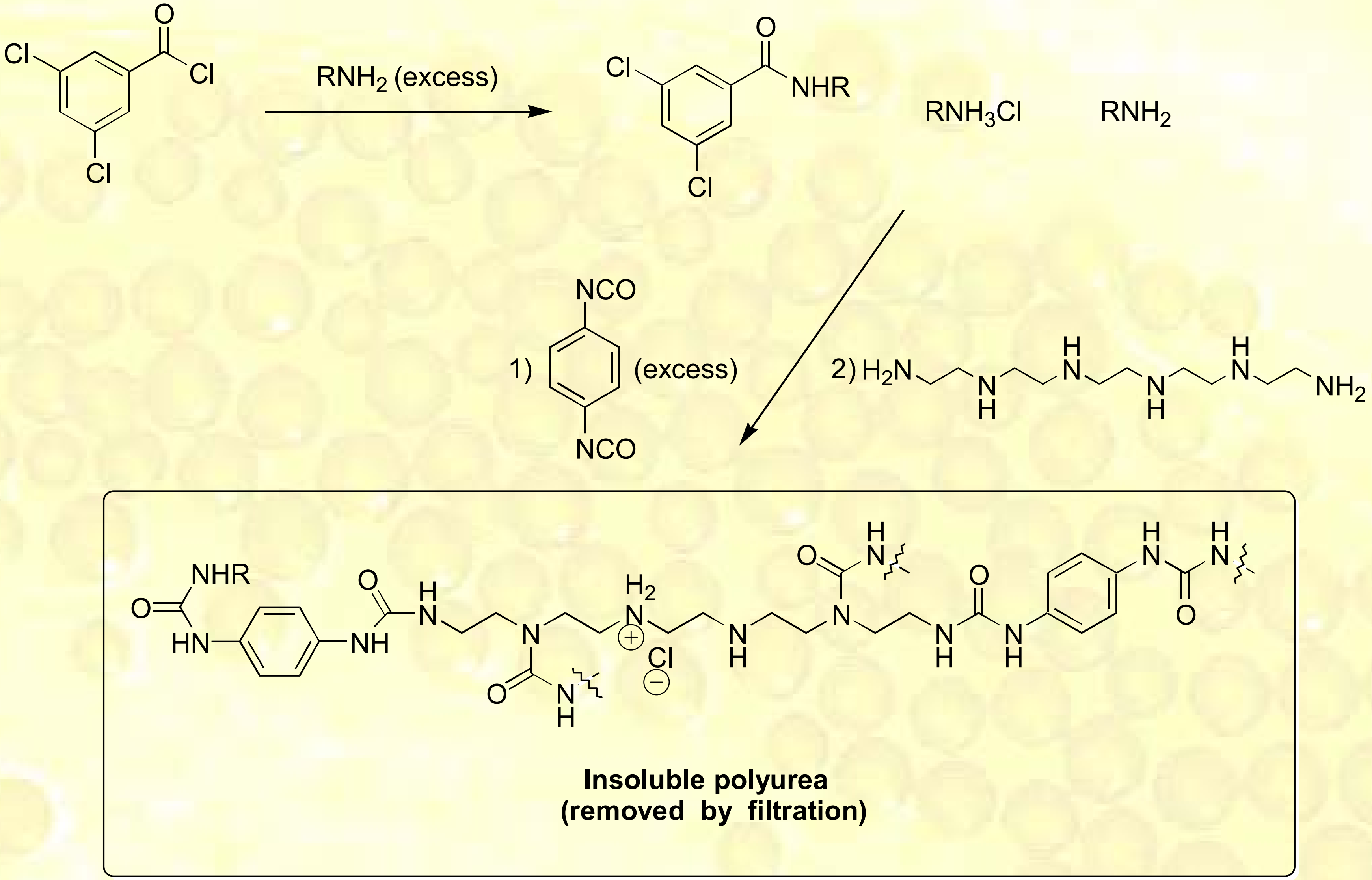
1			Isocyanates, acid chlorides, sulphonyl chlorides.
2			Isocyanates, acid chlorides, sulphonyl chlorides, aldehydes, alkyl chloroformates.
3			Isocyanates
4			Alkylating agents
5			α-haloketones
6			acids

Purification by polymerisation of impurities

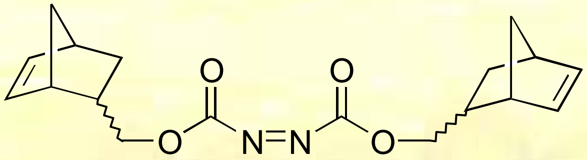
Polyureas



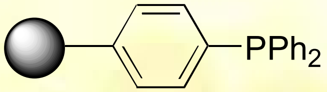
Insoluble polyurea
(removed by filtration)

Purification by polymerisation of impurities

ROMP



1



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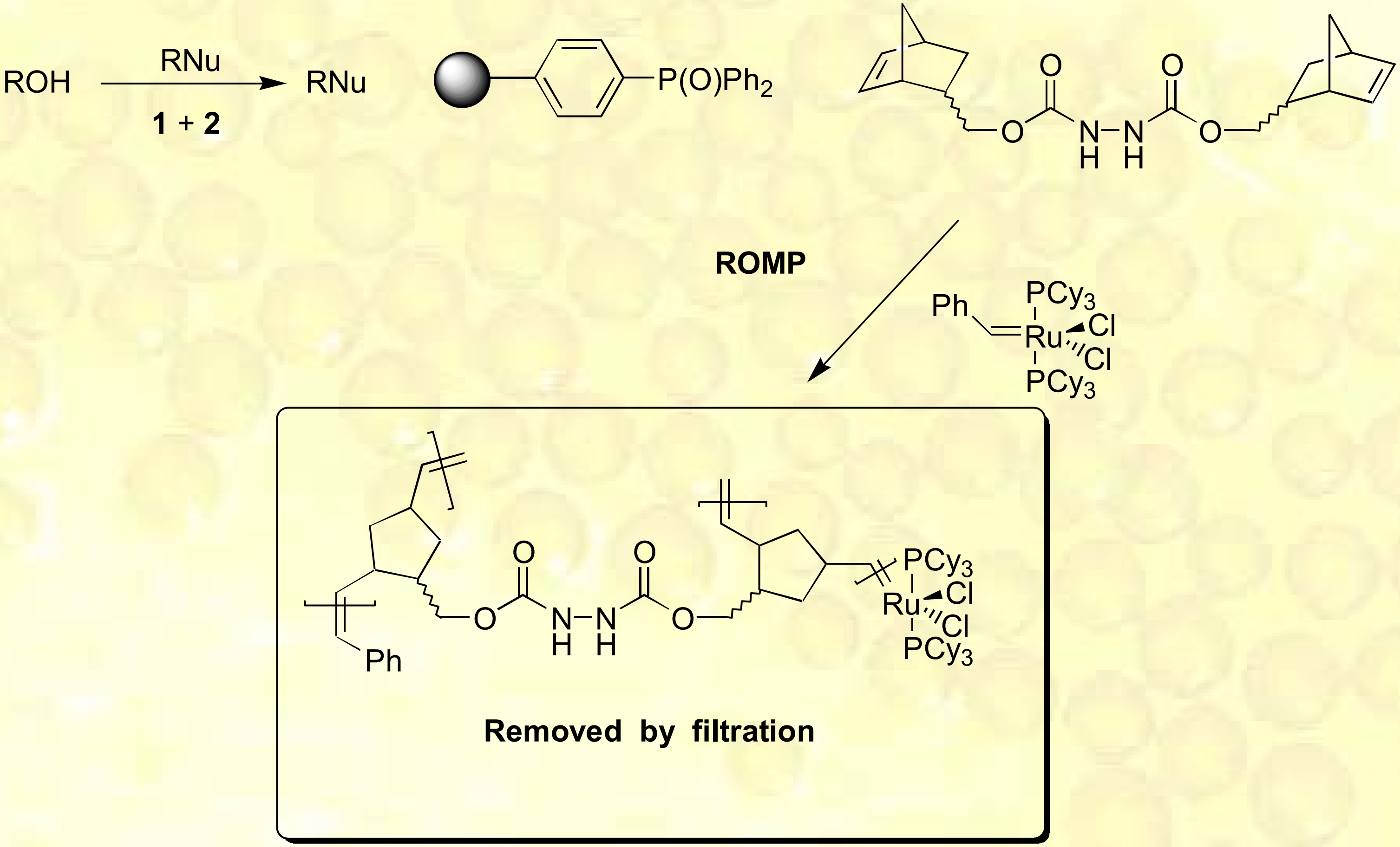
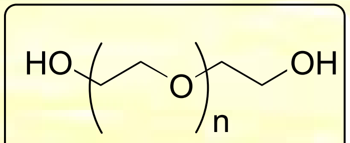


Removed by filtration

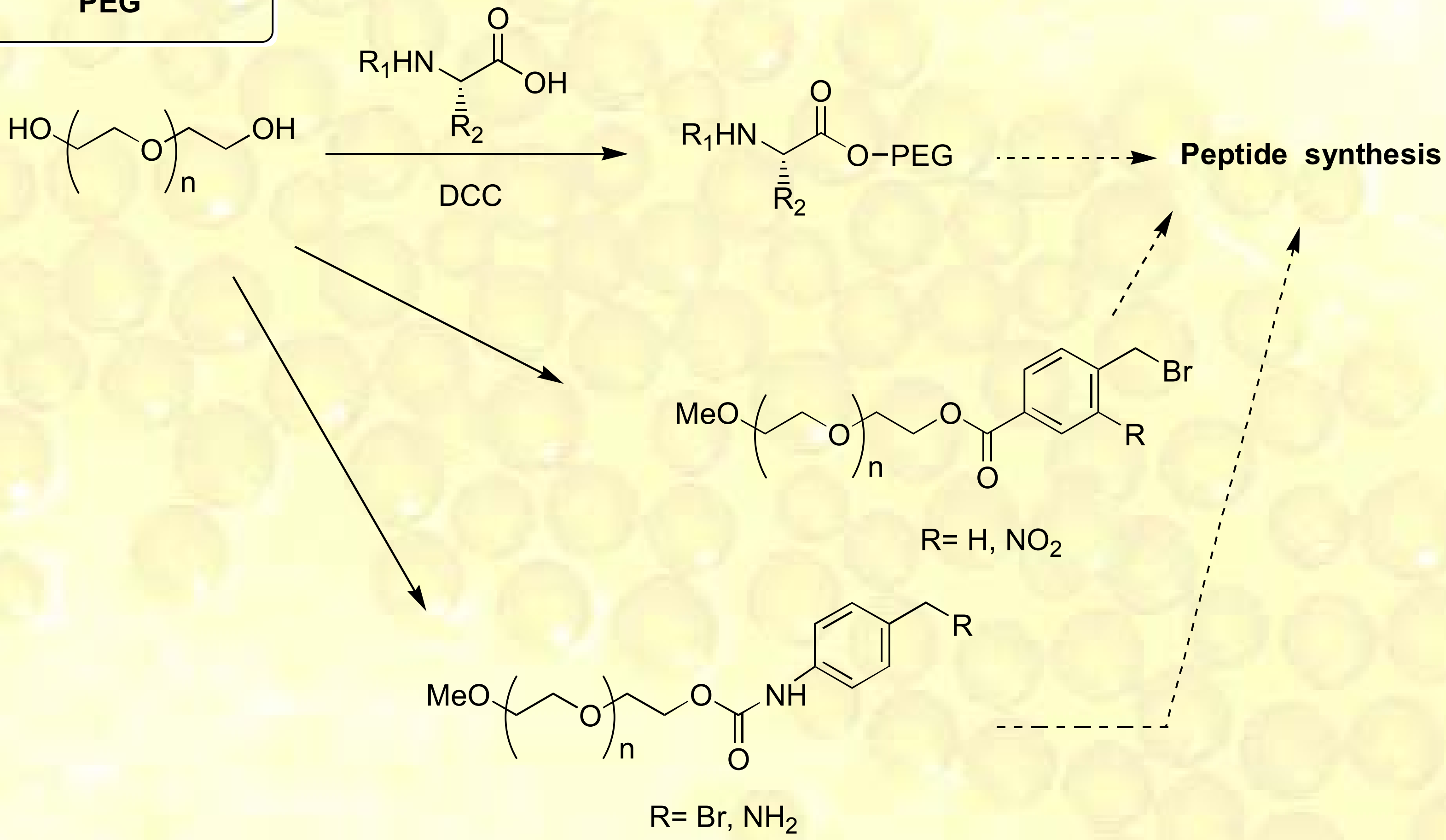
Soluble polymer supports

PEG



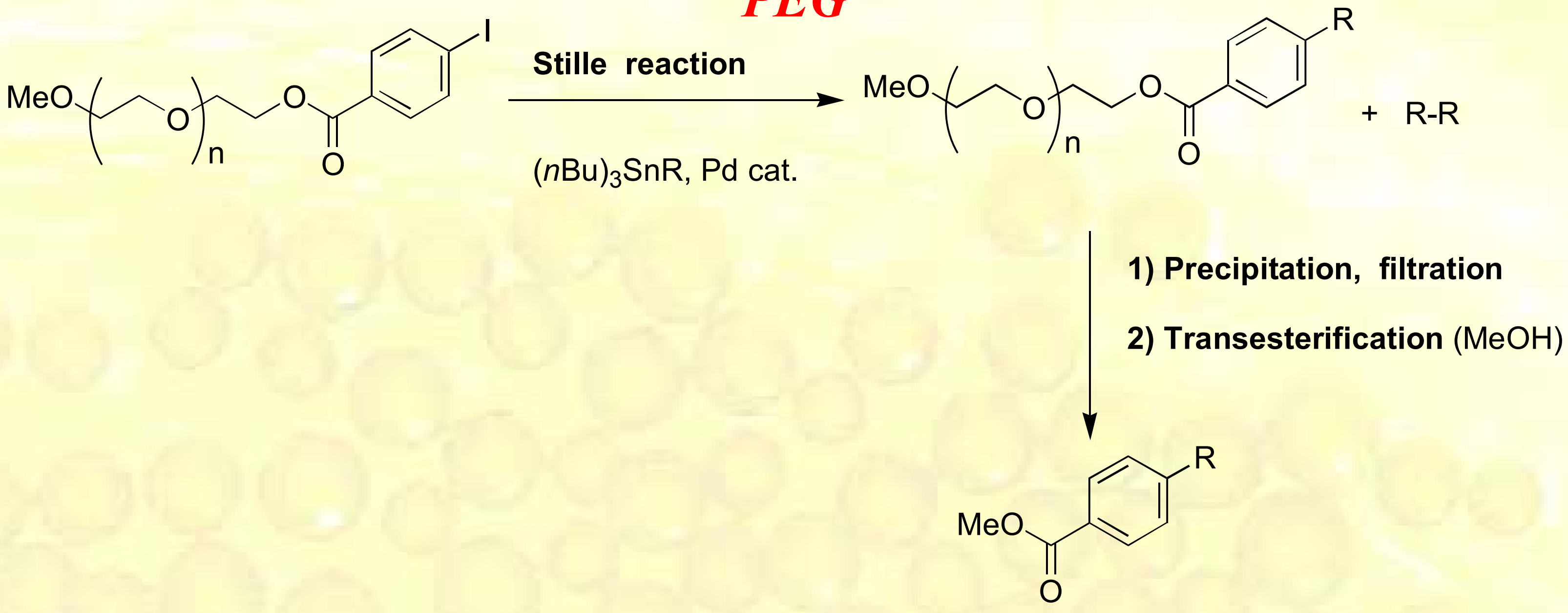
n=100 to 450

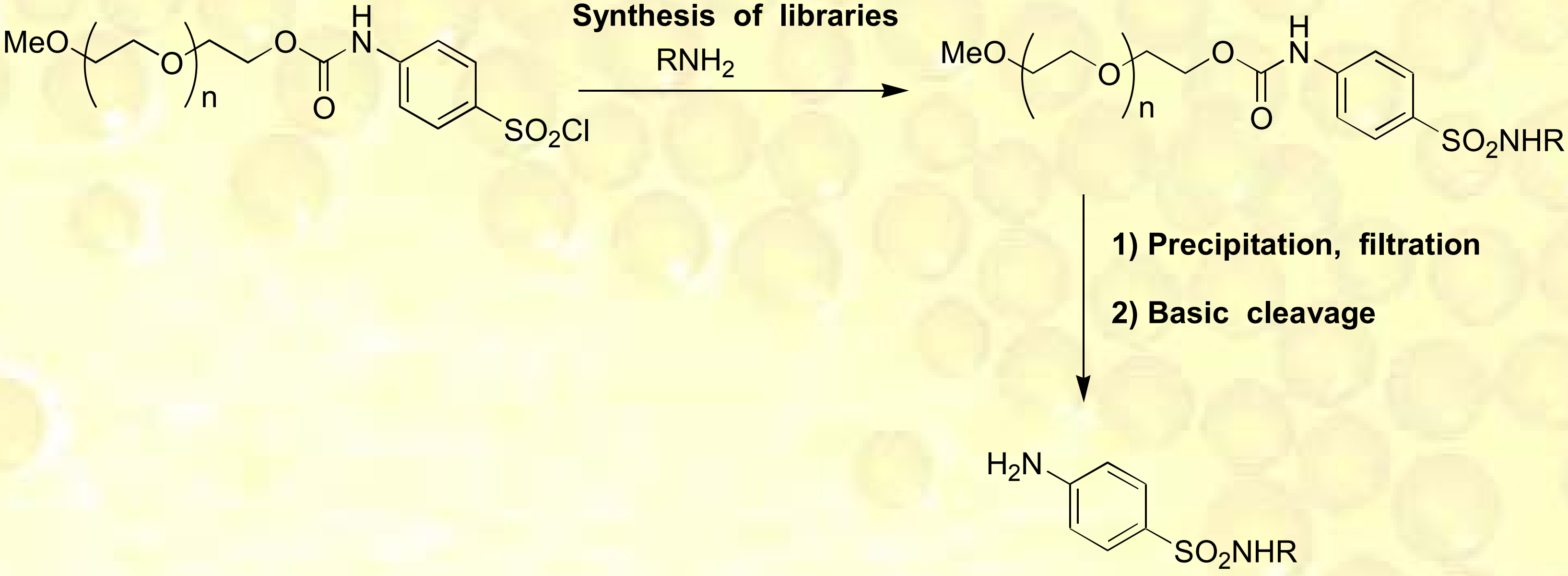
PEG



Soluble polymer supports

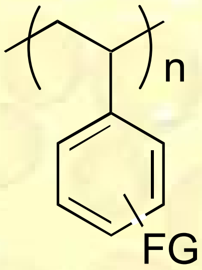
PEG





Soluble polymer supports

Other soluble supports



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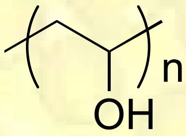
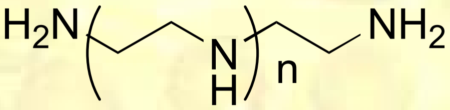
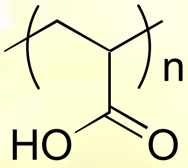


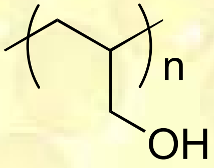
PVA



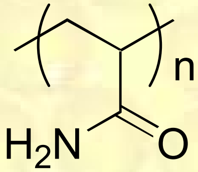
PEI



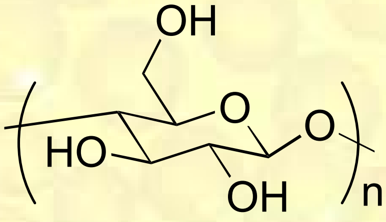
PAAc



PAA



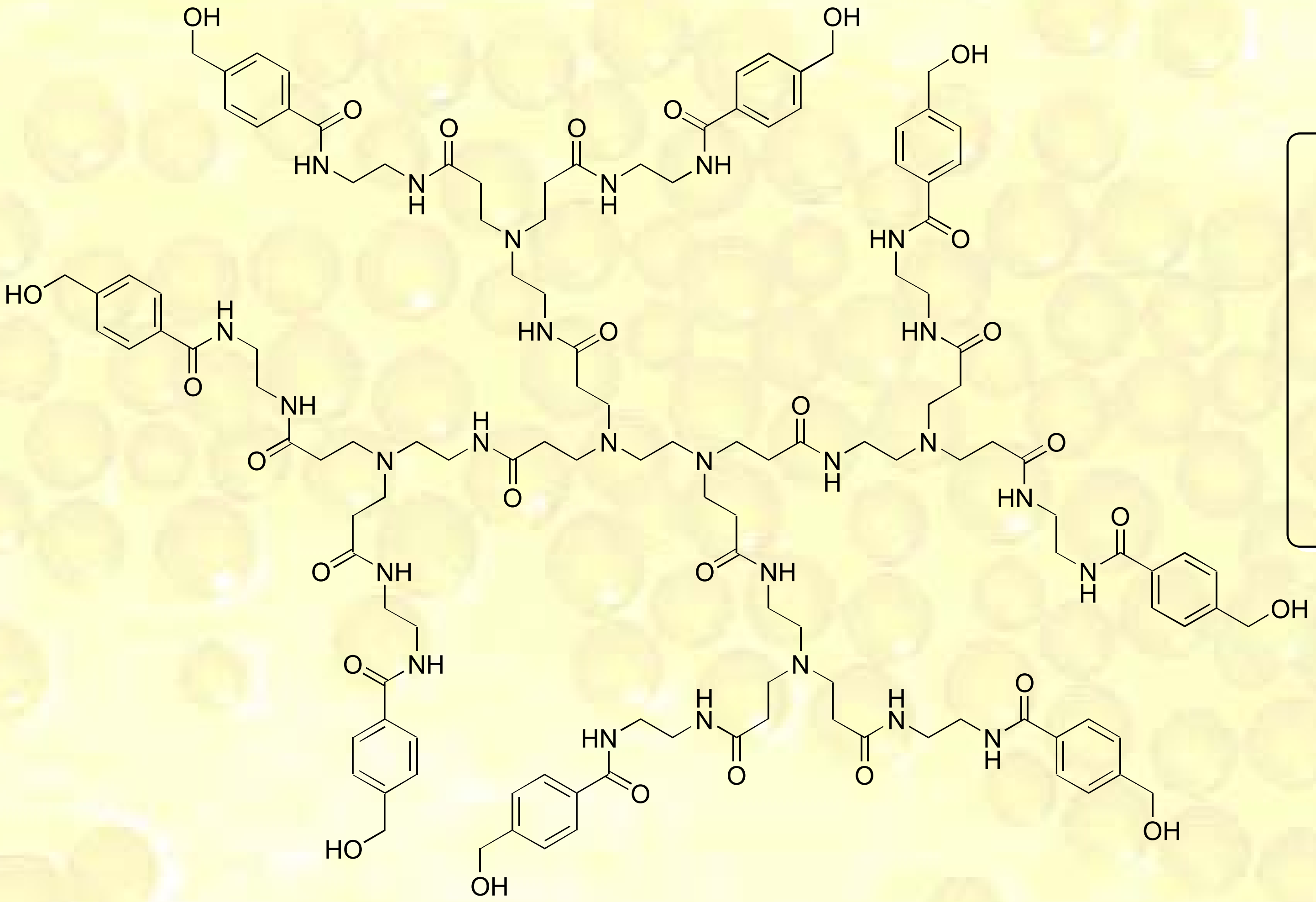
PAAm

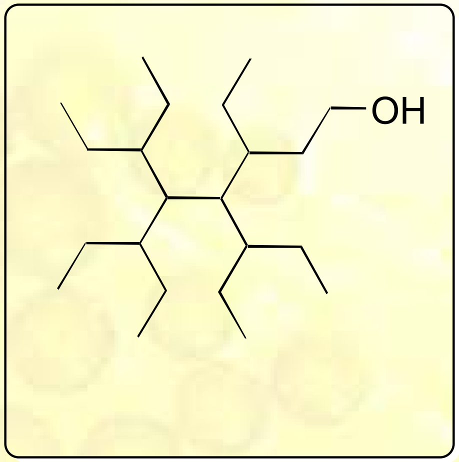


Cellulose

Soluble polymer supports

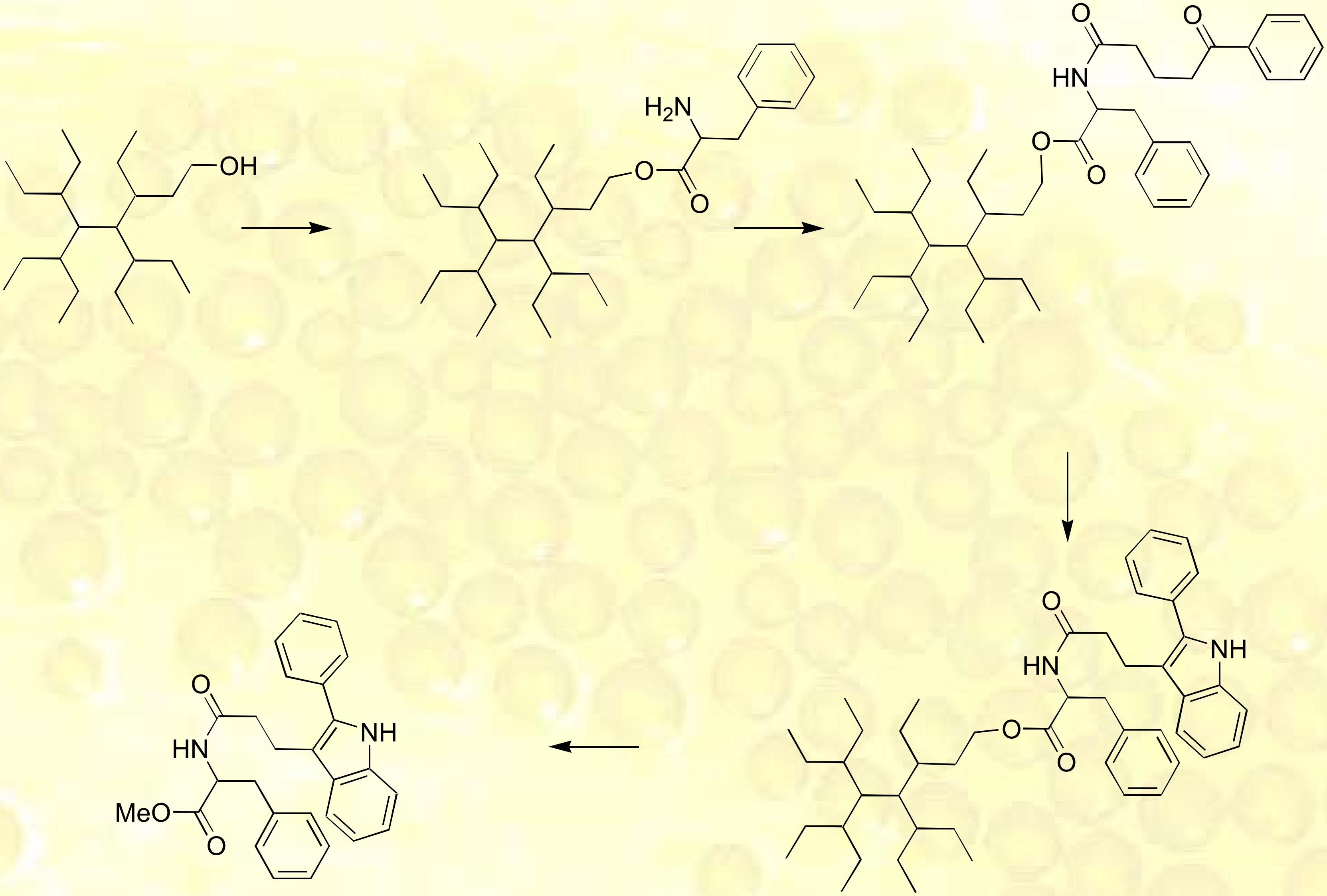
Dendrimer and hyperbranched supports





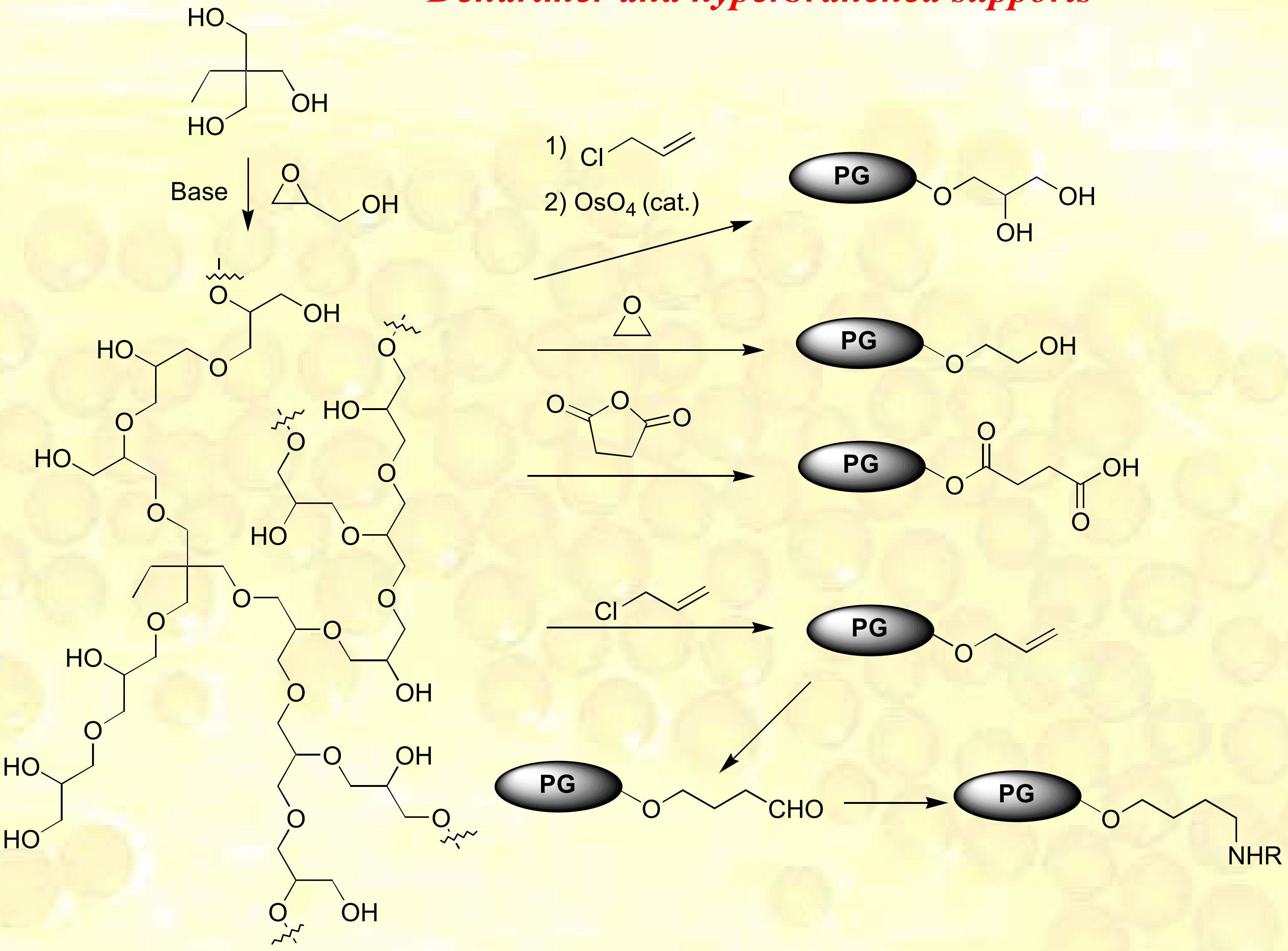
Soluble polymer supports

Dendrimer and hyperbranched supports



Soluble polymer supports

Dendrimer and hyperbranched supports



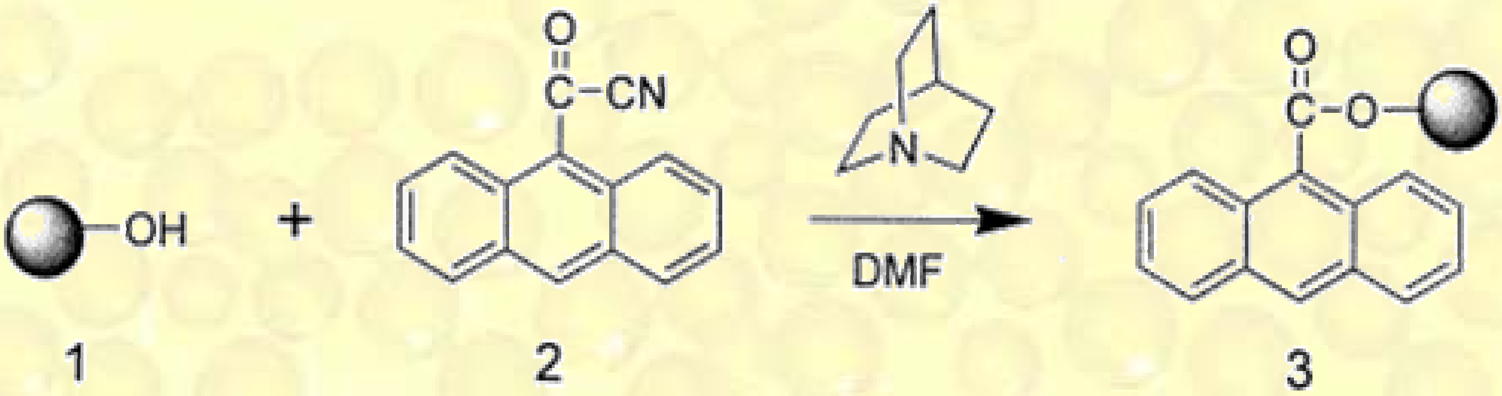
Hyperbranched Polyglycerol (PG)

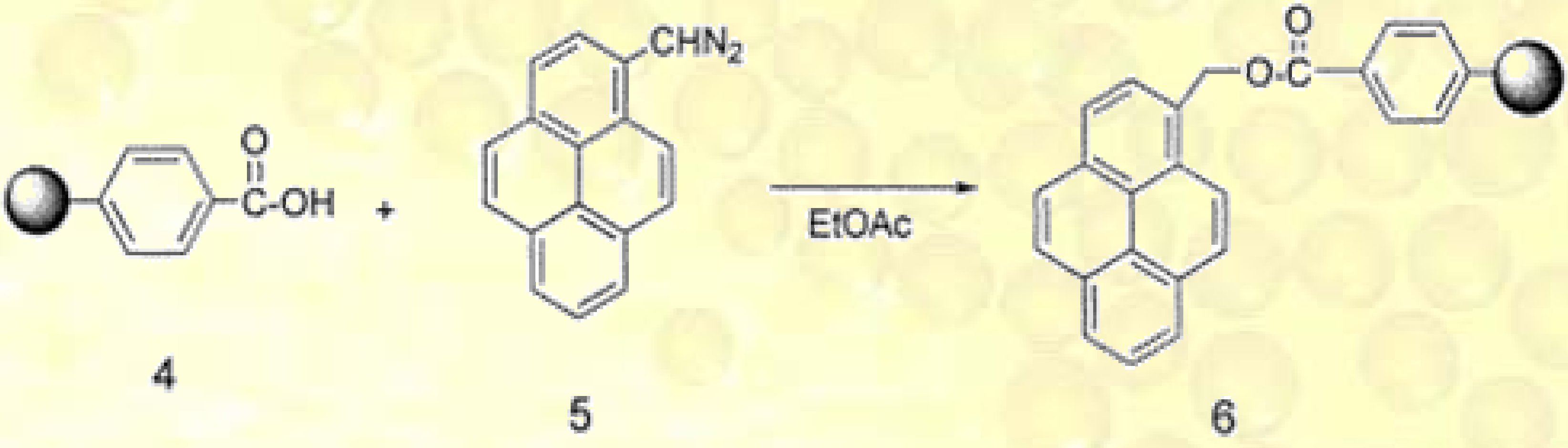
Lecture 5

- **On- and off-bead analysis**
  - Chemical
    - Microanalysis
    - Titration
  - Spectroscopic
    - UV
    - Fluorescence
    - IR
    - MS
    - NMR
  - Issues for Screening

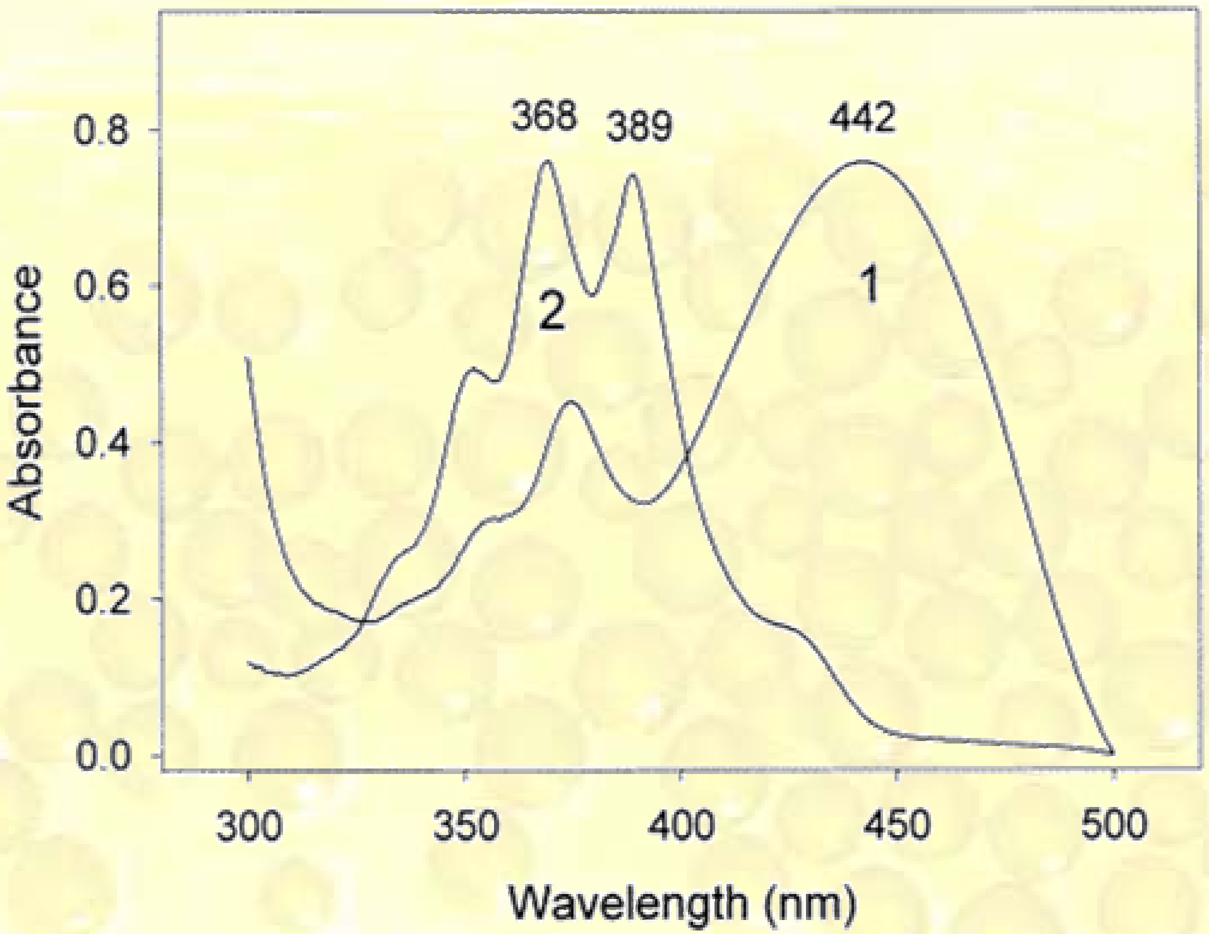
Quantitative UV Titration

The rapid determination of the absolute amount of hydroxyl or carboxyl groups directly on resin support is possible based on specific reactions between reagent 9-anthroylnitrile or 1-pyrenyldiazomethane (PDAM) and resin-bound hydroxyl or carboxyl groups. After the reaction, the remaining reagent molecules in the supernatant are quantitatively determined by UV-visible spectroscopy. The quantitation can be accomplished by analysing 2-10 mg of resin sample in 30-60 min down to 0.05 mmol/g of resin.



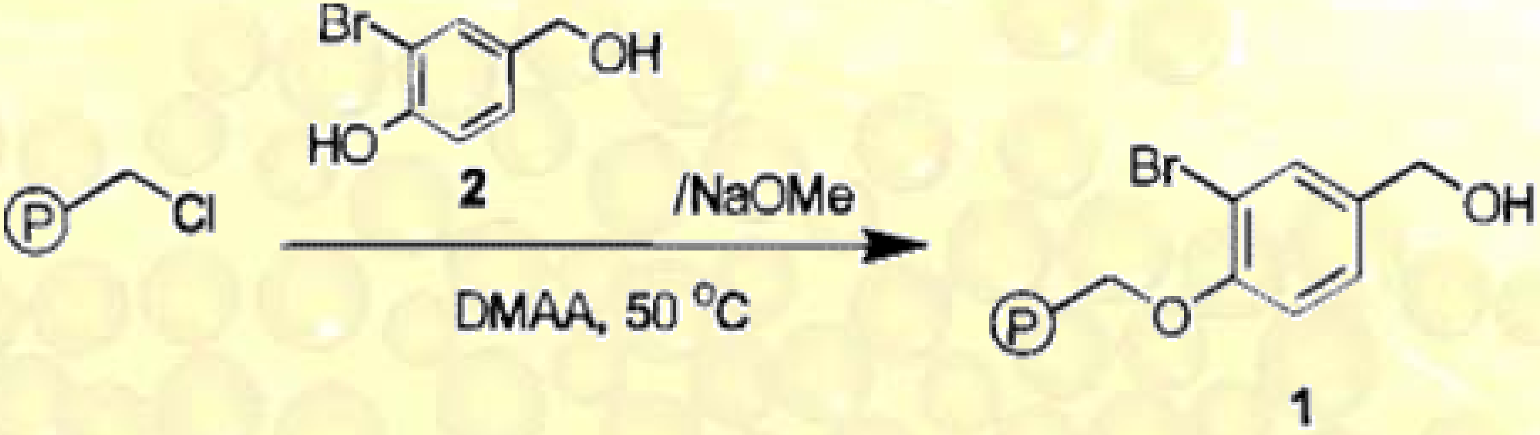


Quantitative UV Titration



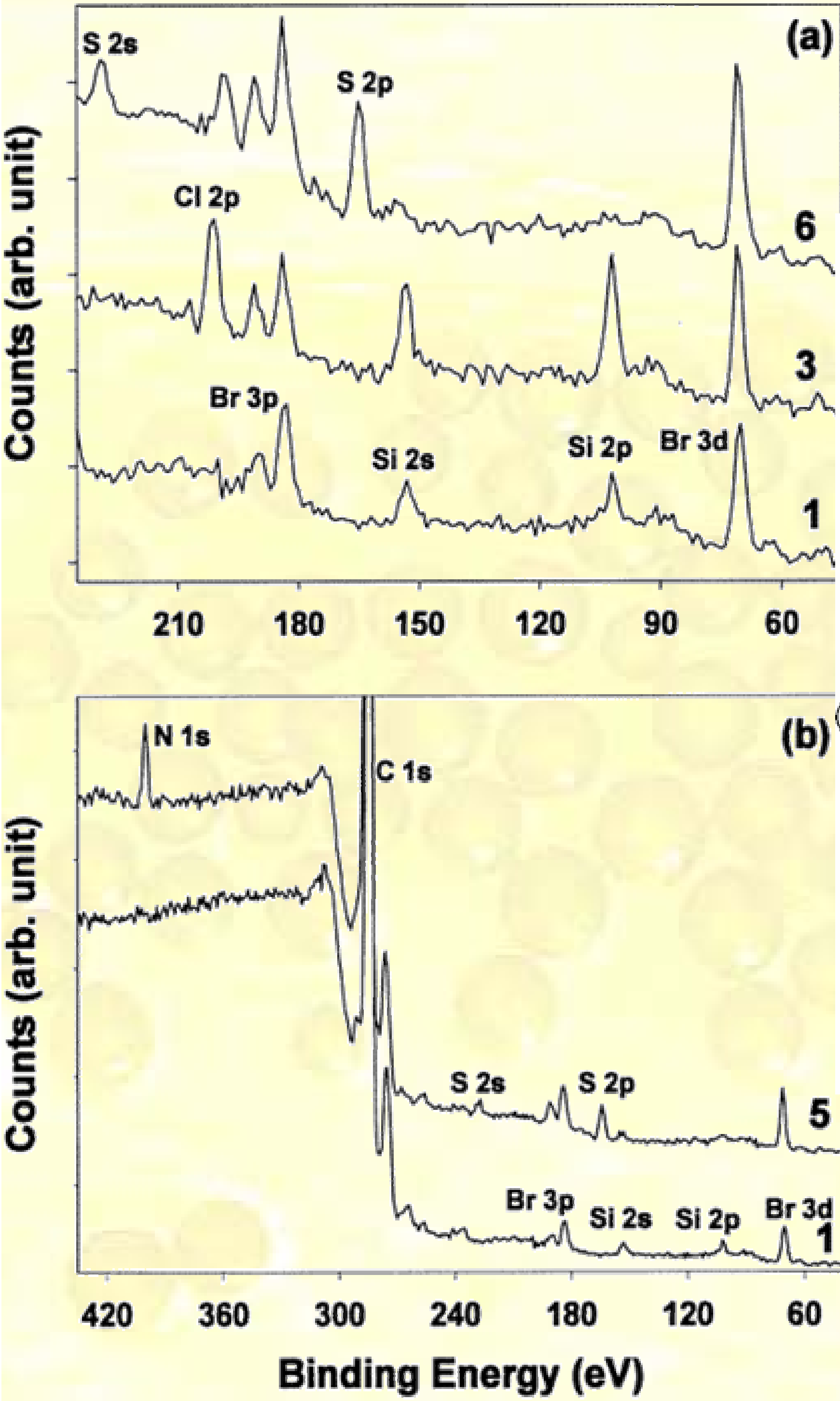
UV-visible absorption spectra of 9-anthroylnitrile and the 9-anthroylnitrile/quinuclidine adduct. Spectrum 1 is the UV absorption spectrum of 9-anthroylnitrile at a concentration of 1.46 × 10-4 M. Spectrum 2 is the absorption spectrum of the 9-anthroylnitrile/quinuclidine adduct. The concentrations of 9-anthroylnitrile and quinuclidine were 1.46 × 10-4 and 5.25 × 10-4 M.

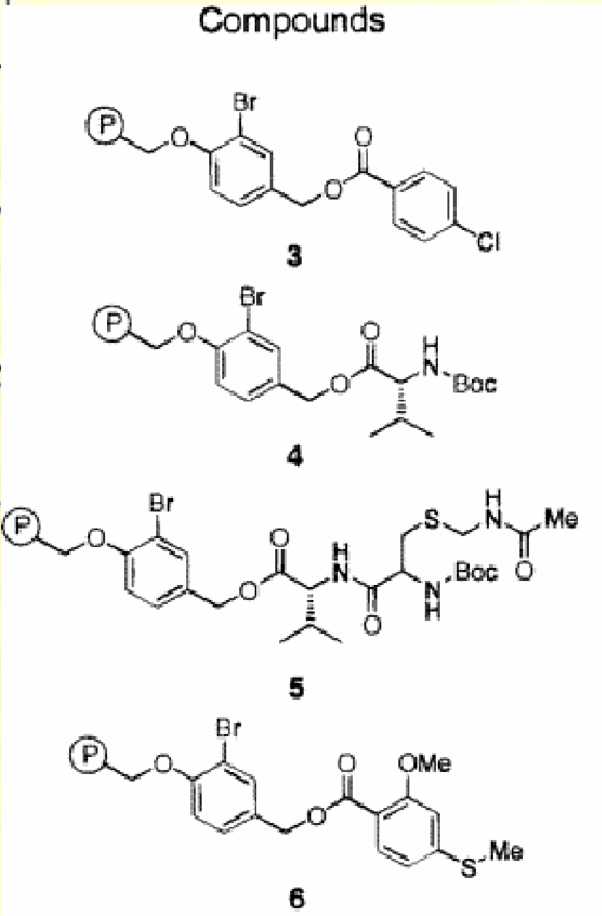
X-ray Photoelectron Spectroscopy



Ⓟ = polystyrene-divinyl benzene

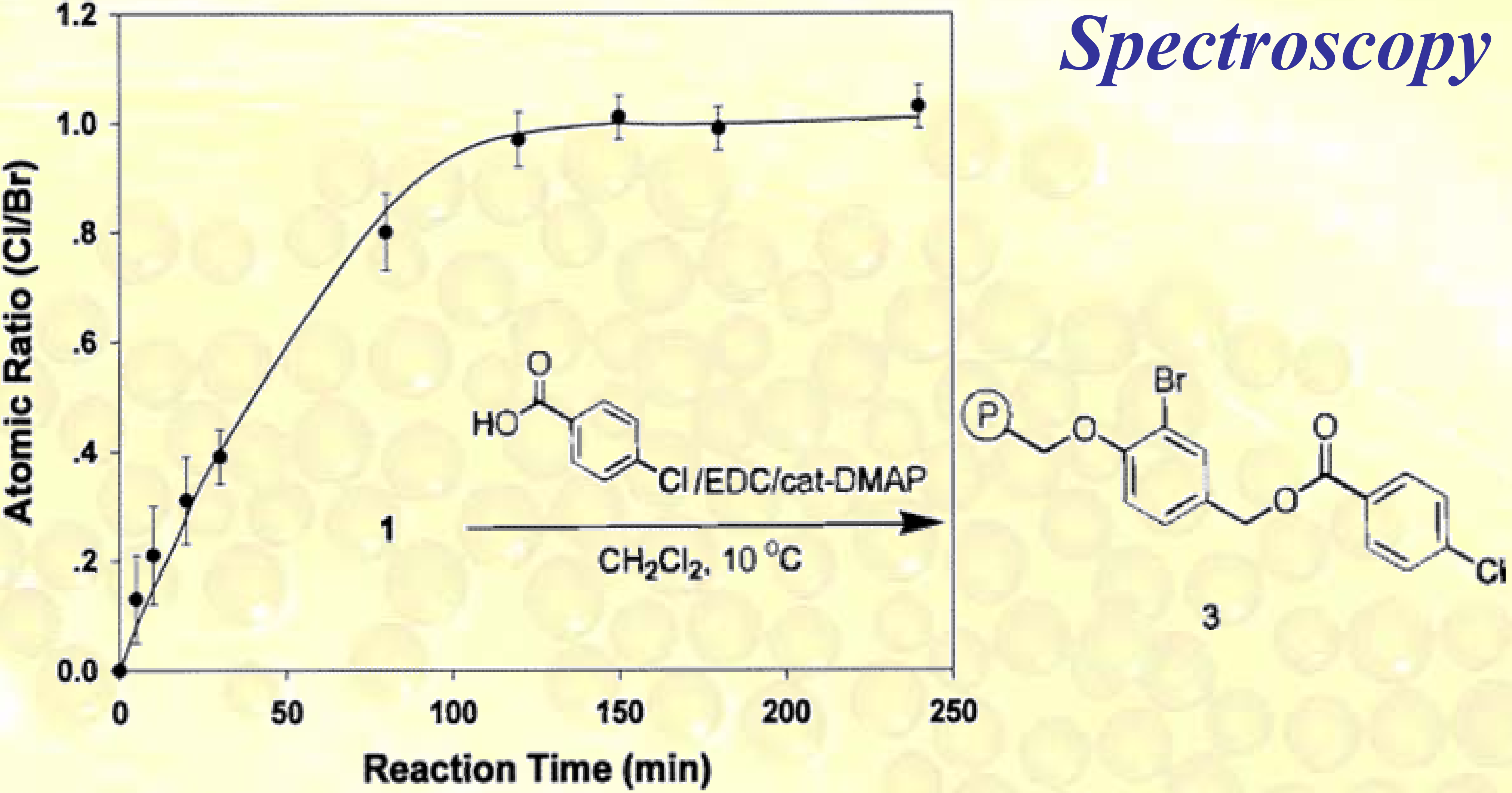
X-ray Photoelectron Spectroscopy





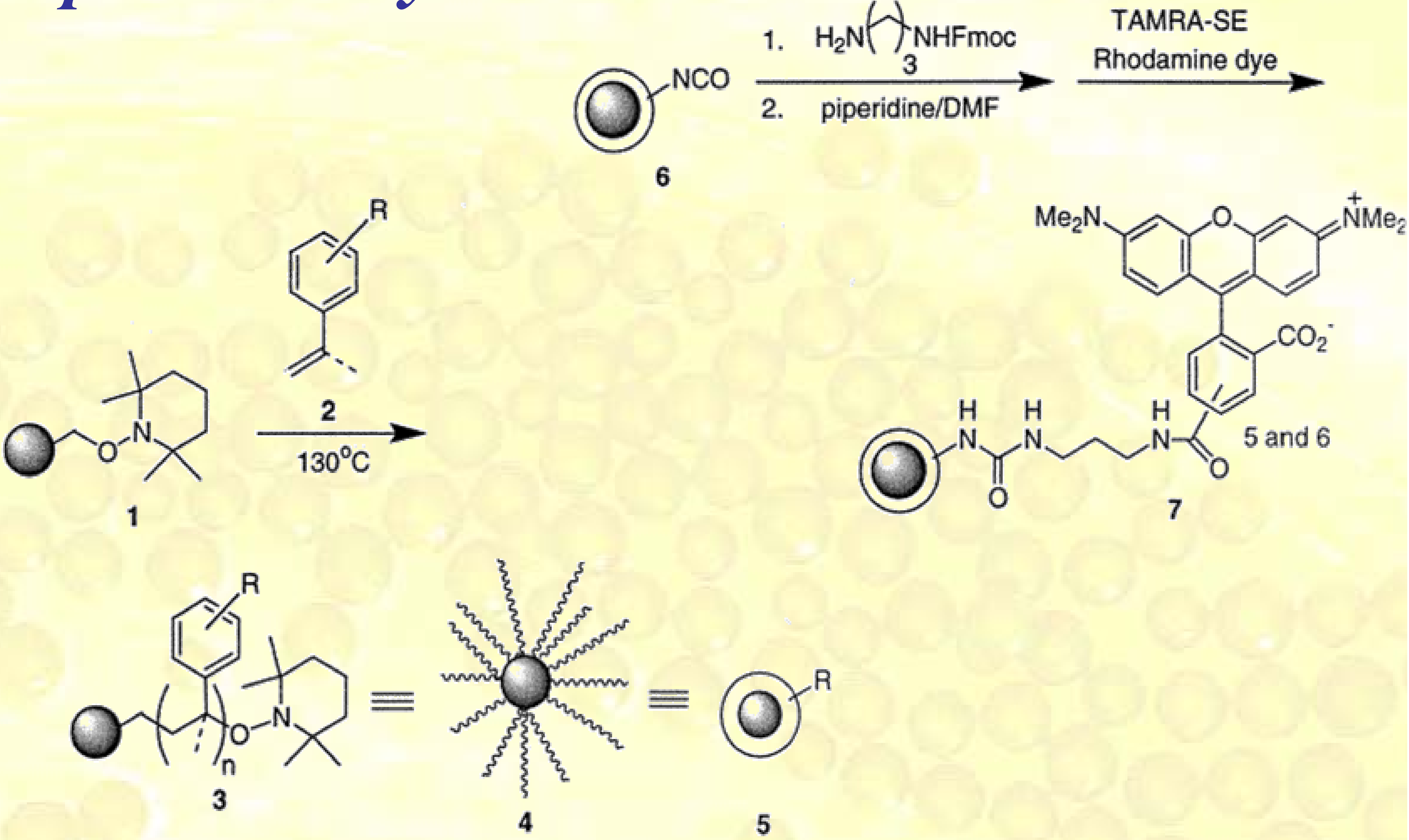
X-ray photoelectron survey spectra for resins 1, 3, 5, and 6. The elements in the polymer-bound compounds can be readily identified by determining the binding energies of the photoelectron peaks.

X-ray Photoelectron Spectroscopy

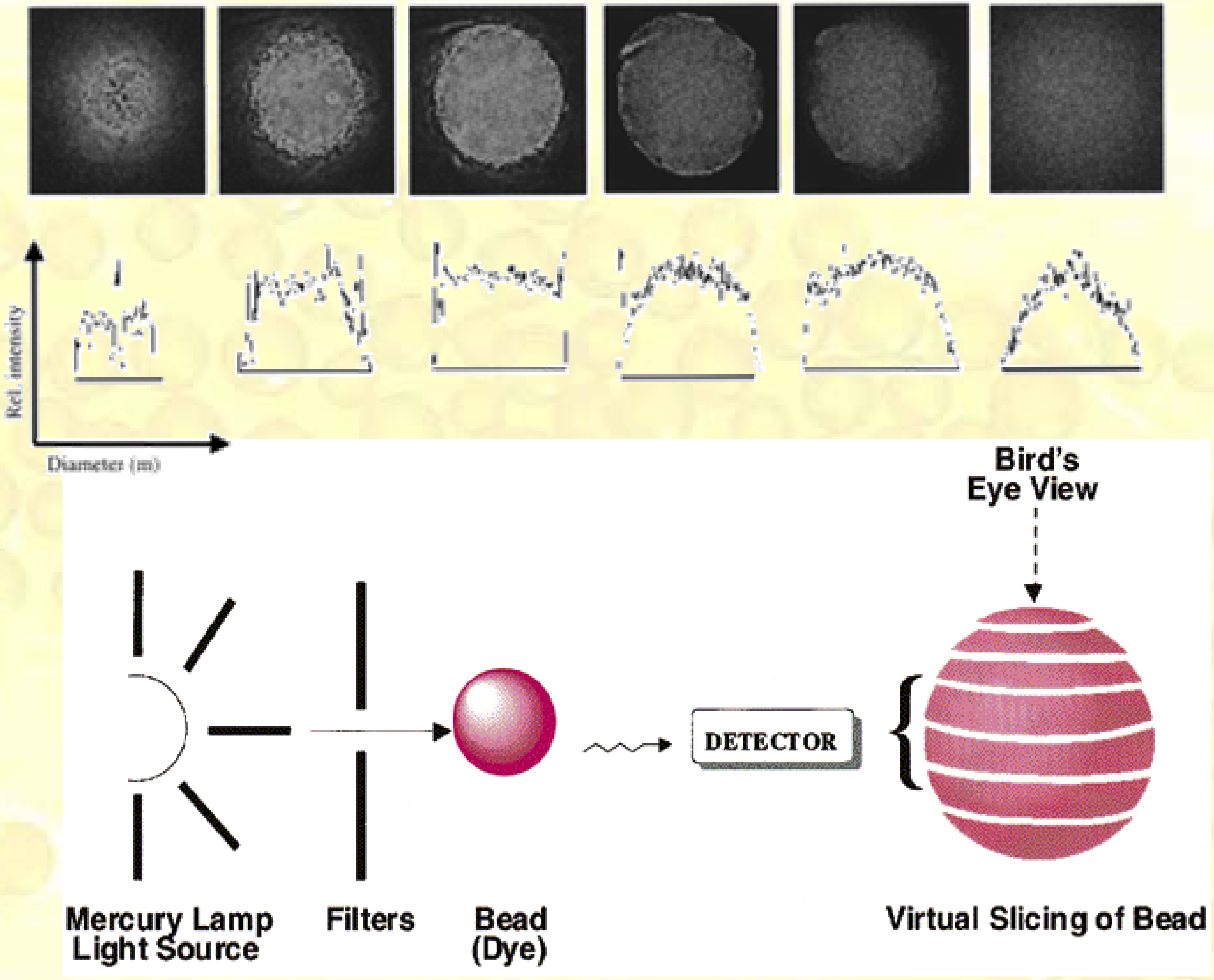


Reaction progress. The XP spectra were taken from resin 3 at 0, 5, 10, 20, 30, 50, and 120 min after the initiation of esterification. The full formation of 3 was indicated by the stoichiometric atomic ratio of 1.

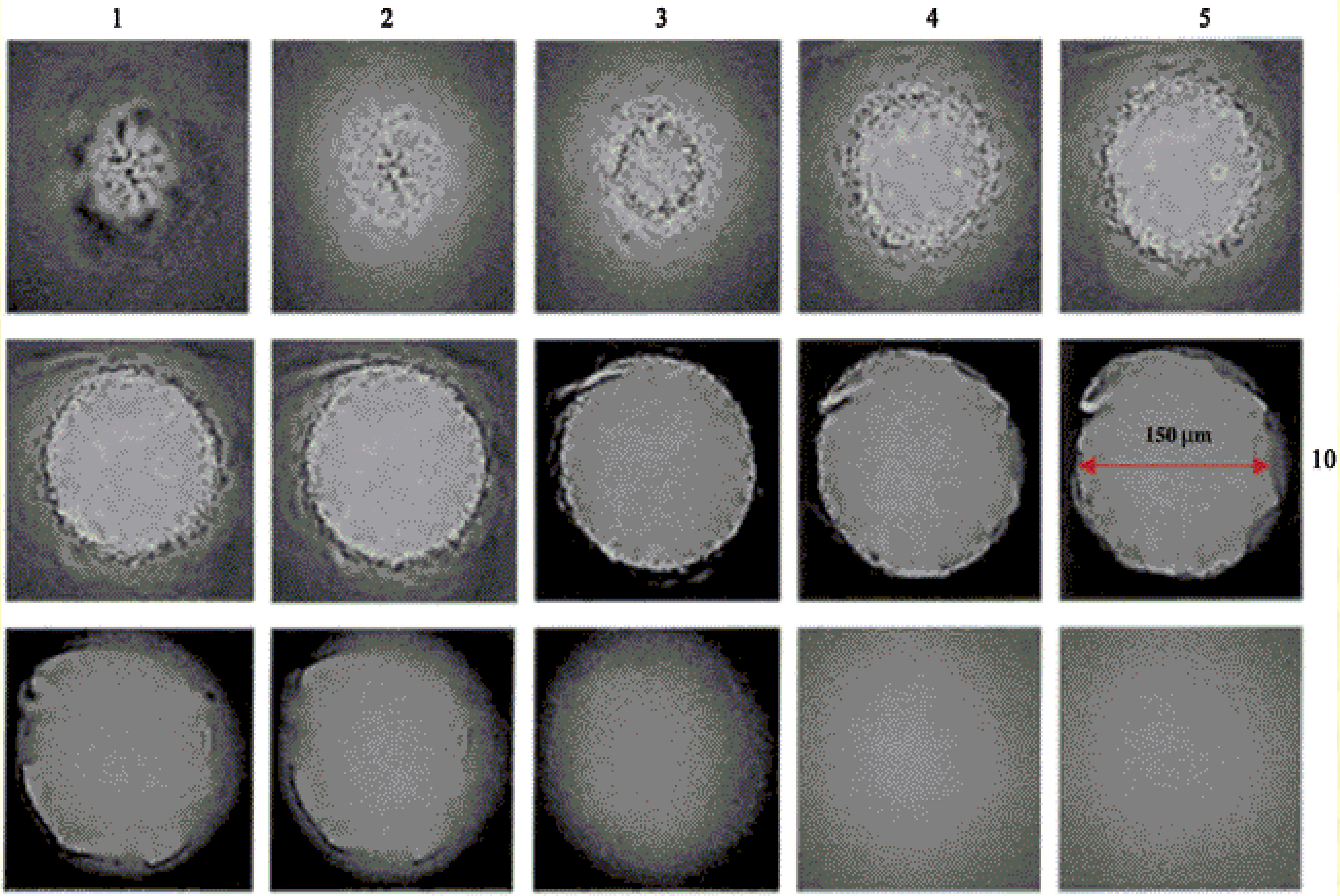
Optical Analysis



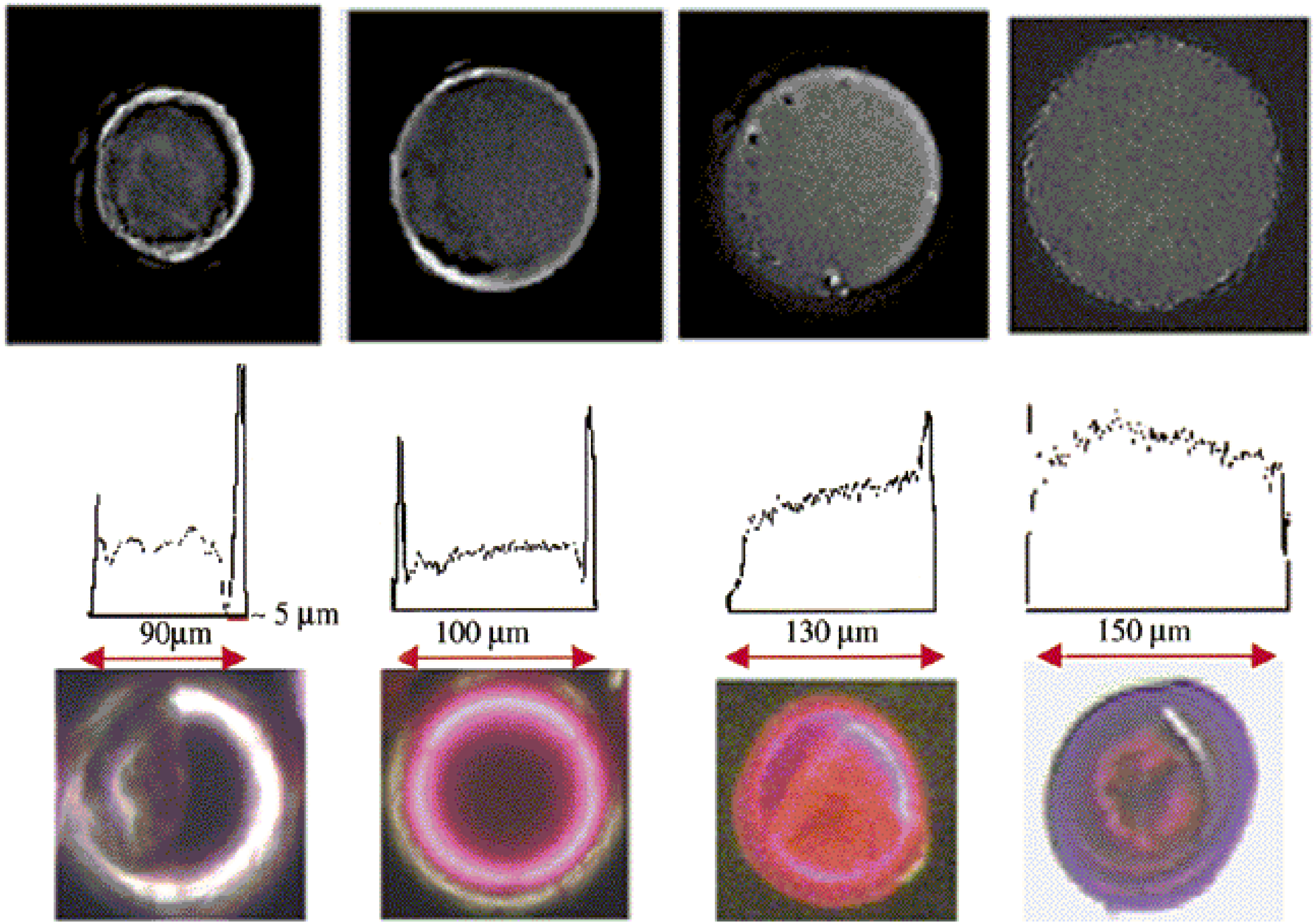
Optical Analysis



Optical Analysis



Optical Analysis

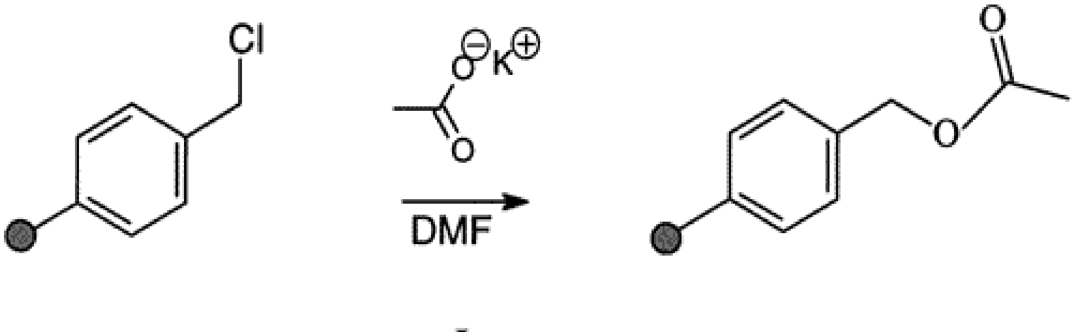


IR

- **On-bead**
  - Gel state
  - Solid state
  - Single bead
  - Reaction monitoring
  - Spatially addressable (FTIR microscope)

- **Off-bead**
  - Identical to solution phase

Single Bead FTIR



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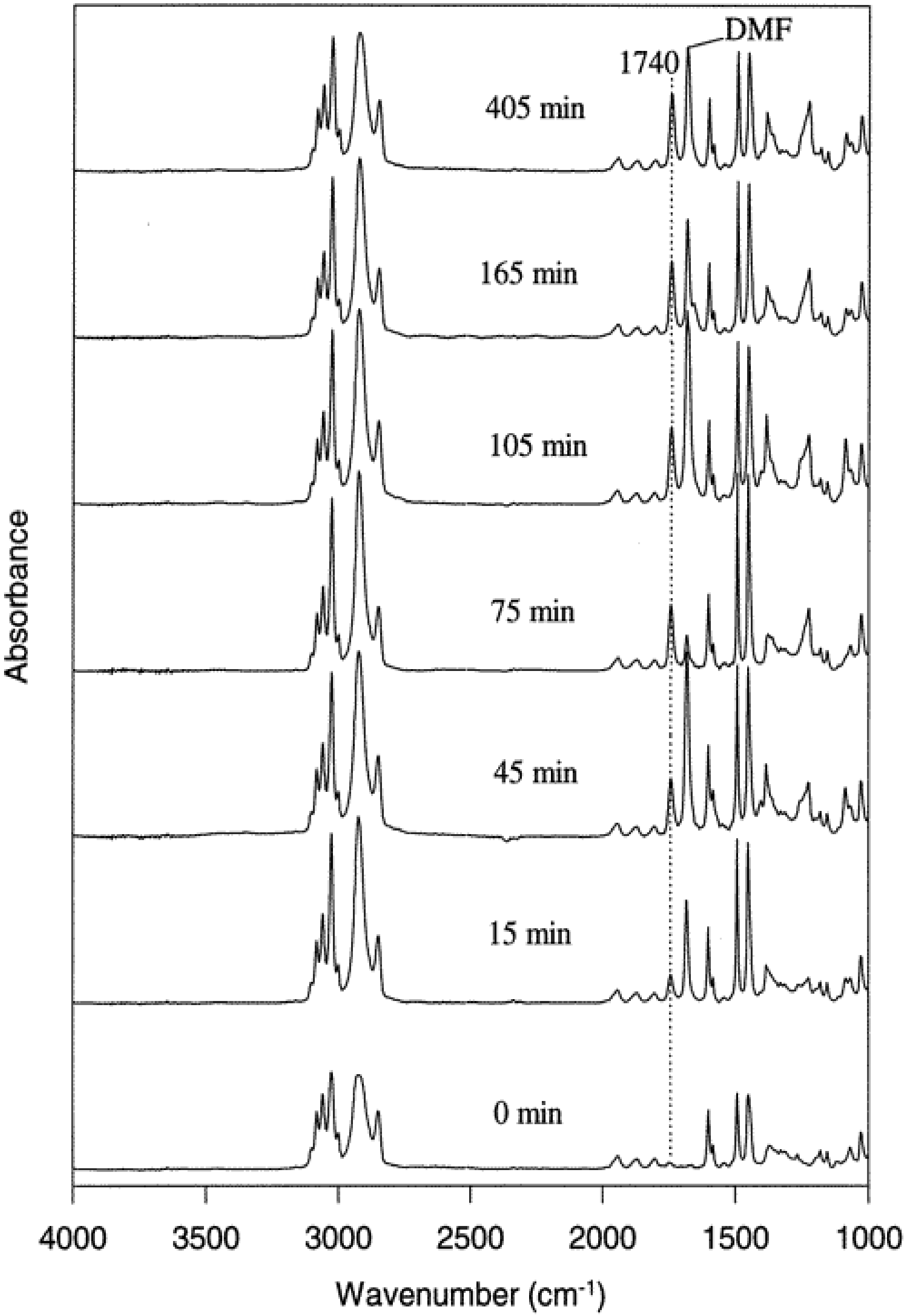
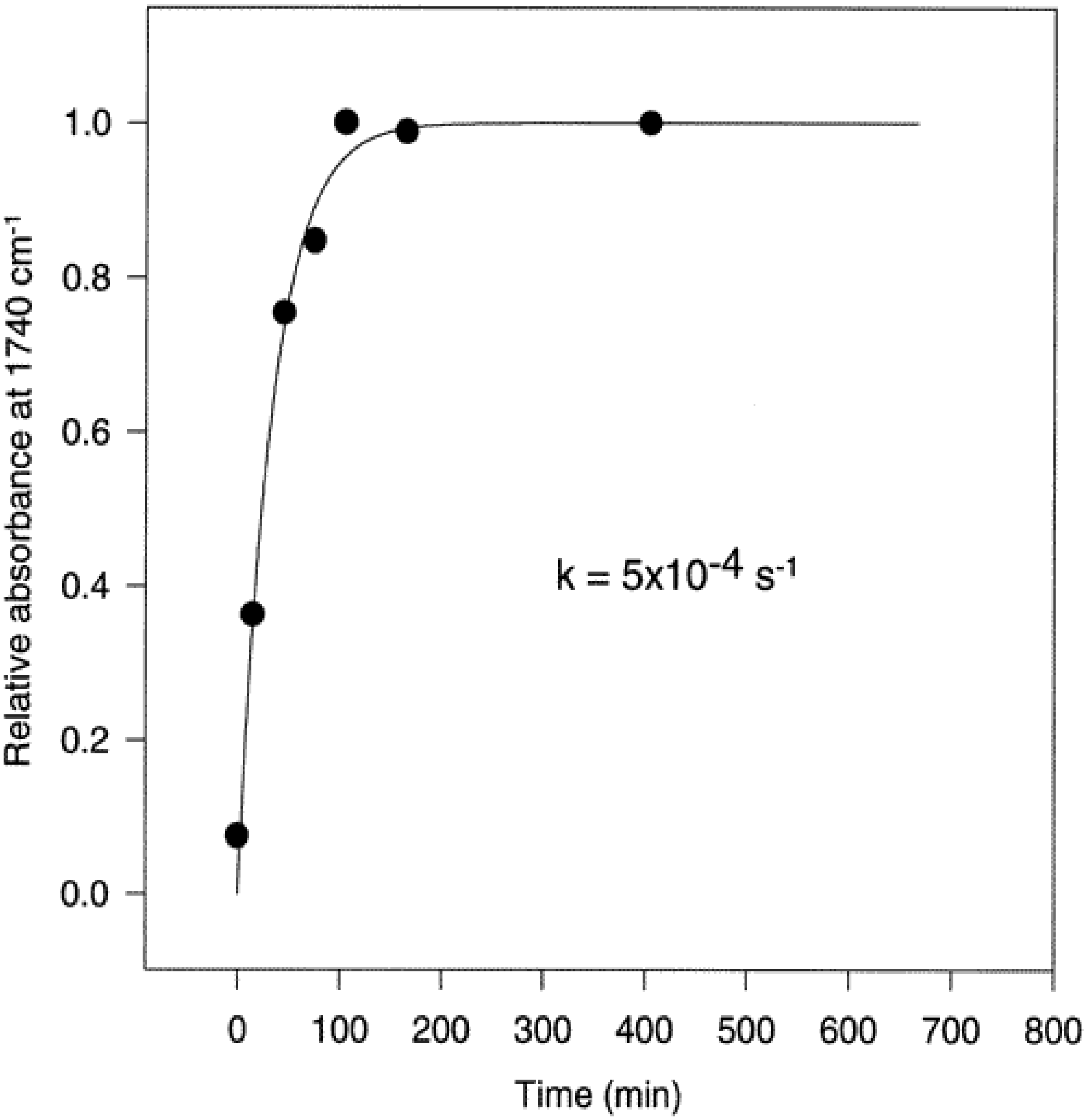


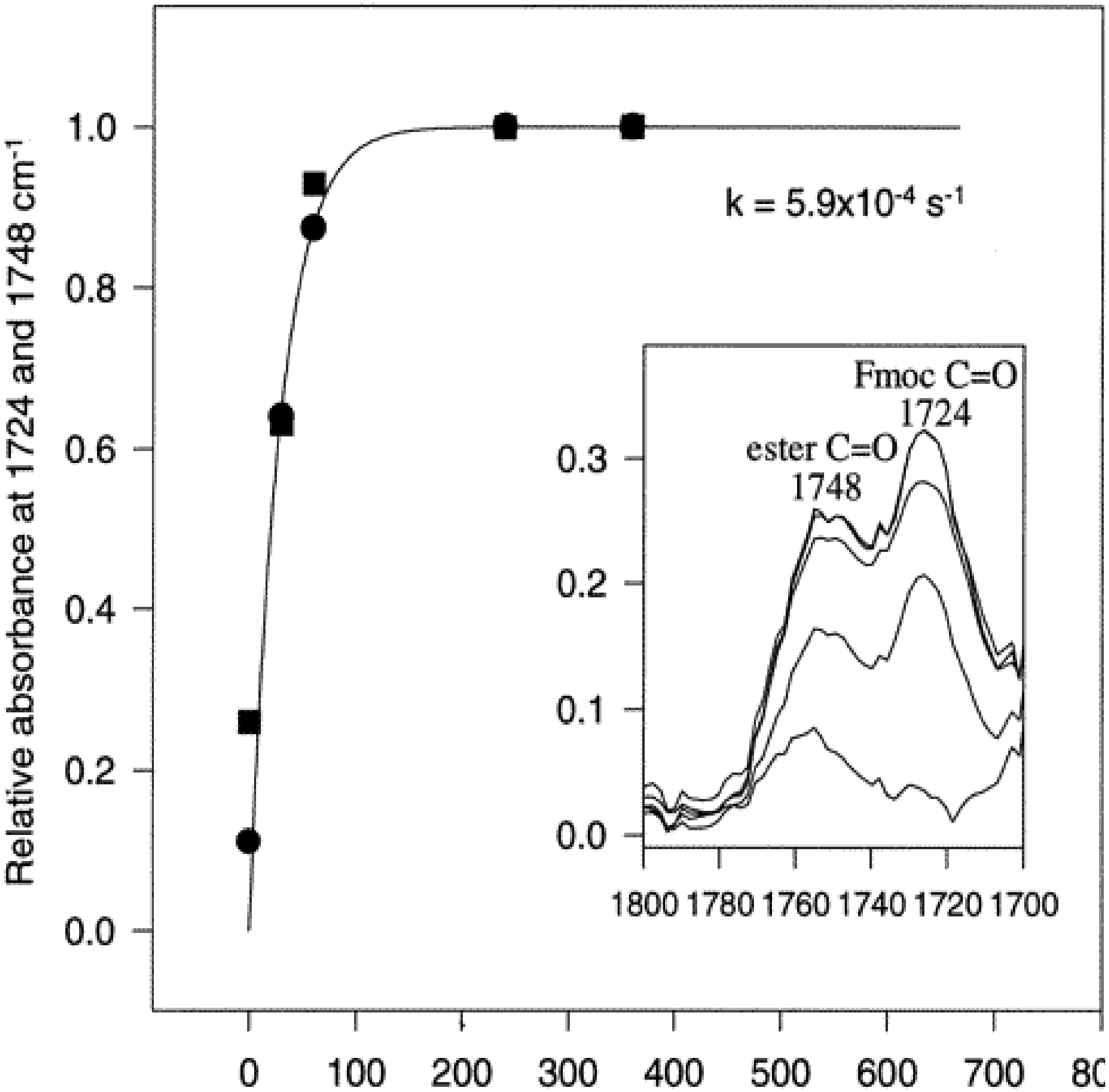
IR spectra from a single bead taken at specified times during the course of reaction I. The carbonyl peak at 1740 cm-1 is highlighted with the dotted line. The peak at 1658 cm-1 is from residual solvent DMF. The irregular intensity of this peak may be due to the insufficient drying and the different solvent-adsorbing property of the individual bead.

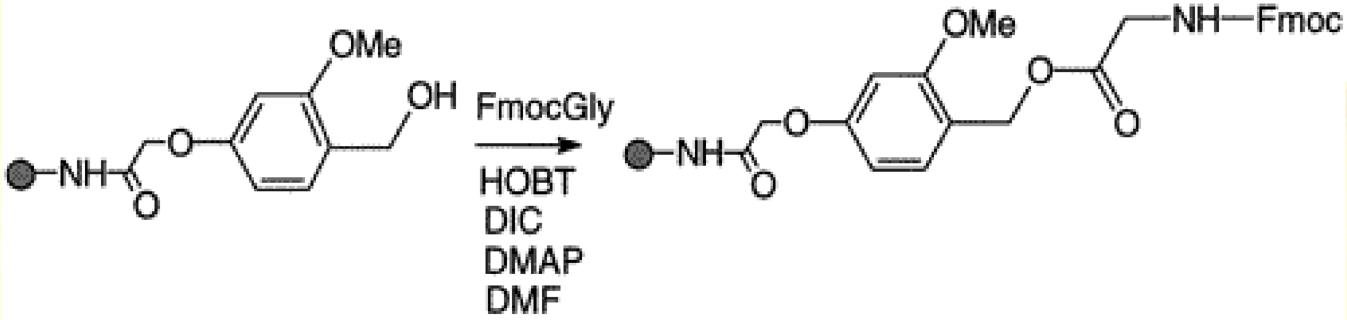
Single Bead FTIR

The time course of reaction I. The progression of the absorbance at 1740 cm-1 was plotted against time. The solid line is the best fit time course with k = 5 × 10-4 s-1.

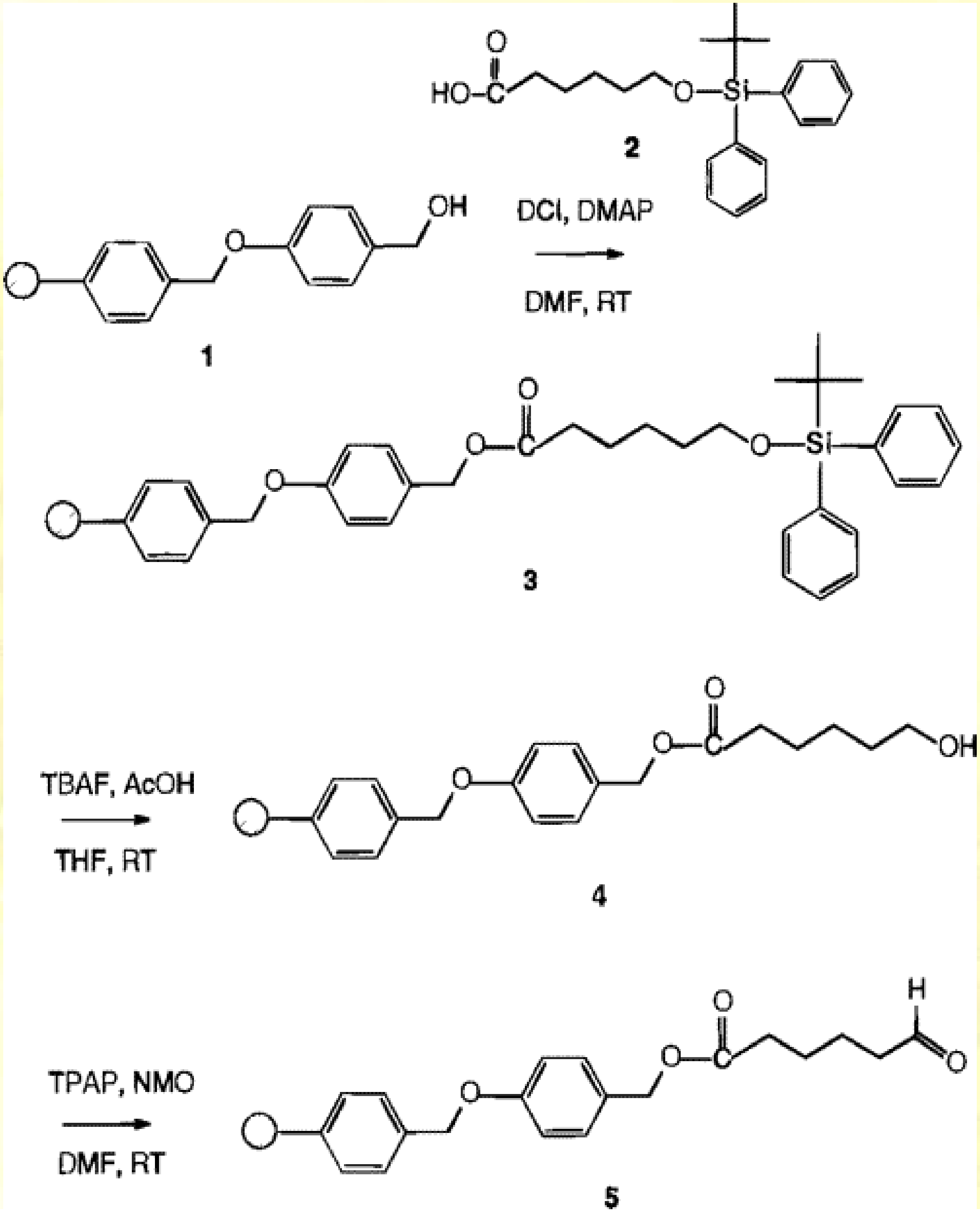


Single Bead FTIR



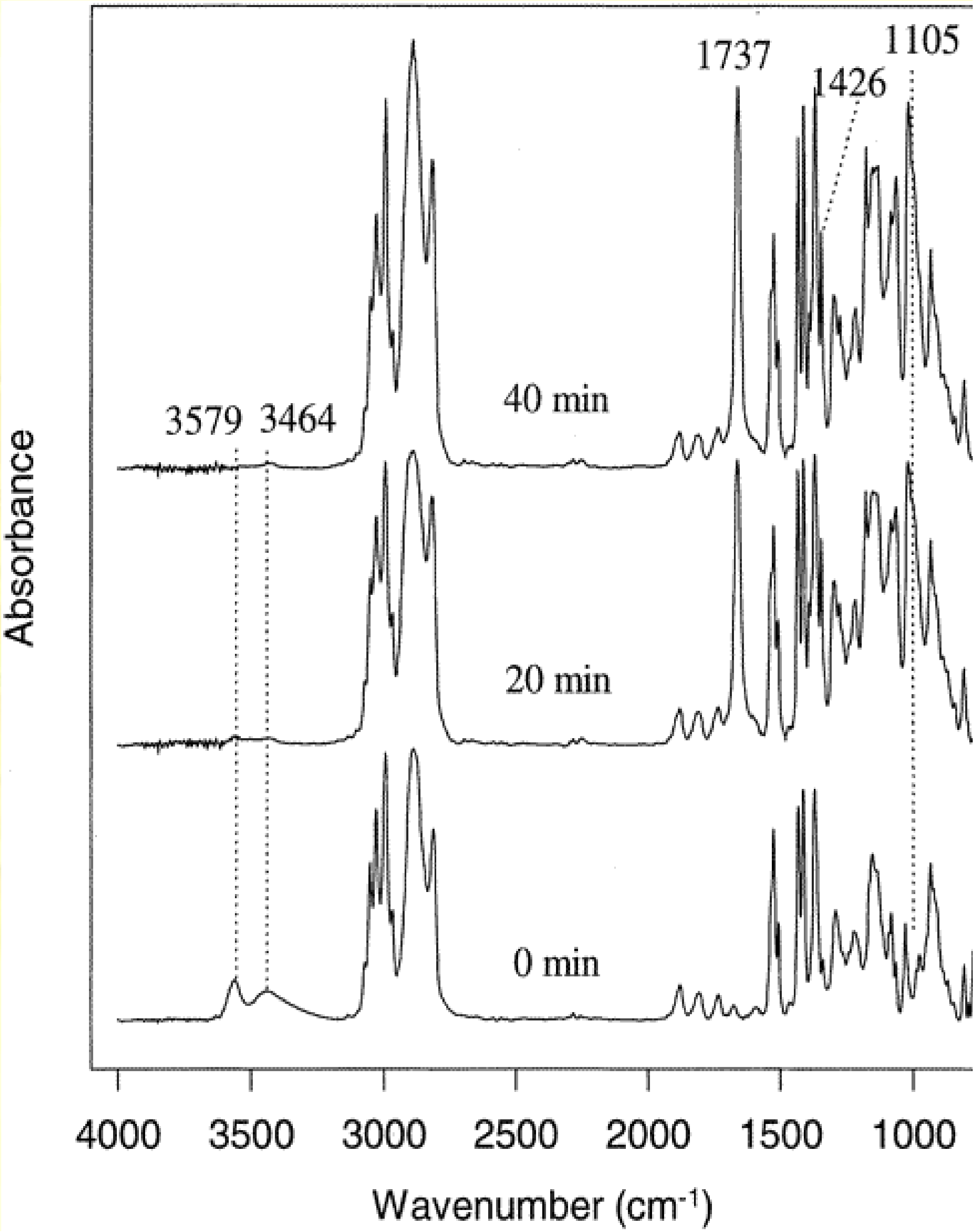


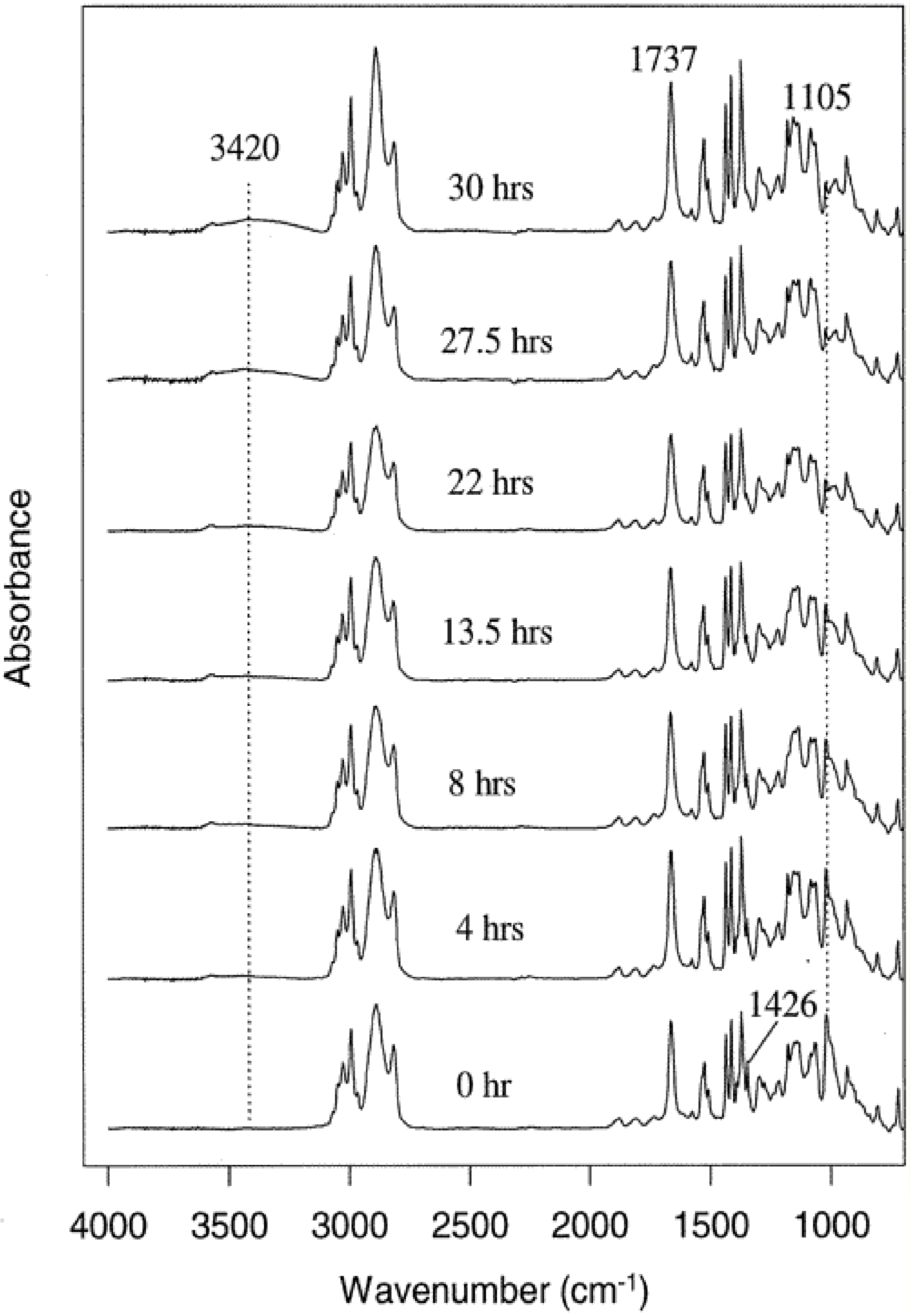
Single Bead FTIR

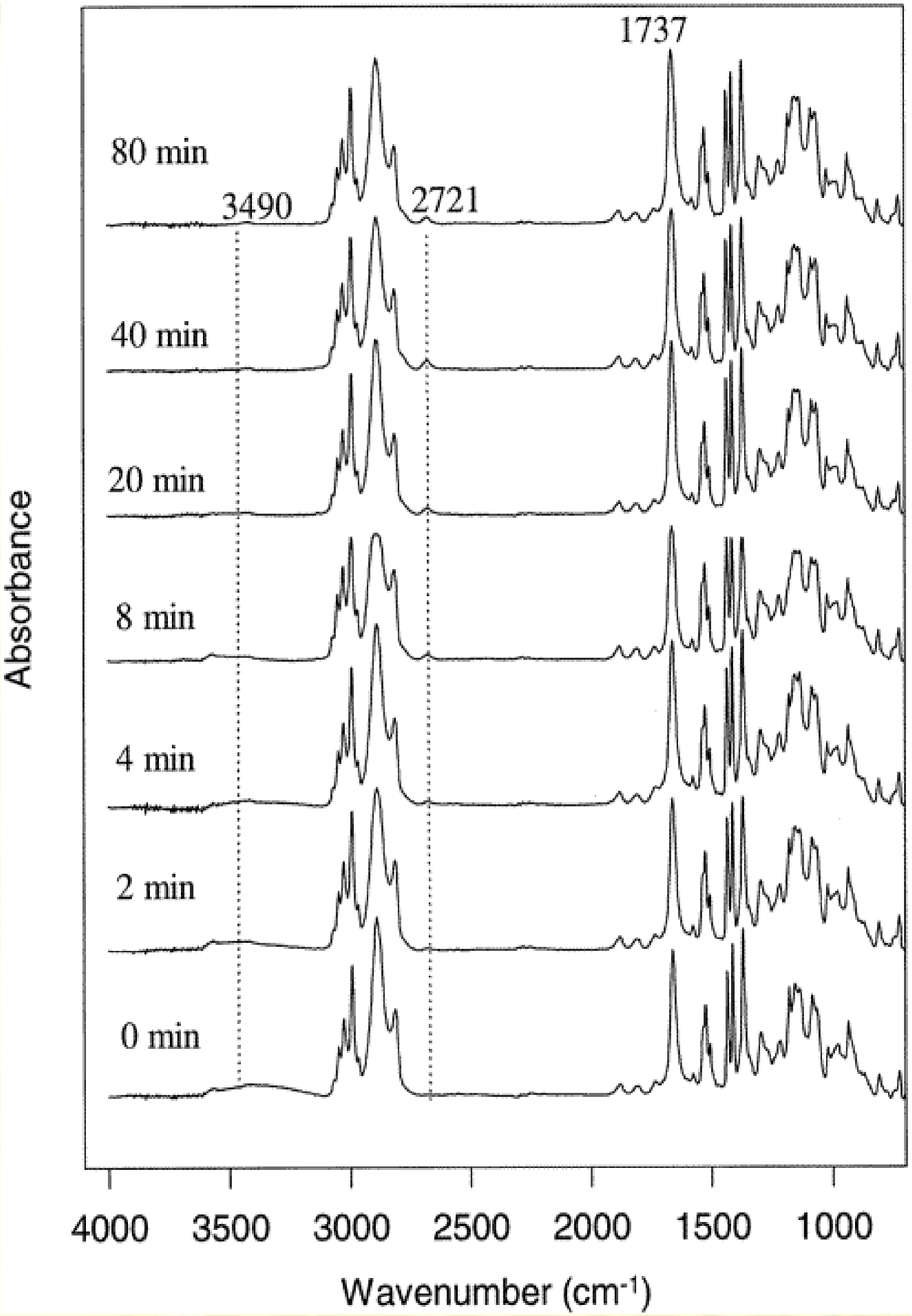


Single Bead FTIR

IR spectra taken from a single bead at various times in the course of the first step in Scheme 1. Spectra were taken from a single flattened bead at 0, 20, and 40 min after the initiation of the reaction. All spectra were taken using the transmission mode at room temperature. The hydrogen-bonded and unbonded hydroxyl stretches at 3464 and 3579 cm-1 disappear as the ester band (1737 cm-1) and theSi-Ph and Si-O (1426 and 1105 cm-1) stretching signals increase.



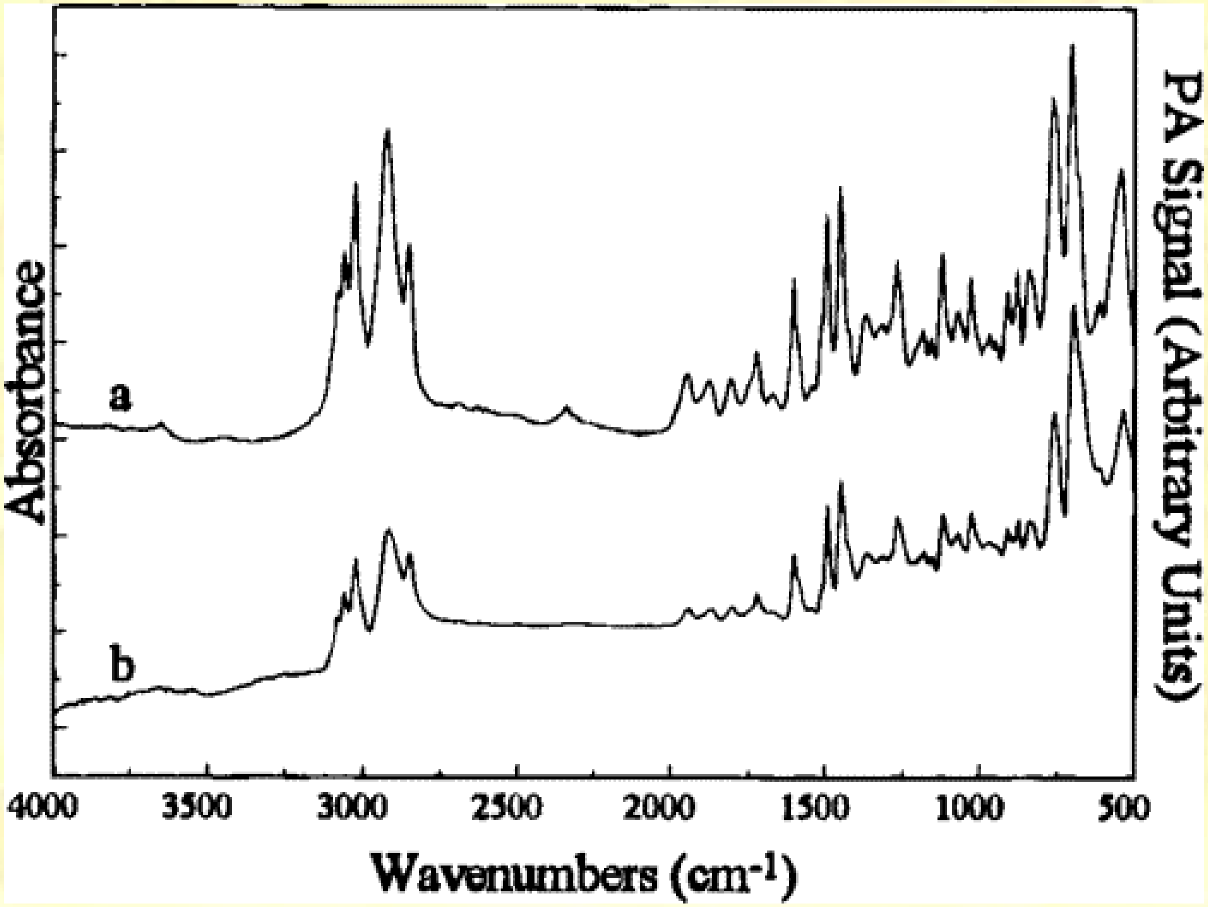




On the right: IR spectra taken from a single bead at various times in the course of the third step. Spectra were taken from a single flattened bead at 0, 2, 4, 8, 20, 40, and 80 min after the initiation of the oxidation reaction. The hydrogen-bonded and unbonded hydroxyl stretches near 3490 cm-1 disappear as the band for the aldehyde C-H (2721 cm-1) stretching increases.

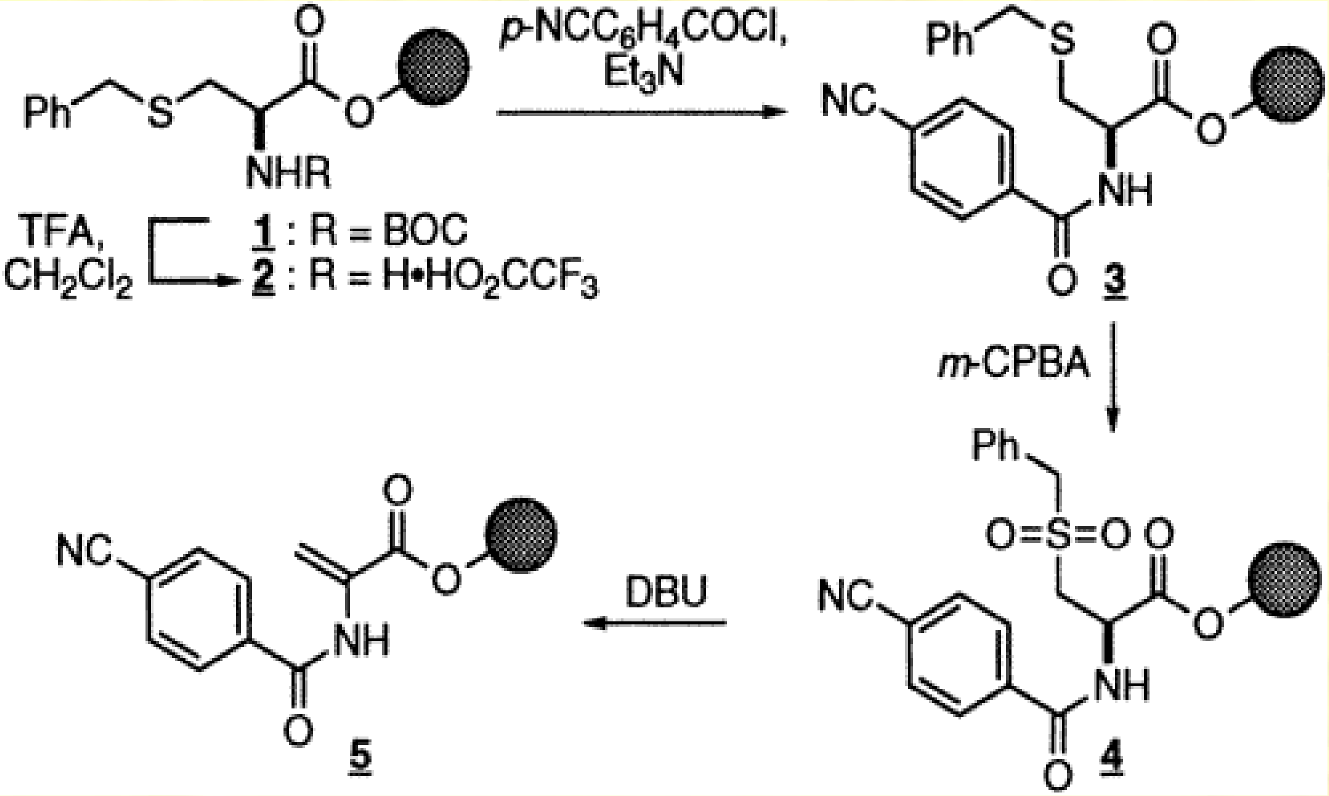
Photoacoustic FTIR

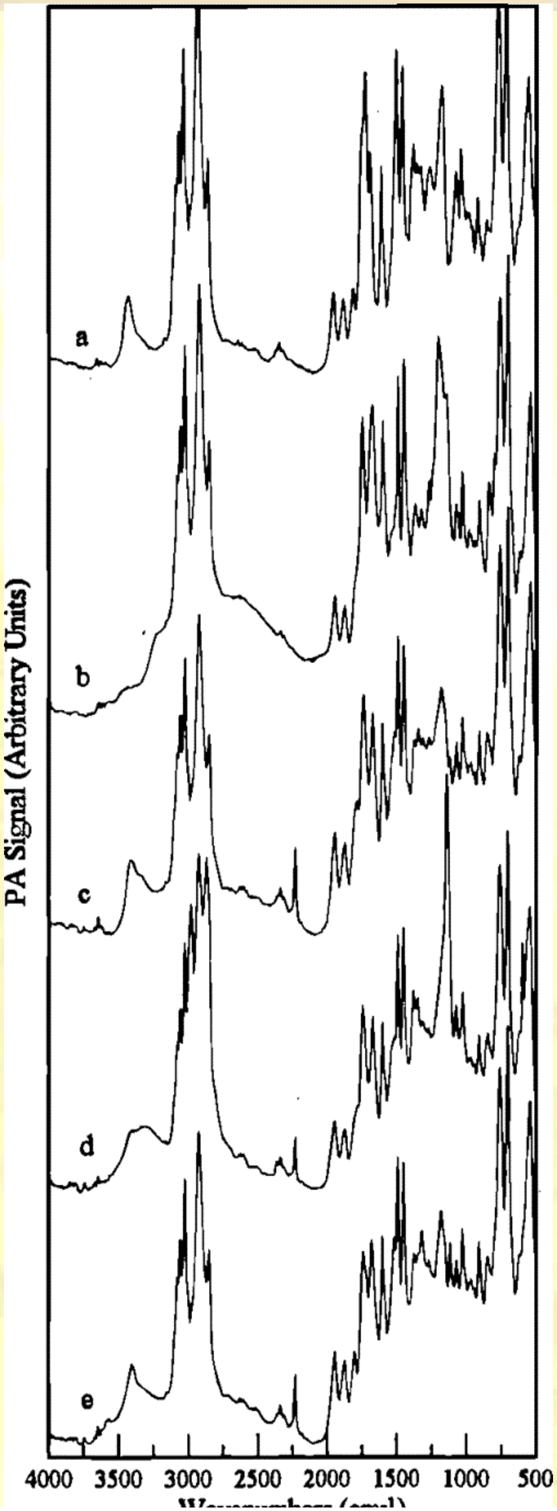
Figure 1 FTIR spectra of Merrifield's resin:
(a) PA-FTIR; (b) FTIR of KBr pellet.



Photoacoustic FTIR

Synthesis of Resino Dehydroalanine 5





(a-e) PA-FTIR spectra of resino compounds 1-5.

Mass Spectrometry

- **On-bead**
  - Ion beam (strong ionisation source required)
  - Ionisation an issue

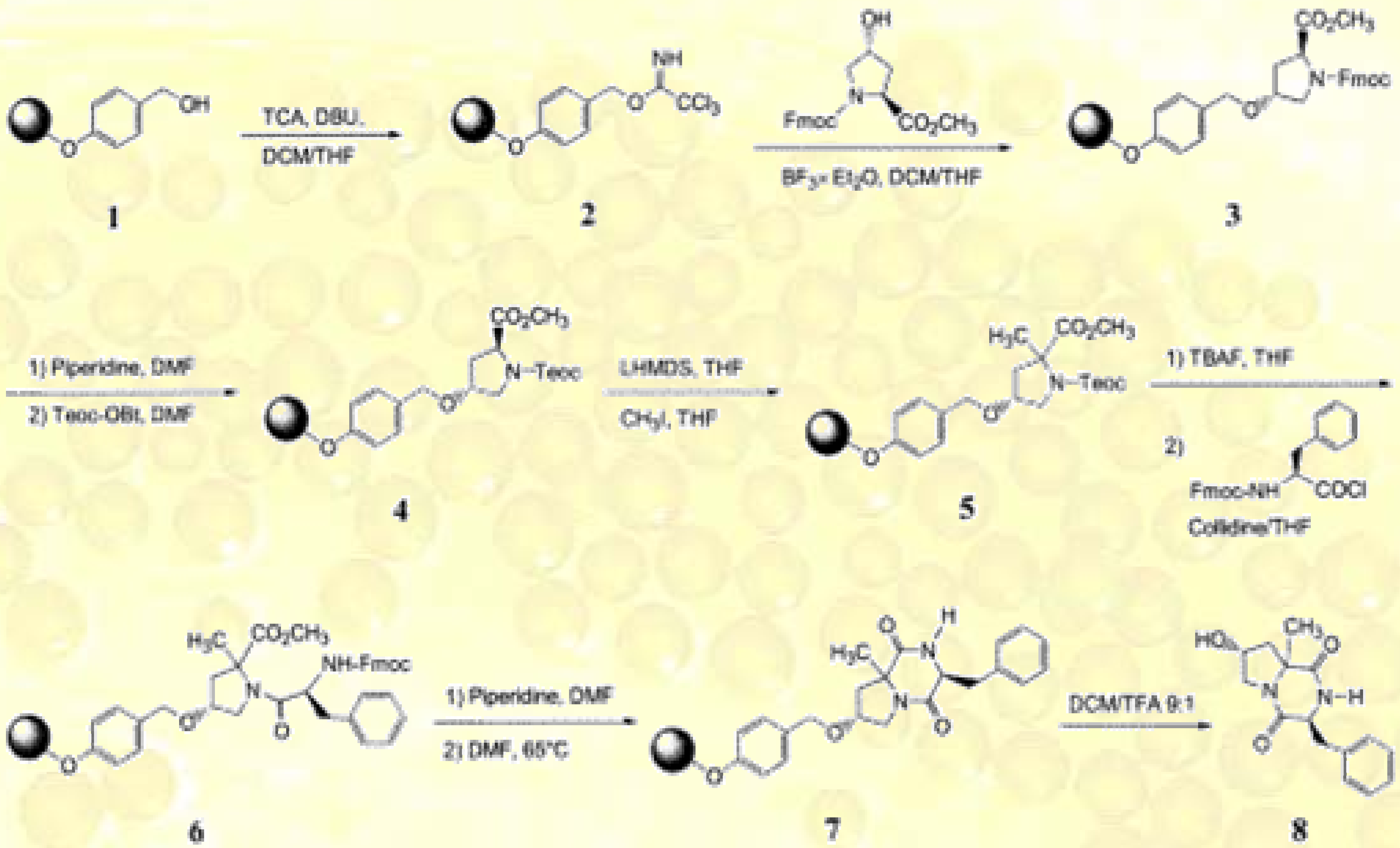
- **Off-bead**
  - All standard techniques available (+ -hyphenated (e.g. GC))
    - MALDI, FAB, Electron spray (nanospray), EI etc.
  - Chemically cleaved (prior)
  - Photochemically cleaved (in situ)
  - Powerful
  - Spatially addressable (bead location known)

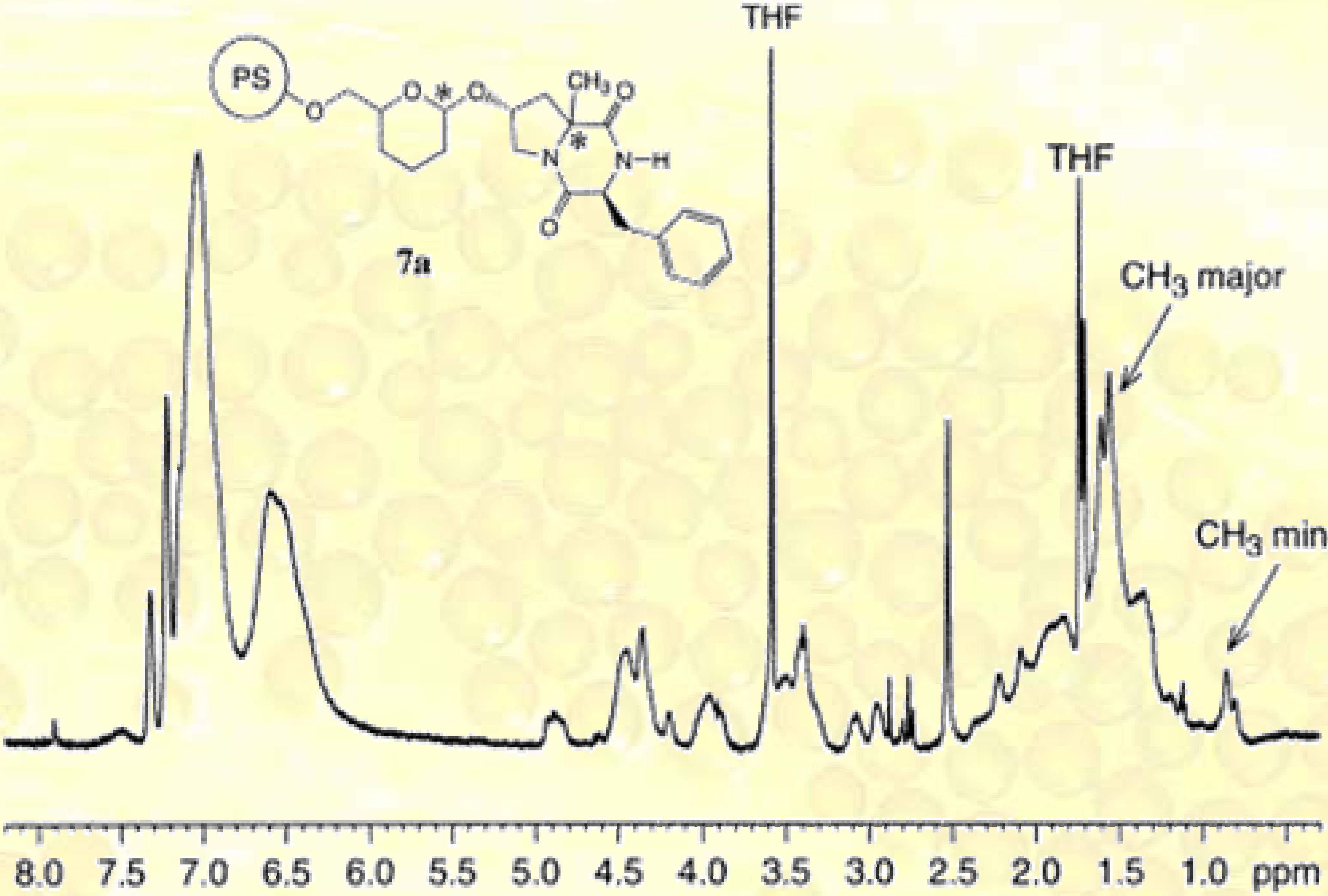
NMR spectroscopy

- **On-bead**
  - ^{1}H, ^{13}C, ^{19}F
  - Gel and Solid state NMR
  - Magic Angle Spinning (MAS)
  - Nanoprobe
  - Pulsed field gradient (PFG)
  - New pulse sequences and other experimental conditions

- **Off-bead**
  - “the usual”

^1H Gel NMR

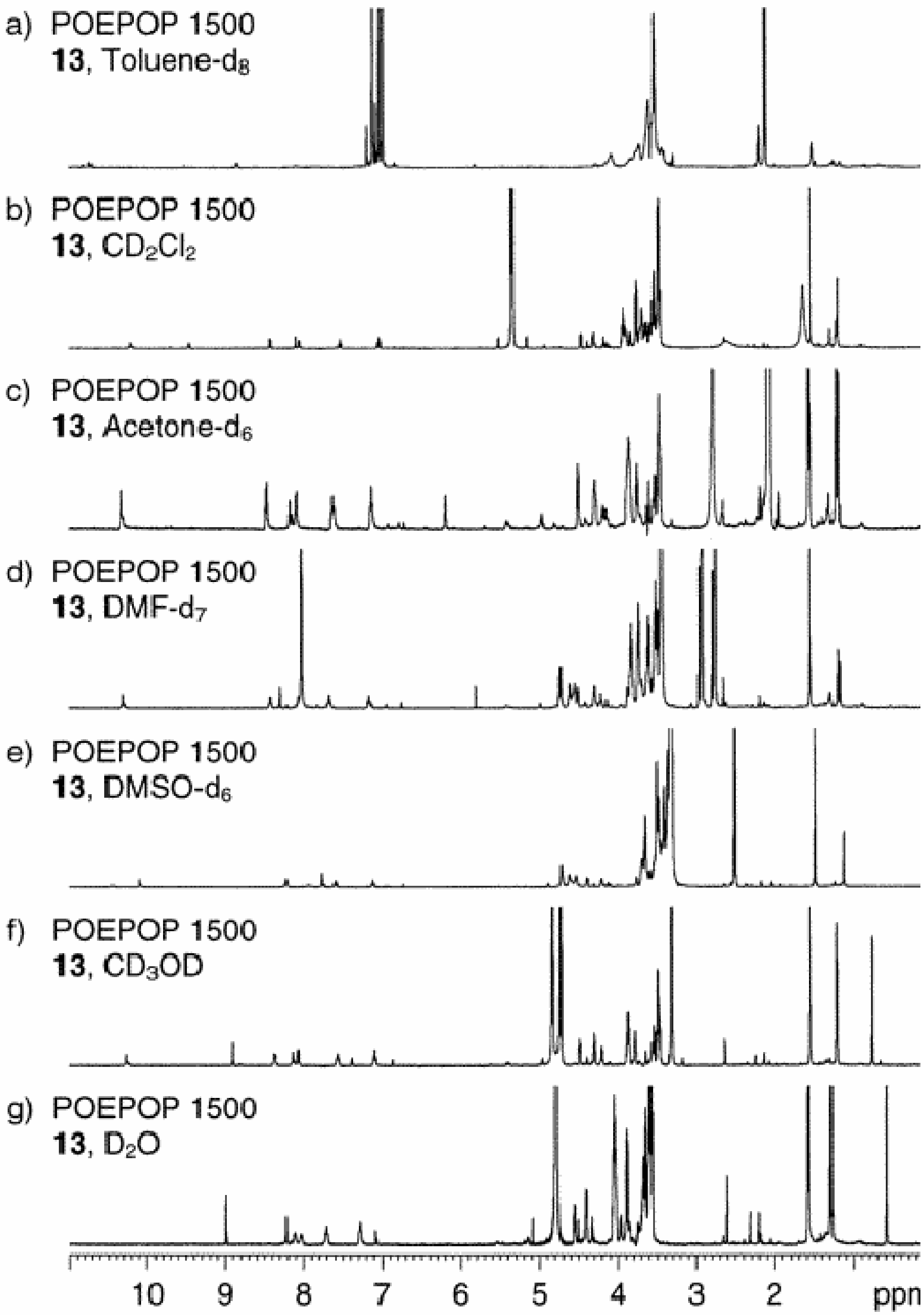

OH
TCA, DBU,
DCM/THF
NH
CCl3
OH
Fmoc
N
CO2CH3
BF3·Et2O, DCM/THF
CO2CH3
N-Fmoc
1
2
3
1) Piperidine, DMF
2) Teoc-OBt, DMF
CO2CH3
N-Teoc
LHMDS, THF
CH3I, THF
H3C
CO2CH3
N-Teoc
1) TBAF, THF
2)
Fmoc-NH
COCl
Collidine/THF
4
5
H3C
CO2CH3
NH-Fmoc
N
O
1) Piperidine, DMF
2) DMF, 65°C
H3C
O
H
N
N
O
DCM/TFA 9:1
HO
CH3
O
N
N-H
O
6
7
8

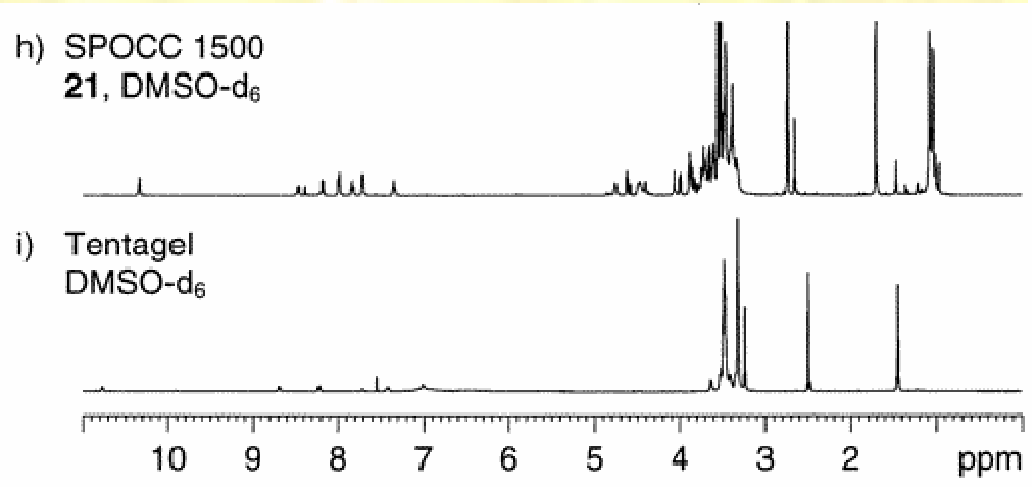


THF
THF
CH3 major
CH3 minor
PS
CH3
N–H
O
7a
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

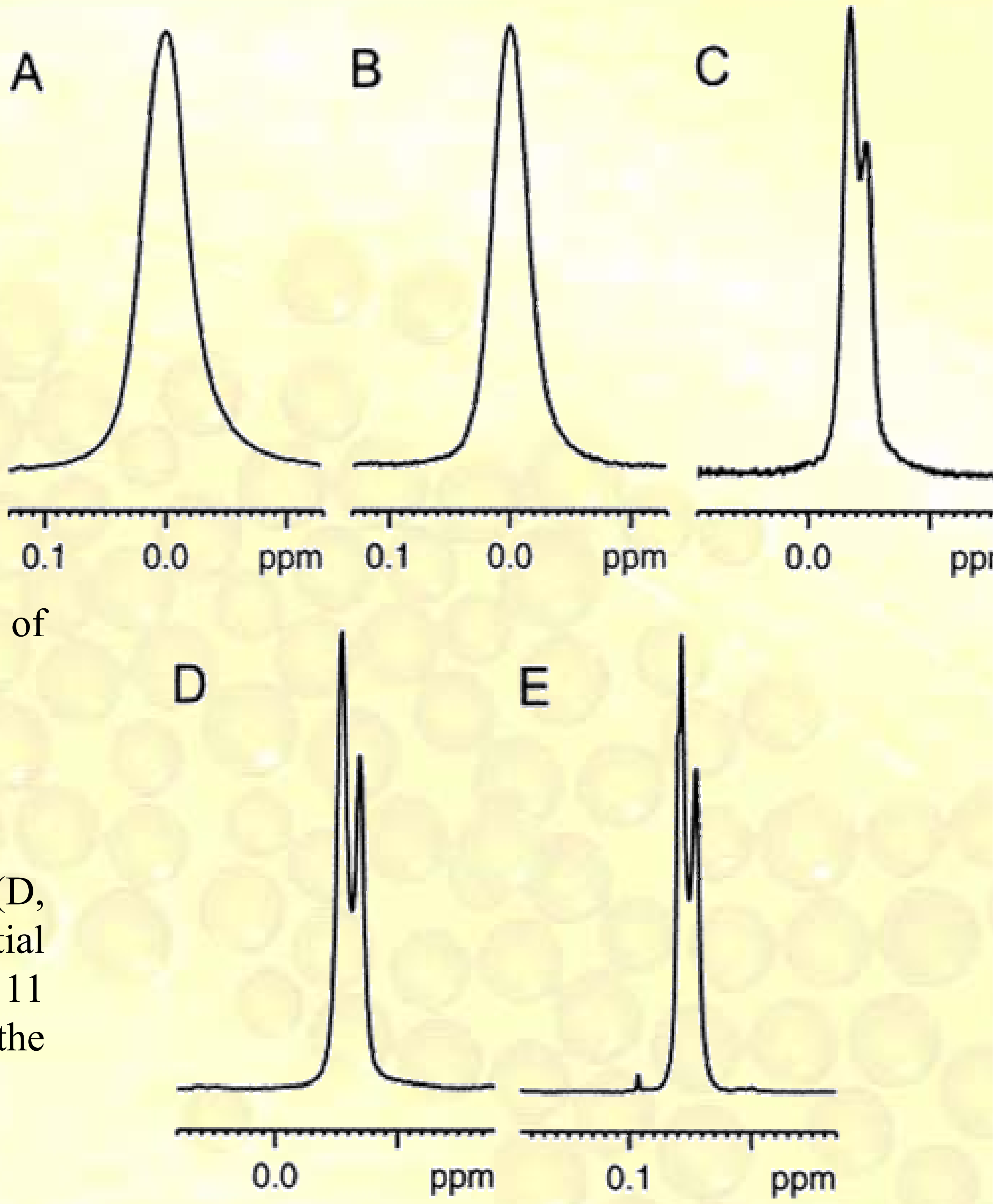
Polyether Resins

- PEG-crosslinked vs PEG-grafted
  - 1H NMR differences





^{1}H Gel NMR



Partial 500 MHz 1H HRMAS NMR spectra of resin-bound intermediates

5a (A, Ellman's dihydropyran resin),

5b (B, Wang resin),

5c (C, NovaSyn TG resin), and 5d (D, POEPOP resin) swollen in CDCl3, and partial 400 MHz 1H NMR spectrum of compound 11 (E, solution) in CDCl3, showing the trimethylsilyl group chemical shift.