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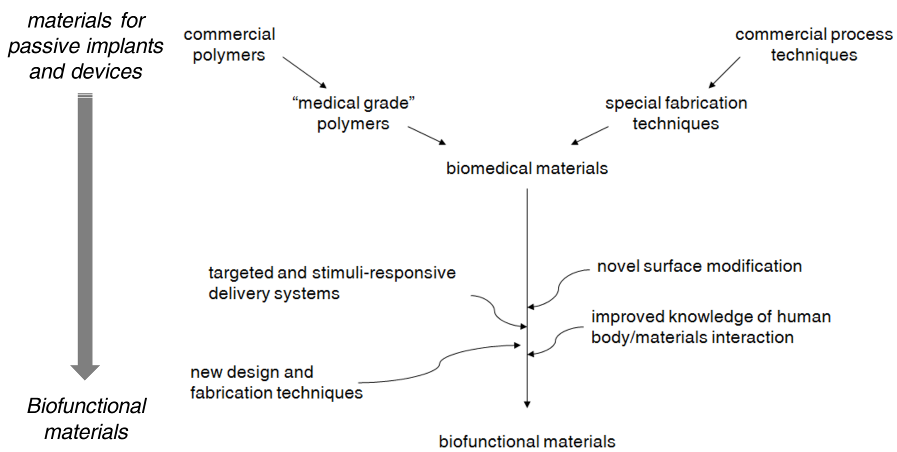
Biodegradable Polymers

Paola Petrini

The evolution of biomaterials



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Design of biomaterials

- (Biocompatible)
- Processable
- Sterilizable
- Possibility to scale-up the production process
- Reasonable storage and shelf life
- Cost-effective production

- Biodegradable biomaterials

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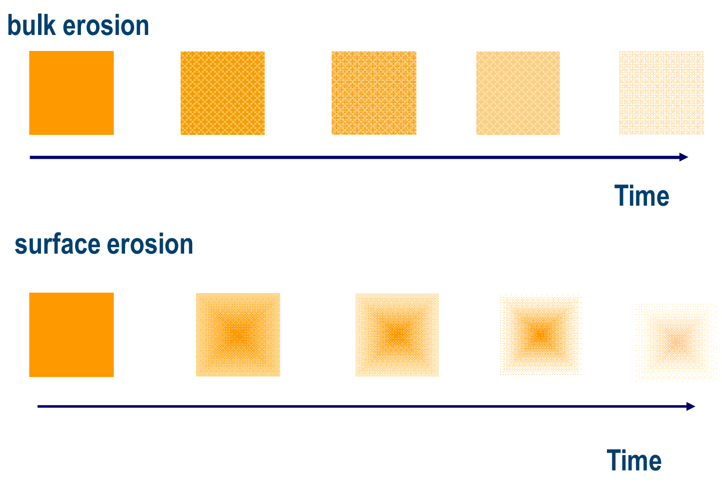
Biodegradable materials



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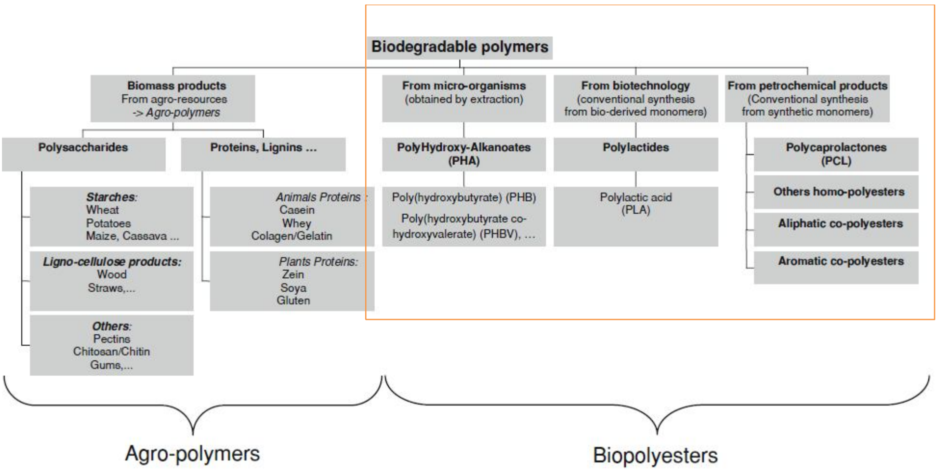
Biodegradable polymers



L. Avérous and E. Pollet (eds.), "Biodegradable polymers" in Environmental Silicate Nano-Biocomposites, Green Energy and Technology, DOI: 10.1007/978-1-4471-4108-2_2, Springer-Verlag London 2012

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Biodegradable polymers

Polyesters
Biotechnologically Produced Biodegradable Polyesters
Polyanhydrides
Poly(Ortho Esters)
Biodegradable Polymers Composed of Naturally Occurring α-Amino Acids
Biodegradable Polyurethanes and Poly(ester amide)s
….

Andreas Lendlein, Adam Sisson (2011) Wiley
Handbook of Biodegradable Polymers:
Isolation, Synthesis, Characterization and Applications

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Esters: condensation

$$R\text{-}COOH + R'\text{-}OH \rightleftharpoons R\text{-}COO\text{-}R' + H_2O$$

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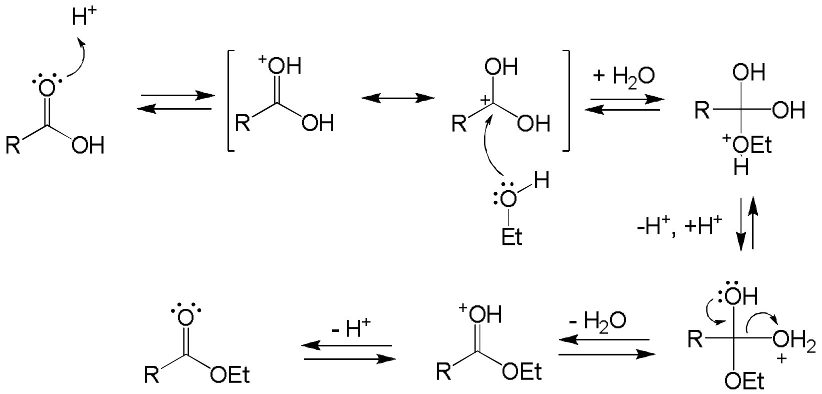
Esters: condensation

This is simply the reverse of the acid-catalyzed hydrolysis of esters



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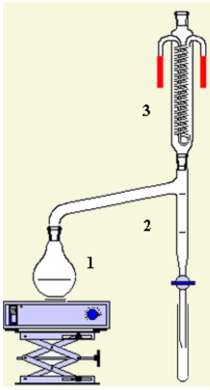
Polyesters

One method for driving the reaction toward completion is to remove the product water by azeotropic distillation using a Dean-Stark apparatus



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"Poly"condensation

$$\text{R-COOH} + \text{R'-OH} \rightleftharpoons \text{R-COO-R'} + H_2O$$

"Poly"esters ?

- di-acids + diols
- hydroxyacids + hydroxyacids
  - α-hydroxyacids
  - α, ω-hydroxyacids
- Polyfunctional monomers

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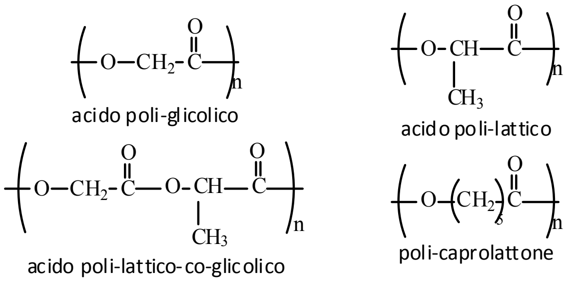
Traditional polyesters

- poly(glycolic acid) (PGA)
- poly(lactic acid) (PLA),
- copolymers poly(lactic acid-co-glycolic acid) (PLGA)
- polycaprolactones (PCL)



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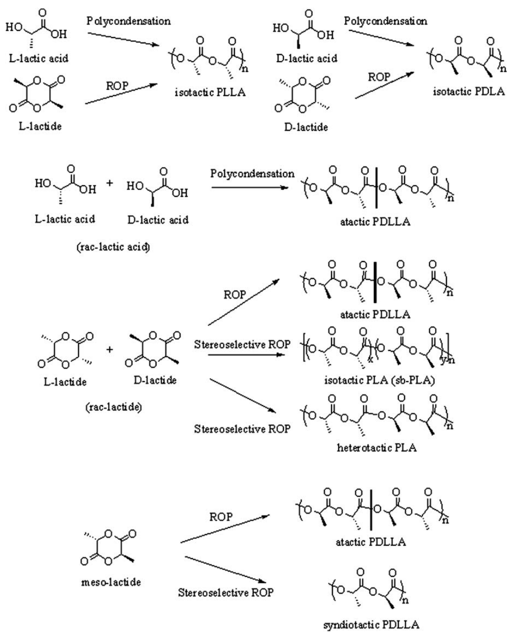

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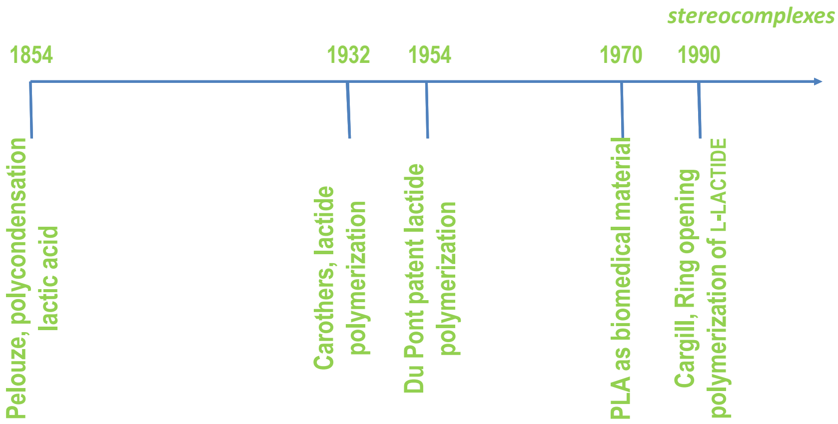
Polyesters: Poly(α-hydroxy acids) PLA

Synthesis of PLA



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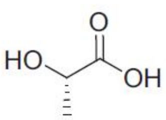
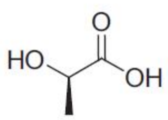
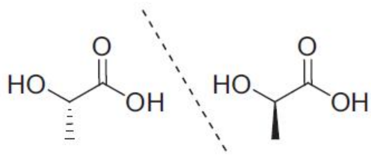
Polyesters: polycondensation from lactic acid to PLA (glycolic acid to PGA)



L-lactic acid

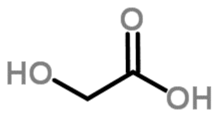


D-lactic acid



DL-lactic acid

lactic acid = 2-hydroxypropanoic acid



glycolic acid = 2-hydroxyethanoic acid

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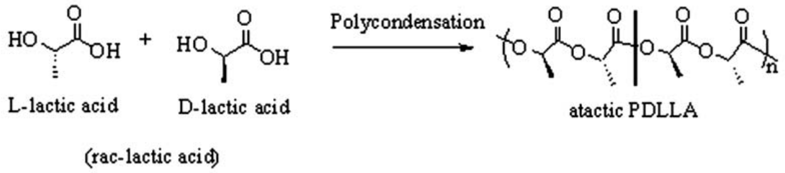
Polyesters: polycondensation fo lactic acid to PLA



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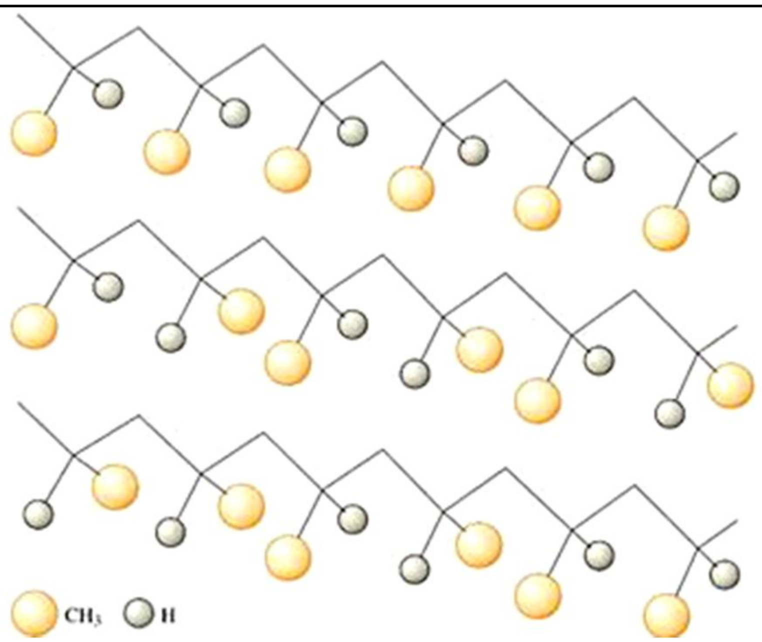

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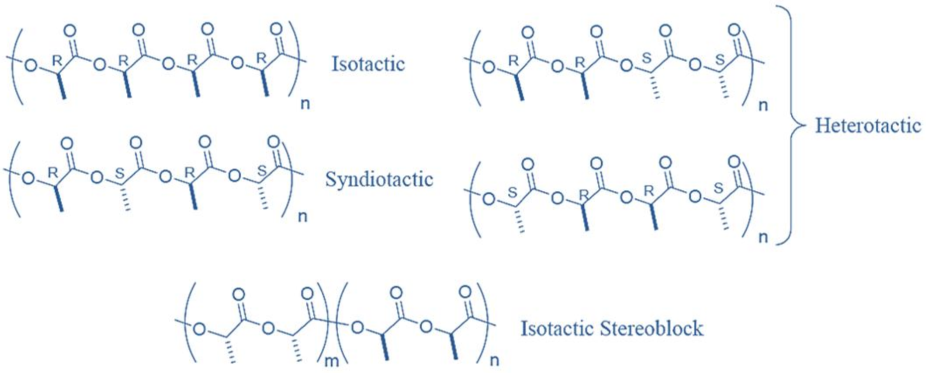

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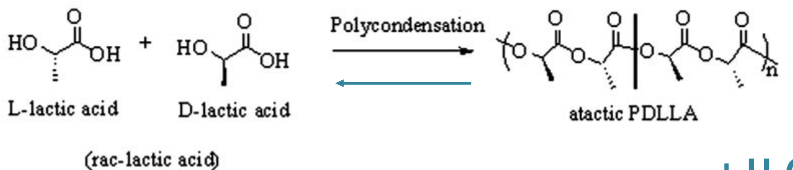
Polyesters: polycondensation fo lactic acid to PLA



+ H_2O

equilibrium reaction: difficulties completely removing water can limit the maximum molecular weight attained due to hydrolysis of the ester bonds

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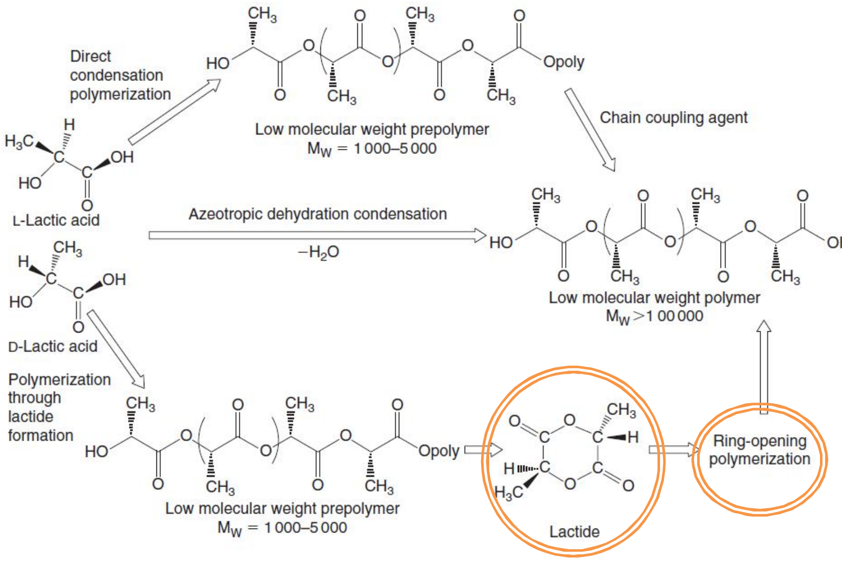
Synthesis of PLA

PLA Synthesis. From the Monomer to the Polymer Poly(lactic acid) Science and Technology: Processing, Properties, Additives and Applications, 2014, 1-36



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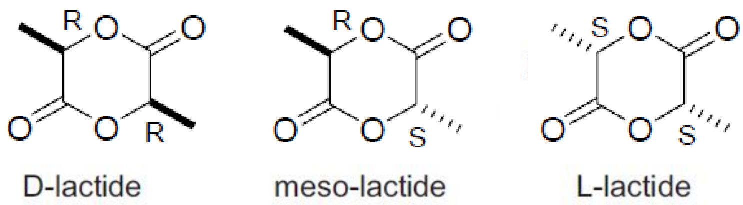
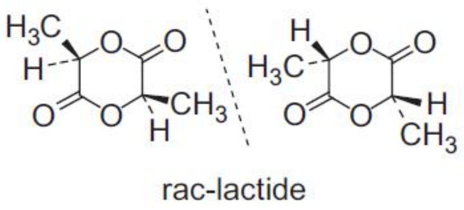
Polyesters: ROP (ring opening polymerization) from lactide to PLA



D- and L-lactides = two D- and L-lactic acids
meso-lactide = both D- and L-lactic acids



Racemic lactide (rac-lactide) = equimolar mixture of D- and L-lactides

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Polyesters: Poly(α-hydroxy acids) PLA

	Melting point (°C)
L-lactide	95–98
D-lactide	95–98
meso-lactide	53–54
rac-lactide	122–126

The crude lactide can be purified by melt crystallization or ordinary recrystallization from solution

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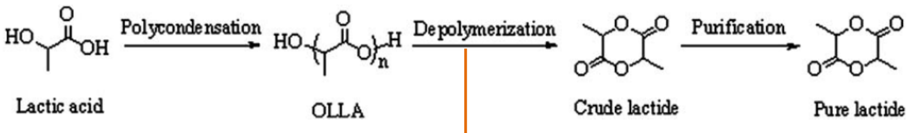
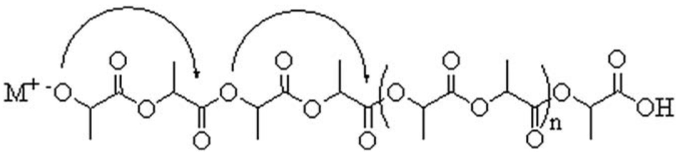
Polyesters: from lactide to PLA



catalyzed by metal compounds involving Sn, Zn, Al and Sb ions, etc



Expected formation mechanism of lactide (back-biting mechanism)

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Mechanisms for Ring Opening Polymerization (ROP)

Cationic mechanism (SN2)
Anionic mechanism (SN1)
Coordination-Insertion Mechanism (metal alkoxide and metal carboxylates as coordination-insertion initiators)

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Polyesters: ROP from lactide to PLA

no water removal, no polycondensation

the precise mechanism of polymerisation depends greatly upon the initiator, monomer and polymerisation conditions

polymer molecules are formed by chain polymerisation mechanisms (sequential additions of monomer to the active centres)

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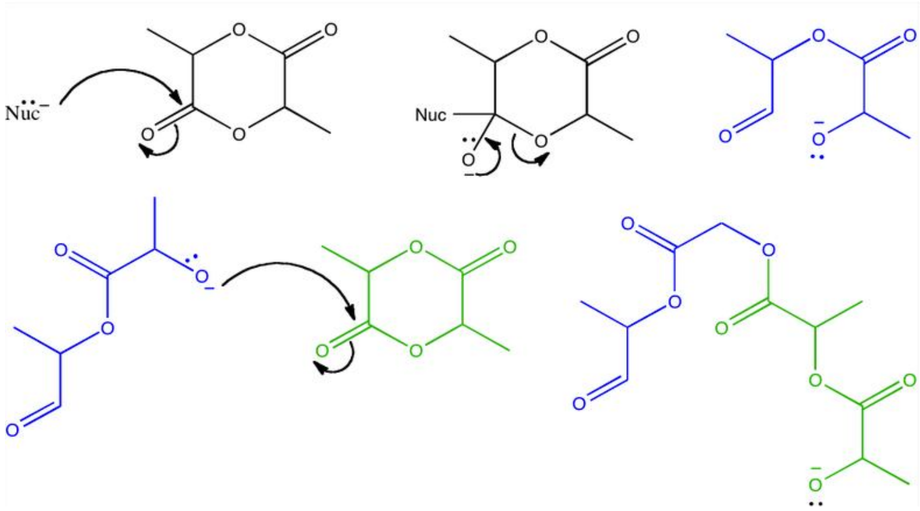
Polyesters: ROP (ring opening polymerization) from lactide to PLA



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Polyesters: ROP (ring opening polymerization) from lactide to PLA

1) Cationic Polymerization
   a) Protic Acid (HBr, HCl, triflic acid, etc)
   b) Lewis acid ($ZnCl_2$ $AlCl_3$, etc)
   c) Alkilating or Acylating agents ($Et_3O^+BF_4$, etc)

2) Anionic Polymerization

   Proceed by nucleophilic reaction of the anion with the carbonyl and the subsequent acyl-oxygen cleavage, this produces an alkoxide end group which continuous propagate.

3) Coordination / Insertion Polymerization

   Use less reactive metal carboxylates, oxides, and alkoxides. Polymerization by tin, zinc, aluminum, and other heavy metal catalysts with thin (II) and zinc yielding the purest polymers.

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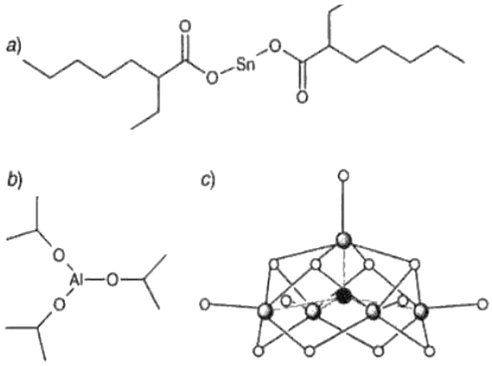
Mechanism of ROP: Coordination-Insertion Initiators



Chemical structures of some coordination-insertion initiators used in the ROP of lactones and lactides (a) stannous octoate, (b) aluminium isopropoxide, (c) lanthanide isopropoxide (where the lanthanum atoms are represented by gray circles and the oxygen atoms by white circles; the black circle represents the bridging oxygen atom connecting all of the lanthanum atoms; alkyl groups are omitted for clarity)

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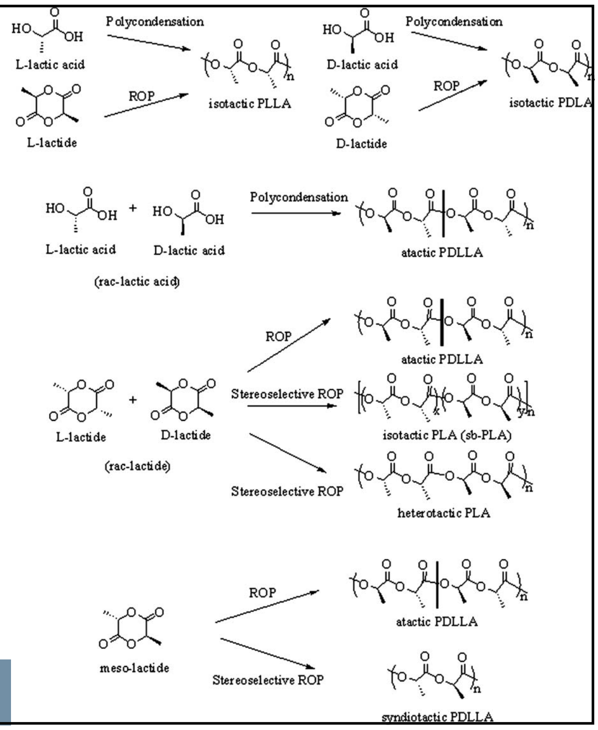
Steroselectivity in the synthesis of PLAs



Steroselectivity in the synthesis of PLAs

PLLA and PDLA are crystalline (Tm ~ 180°C).
Their crystallinity and Tm usually decrease with decreasing optical purity (OP) of the lactate units

Optically inactive poly(DL-lactide) (PDLLA), prepared from rac- and mesolactides, is an amorphous polymer.

Crystalline polymers can be obtained when the sequence of both D and L units are stereo-regularly controlled

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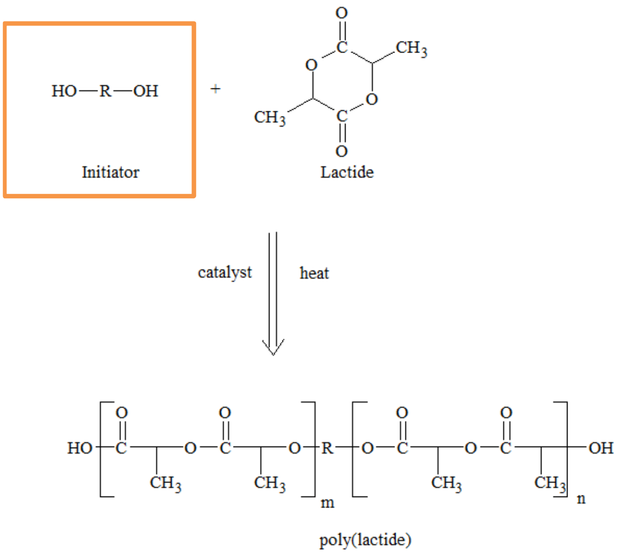
Polyesters: ROP (ring opening polymerization) from lactide to PLA



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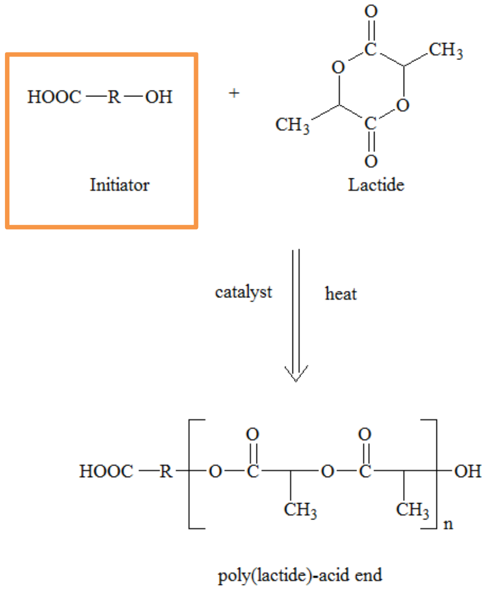
Polyesters: ROP (ring opening polymerization) from lactide to PLA



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Polyesters: Poly(α-hydroxy acids)

Poly(α-hydroxy acids) (PGA, PLA, and their copolymers)
no functional groups available → copolymerize with monomers containing functional pendant groups (e.g. amino- and carboxyl- groups)

Examples:
- poly(L-lactide-co-RS-b-malic acid) with pendant carboxyl groups [He, B. et al., Polymer 2003]
-hydroxylated PLLA copolymers [Leemhuis, M., et al.,Macromolecules, 2006]
- PLLA copolymers with succinic anhydride to obtain the corresponding carboxylic acid functions to attach amine-containing biological molecules [Noga, D.E., et al., Biomacromolecules, 2008]
-Copolymers of D,L-lactide to incorporate acryloyl groups [Chen, W., et al., Macromolecules, 2010]
- Copolymers poly(L-lactic acid-co-L-lysine) [Deng, C., et al, Biomacromolecules, 2006]

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Polyesters: Poly(α-hydroxy acids)

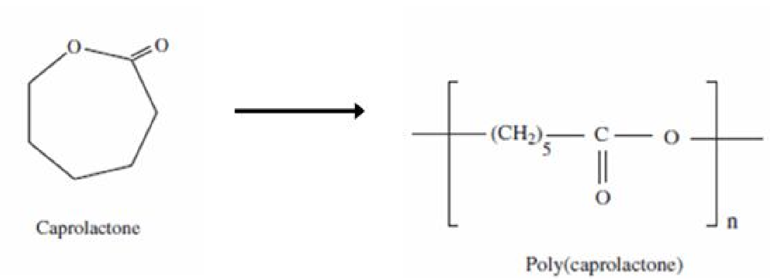
A number of poly(alpha-hydroxy acids)-based **block** and **graft copolymers** have been designed and synthesized

Examples:

-**Diblock, triblock, and multiblock copolymers** of **PL(G)A/PEG** have been synthesized by ring opening polymerization of lactide/glycolide in the presence of **PEG** and selected catalysts [Wang, Y.Q., et al., Advanced Functional Materials, 2008; Li, S.M. and M. Vert, Macromolecules, 2003; Wan, Y.Q., et al, Biomaterials, 2003;…]

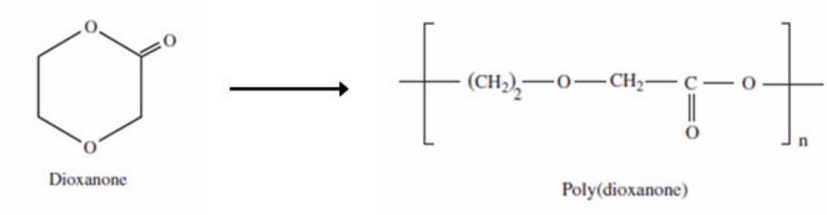
-**non-PEG block and graft** copolymers [Yang, Y.N., et al, Polymer, 2010; Palumbo, F.S., et al, Carbohydrate Polymers, 2006; Liu, X.H. and P.X. Ma, Biomaterials, 2010]

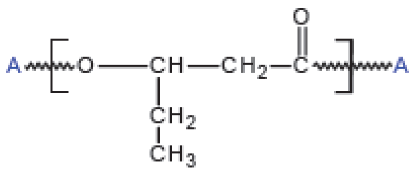
Polyesters: ROP (ring opening polymerization) from ε-caprolactone to PCL



Co-polymerization with other lactones (e.g. γ-valerolactone)

Polyesters: other





Poly(hydoxyvalerate)

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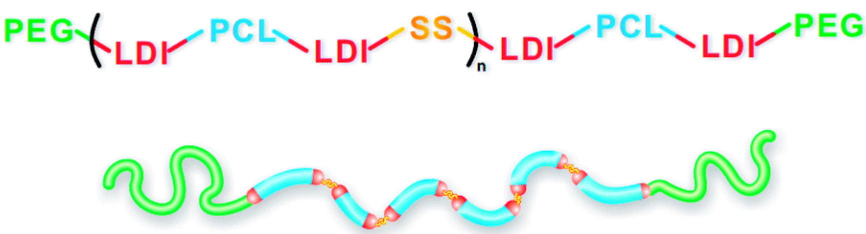
Biodegradable polyurethanes



RSC Adv., 2014, 4, 24736–24746

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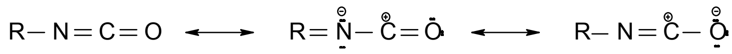
Biodegradable polyurethanes



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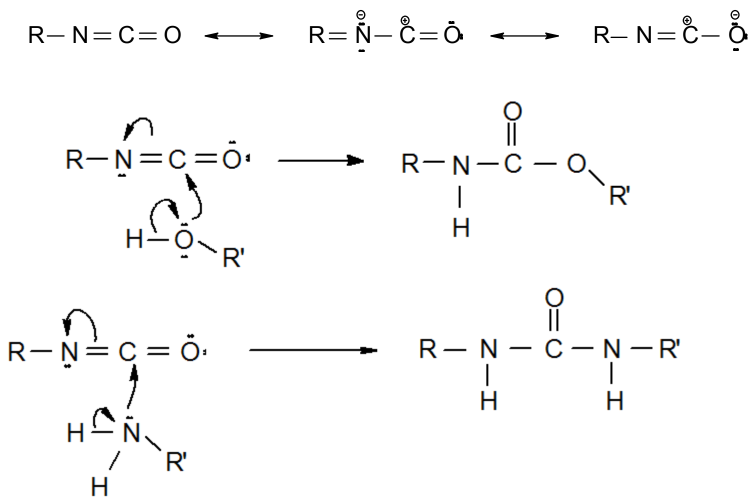
Biodegradable polyurethanes



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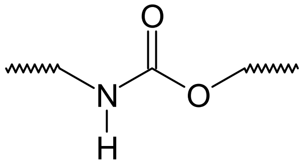

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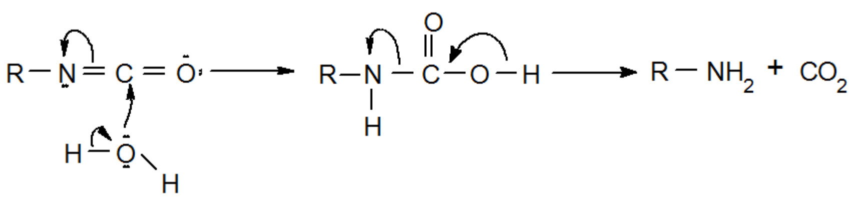
Biodegradable polyurethanes



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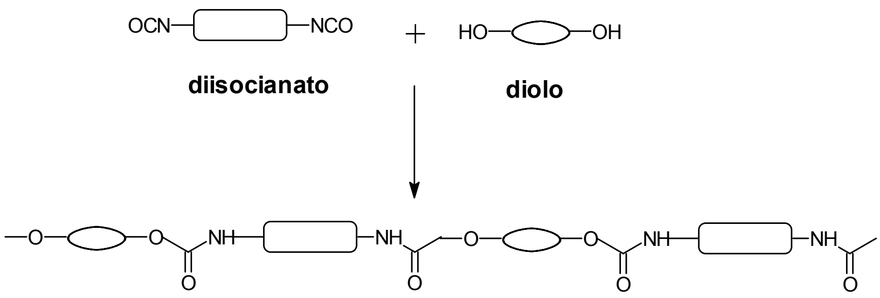
Biodegradable polyurethanes



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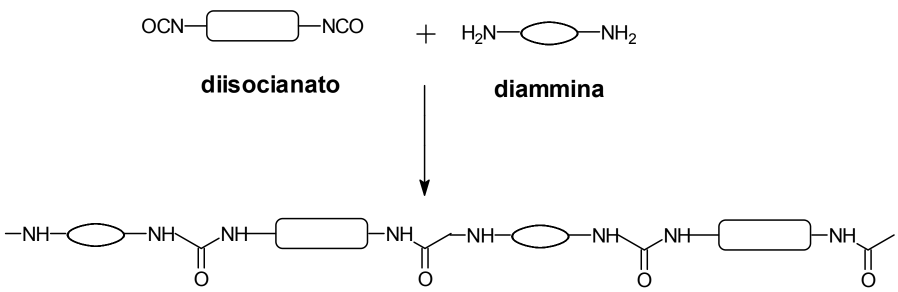
Biodegradable polyurethanes



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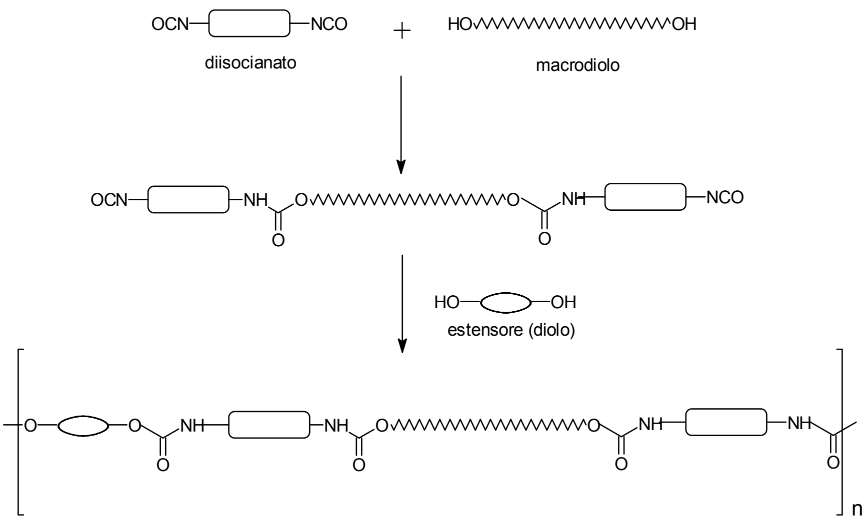
Biodegradable polyurethanes



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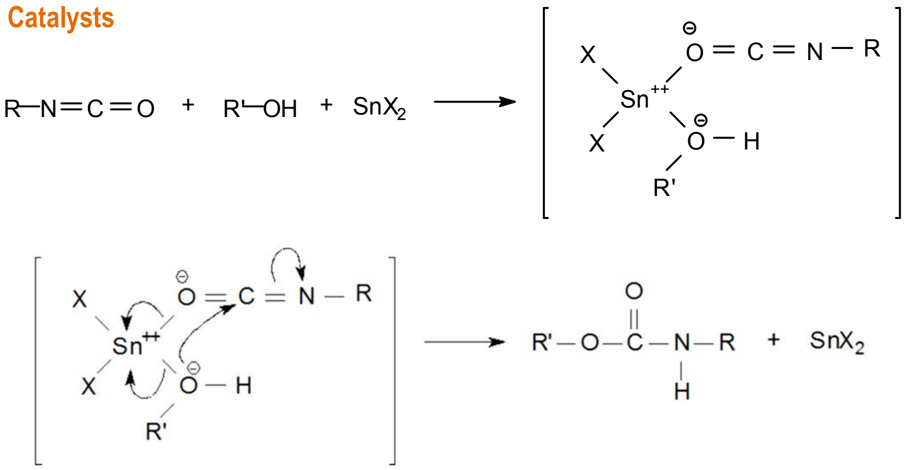
Catalysts



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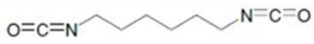
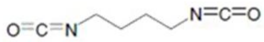
Isocyanates

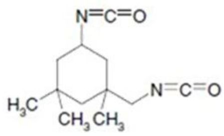
1,6-Diisocyanatohexane (HDI)



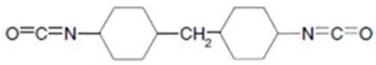
1,4-Diisocyanatobutane (BDI)



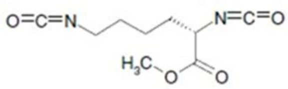
Isophorone diisocyanate (IPDI)



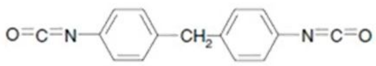
Dicyclohexylmethane diisocyanate (H12MDI)



Lysine methyl ester diisocyanate (LDI)



4,4′-Diphenylmethane diisocyanate (MDI)



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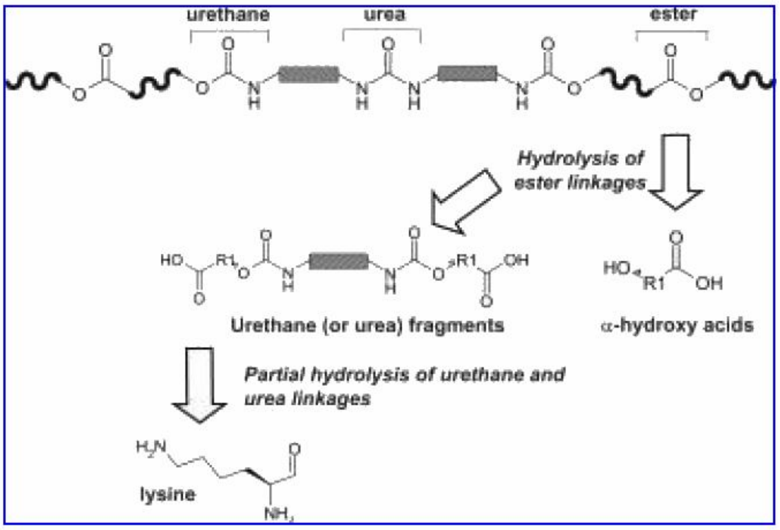
Degradation of PUs



[S.A. Guelcher, Tissue Eng. Part B, 2008]

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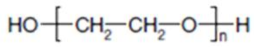
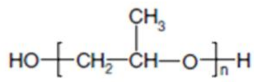
Degradable macrodiols

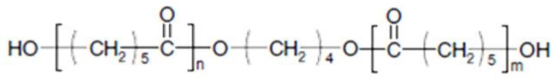
Poly(ethylene oxide) (PEO)



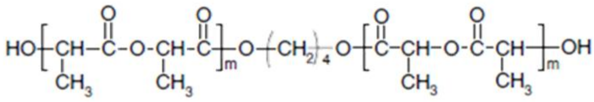
Poly(propylene oxide) (PPO)



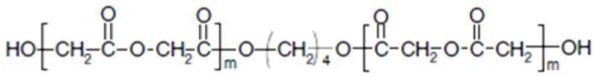
Poly(ε-caprolactone) (PCL)



Poly(D,L-lactide)



Poly(glycolide)



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Polyester-based degradable polyurethane

The DegraPol® is a polyester-urethane and is made from two polyester diols linked through diisocynate unit. P(HB-co-CL) (poly{3-(R-hydroxybutirrate)-co-(ε-caprolactone)}-diol) is the crystalline domain (hard segment), while the amorphous domain (Soft Segment) consist of poly(ε-caprolactone-co-glycolide)-diol.

Using different ratios of hard and soft segment can modulate the mechanical properties of the final product.

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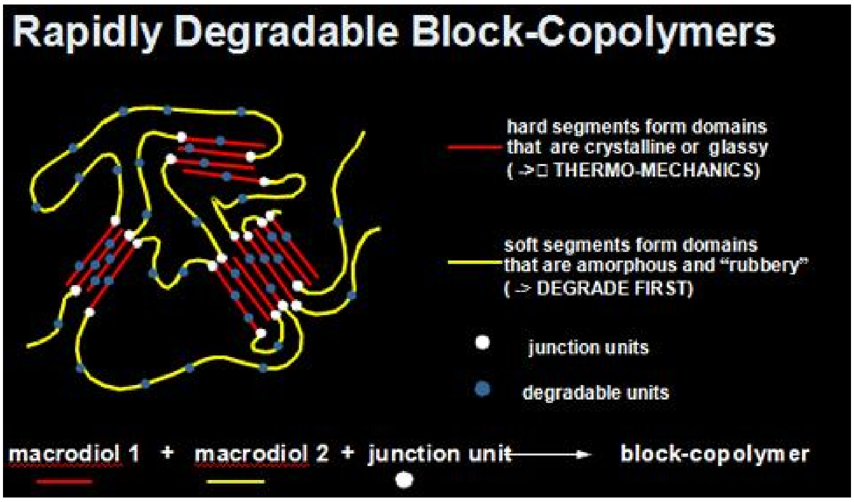
Degrapol®



http://www.degrapol.com/index.php?c=home

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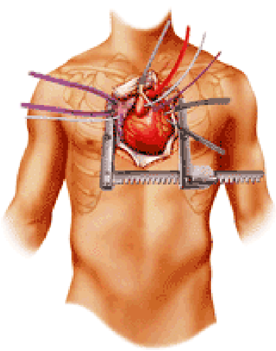
Biodegradable materials for injectable systems



Open surgery

Minimally invasive surgery

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Biodegradable materials for injectable systems

- Soft materials, e.g. hydrogels or preformes pastes
- *In vivo setting materials*
  - *Materials able to undergo in situ polymerization*
  - *Smart materials (thermoresponsive, pH responsive, environment reponsive…)*
- Particle systems (micro- and nano-particles)

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Biodegradable materials for injectable systems

- solidification times
- biocompatible reactions that undergo *in vivo*
- rheology in the sol state
- type of syringe/needle
- good mechanical properties (*in situ*)
- degradation or stability
- easy to be prepared (to be prepared by medical staff!)

- reasonable shelf life
- sterilisable
- (biocompatible)

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Biodegradable materials for injectable systems

Injectability by physical methods

- thermosensitive
- pH sensitive
- sterocomplexed hydrogels
- peptide based (self assembled)
- micro and nanoparticle assembly

Injectability by chemical methods

- reaction of vinyl bearing macromers (redox- or thermally-initiated polymerization or photopolymerization)
- reactions through functional groups (Schiff-base formation, Michael-type additions, peptide ligation as well as “click”chemistry by cycloaddition reactions)
- enzymatically crosslinked (or natural products induced crosslinking

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