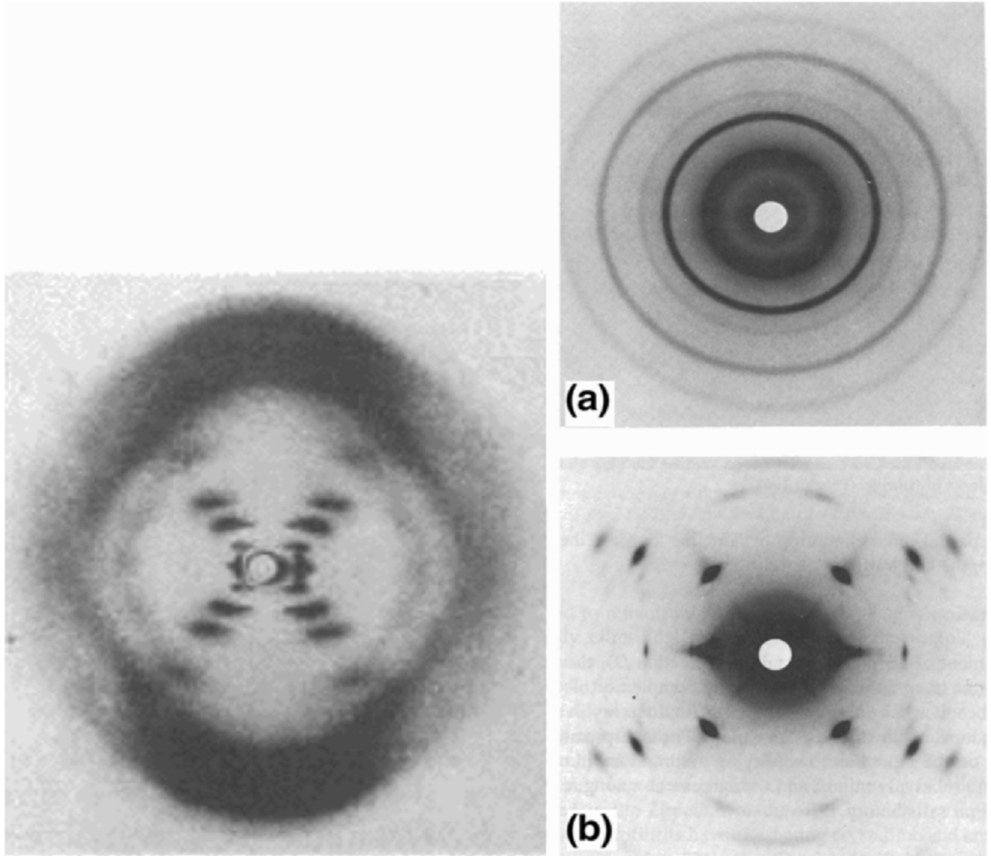
Polymers

- Carbon atoms are usually joined in a linear chainlike structure and substituted with a great variety of atoms, molecules or functional groups.
  - Thermoplastic polymers:

    Basic chains with little or no branching; can be melted and remelted without a basic change in structure.(=crystalline)
  - Thermosetting polymers:

    Side chains form covalent links between chains (three-dimensional network); do not melt uniformly on reheating. (= chemically cross-linked)



Left: X-ray diffraction of wet DNA showing B form double helix. Photo taken by R. Franklin and R. Gosling on May 2, 1952 (http://www.ba-education.demon.co.uk/ for/science/dnamain.html). **Right**: X-ray diffraction pattern of POM (polyoxymethylen) (**a**) before and (**b**) after orientation.

Polymers

- Non-degradable
- Biodegradable

Non-Degradable		*Biodegradable*	
Polyamides	sutures	Polylactic/glycolic acid	sutures
Polycarbonates	device housings	Polyorthoesters	bone plates
Polyesters	vascular grafts	Polyorthoesters	bone plates
PVC	tubing, blood bags	Cyanoacrylates	wound closure
Polyurethanes	tubing, coatings	Polylactic acid	tendon repair
Silicones	tubing, soft tissue reconst.		
UHMWPE	hip & knee bearing surfaces		

Courtesy Rainer Zenz

Polymer synthesis

Two categories of polymerization:

- **Addition polymerization** (chain reaction)
  - Addition of a new monomer by intramolecular rearrangements
  - **Initiation** by Initiators start the polymerization (free radicals, cations, anions, or stereospecific catalysts).
  - Rapid chain growth ensues during the **propagation** step.
  - **Termination** stop the reaction (other radicals, a solvent molecule, or an added chain transfer reagent). Example: poly(methyl-methacrylate)

$$R\cdot + CH_2{=}CHX \Rightarrow RCH_2{-}\underset{X}{\overset{H}{C}}\cdot \qquad RCH_2{-}\underset{X}{\overset{H}{C}}\cdot + CH_2{=}CHX \Rightarrow RCH_2{-}CHX{-}CH_2{-}\underset{X}{\overset{H}{C}}\cdot$$

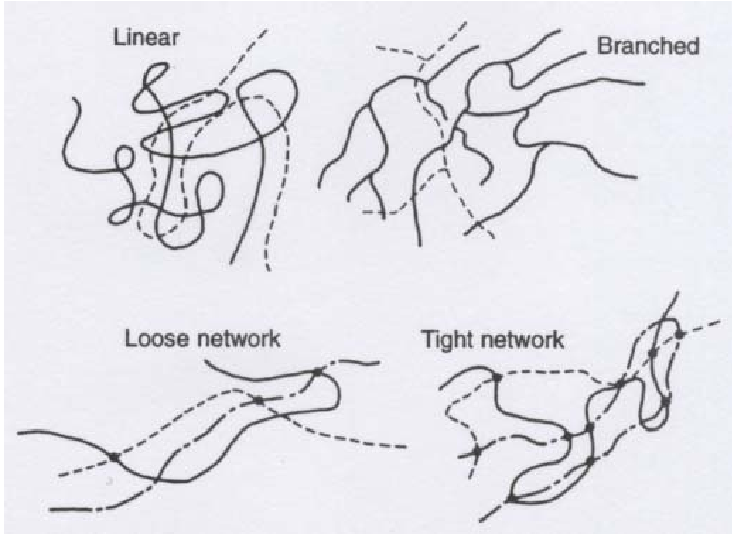
- **Condensation polymerization** (stepwise growth)

  two monomers react to form a covalent bond, usually with elimination of a small molecule (water, hydrochloric acid, methanol, or carbon dioxide) eksample:nylon

R–NH$_2$	+	R'COOH	⇔	R'CONHR	+	H$_2$O
(amine)		(carboxylic acid)		(amide)		(condensation molecule)

Polymer synthesis

- The choice of polymerization method strongly affects the polymer obtained.



- Homopolymers (only one type of monomer) or copolymers (two or more types of monomers) can be produced.

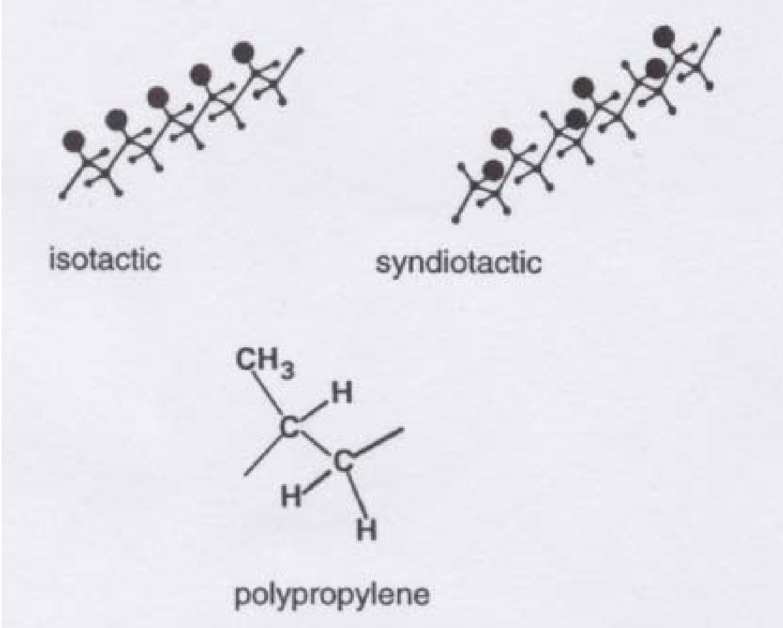
Homopolymer	–A–A–A–A–A–A–A–
Random copolymer	–A–B–B–A–B–A–B–
Alternating copolymer	–A–B–A–B–A–B–A–
Block copolymer	–A–A–A–A–B–B–B–

- Postpolymerization cross-linking (e.g. natural rubber (linear polyisopren-chains): vulcanization with sulfur (1-3%) to stronger rubber or with sulfur(40-50% to hard rubber).

Courtesy Rainer Zenz

Polymer properties

- **Tacticity:** arrangement of sub-stituents around the extended polymer chain.
  - Isotactic
  - Syndiotactic
  - Atactic



- Atactic polymers usually cannot crystalize; isotactic and syndiotactic polymers may crystalize if conditions are favorable. Crystallization is never complete, only crystallite structures form due to **amorphous** regions
- Presence of **crystallites** in the polymer leads to enhanced mechanical properties and fatigue strenght.

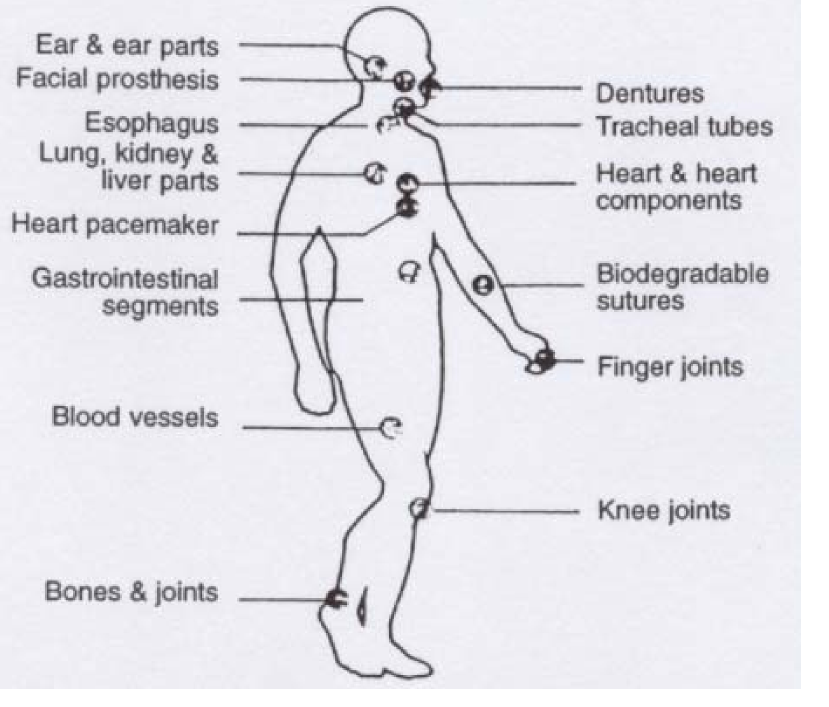
Thermal properties:

Liquid melt state (Brownian motion) – (T_m only for crystallites) – $\mathbf{T_{glass}}$ – solid state

Courtesy Rainer Zenz

Polymer-classes used in medicine

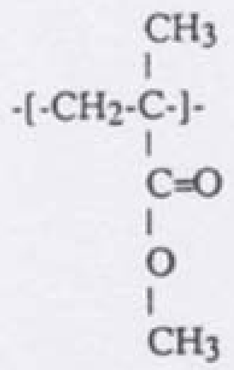
Ear & ear parts: acrylic, polyethylene, silicone, poly(vinyl chloride) (PVC)
Dentures: acrylic, ultrahigh molecular weight polyethylene (UHMWPE), epoxy
Facial prosthesis: acrylic, PVC, polyurethane (PUR)
Tracheal tubes: acrylic, silicone, nylon
Heart & heart components: polyester, silicone, PVC
Heart pacemaker: polyethylene, acetal
Lung, kidney & liver parts: polyester, polyaldehyde, PVC
Esophagus segments: polyethylene, polypropylene (PP), PVC
Blood vessels: PVC, polyester
Biodegradable sutures: PUR
Gastrointestinal segments: silicones, PVC, nylon
Finger joints: silicone, UHMWPE
Bones & joints: acrylic, nylon, silicone, PUR, PP, UHMWPE
Knee joints: polyethylene



Courtesy Rainer Zenz

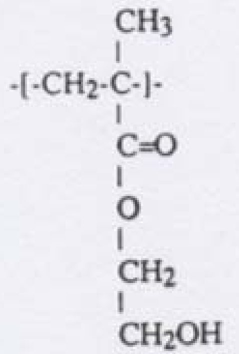
Homopolymers

- PMMA (Plexiglass): linear polymer, glassy at room temperature; intraocular lenses, hard contact lenses.

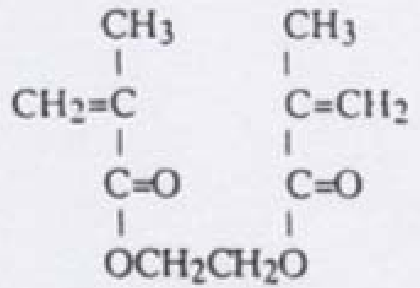


Poly(methyl methacrylate) (PMMA)

- HEMA slightly crosslinked with EGDM: fully hydrated it is a swollen hydrogel; soft contact lenses.



Poly(2-hydroxyethyl methacrylate) poly(HEMA)

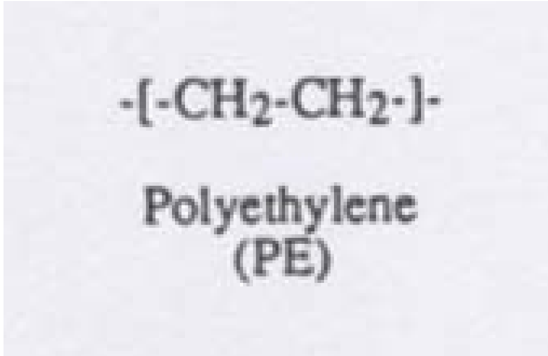


Ethylene glycol dimethacrylate (EGDM)

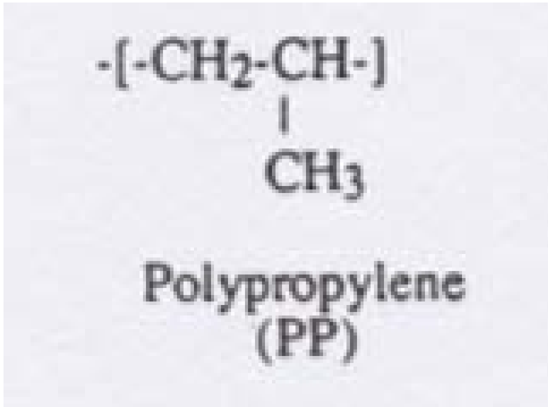
Courtesy Rainer Zenz

Homopolymers

- PE; good toughness, resistance to fats and oils, used in tubing for drains and catheters, acetabular component in artificial hips.



- PP; closely related to PE, good chem. resistance, good tensile strenght, many of the same applications as PE.



Courtesy Rainer Zenz

Homopolymers

- PTFE (Teflon): thermally and chemically very stable, very hydrophobic; in micro-porous form (Gore-Tex) used in vascular grafts.

$-[-CF_2-CF_2-]-$

Poly(tetrafluoroethylene)
(PTFE)

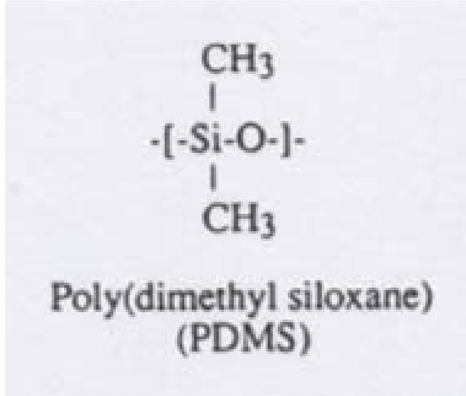
- PVC: pure very hard and brittel; soft and flexible after addition of plasticizers (can be extracted by the body: problem for long-time applications: less flexible); typical material for tubing (blood transfusion, feeding, and dialysis).

$-[-CH_2-CHCl-]-$

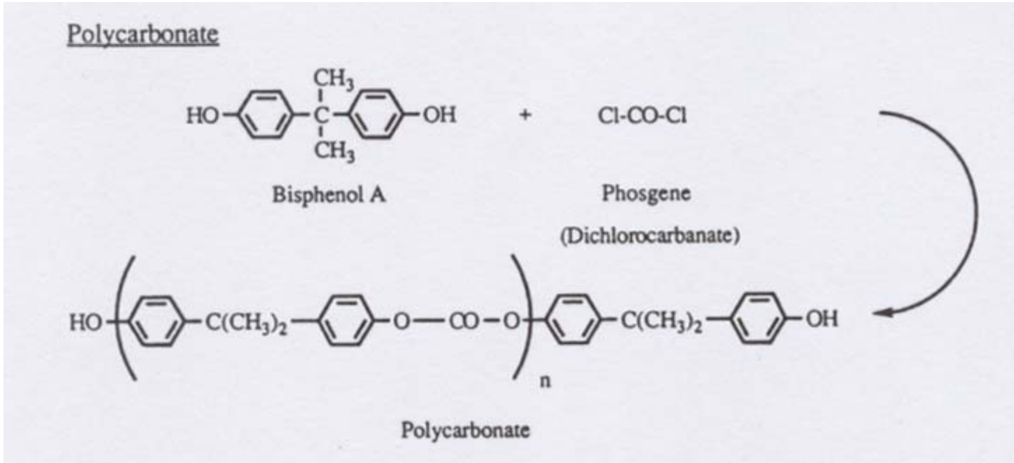
Poly(vinyl chloride)
(PVC)

Homopolymers

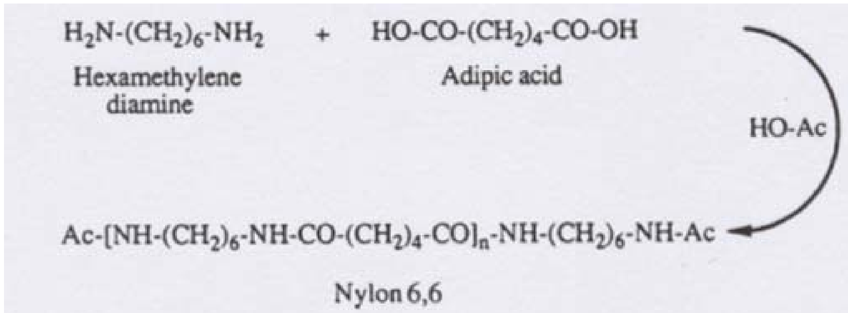
- PDMS: very versatile; catheters and drainage tubing, insulation of pacemaker leads, membrane oxygenators (high oxygen permeability), prostheses (finger, blood vesels, heart valves, breast implants,...)



- Polycarbonate: clear, tough material; lenses for eye-glasses and safety glasses

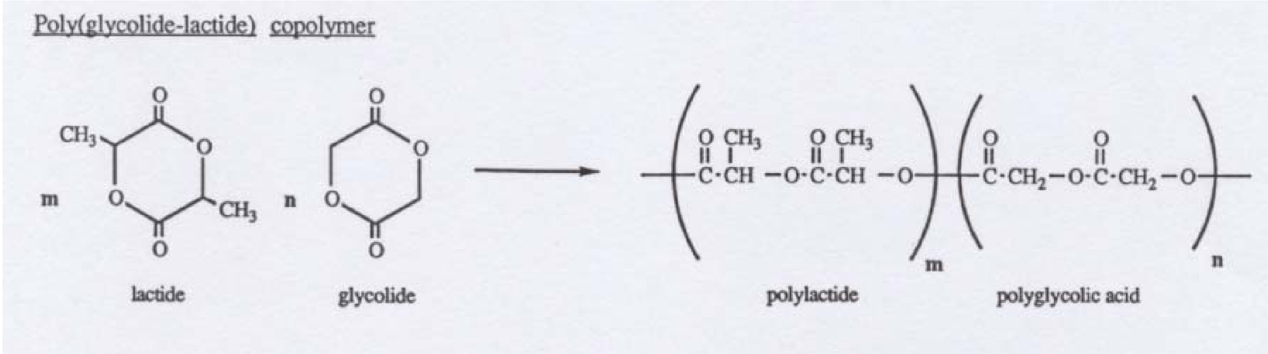


- Nylon: polyamide-family used in surgical sutures

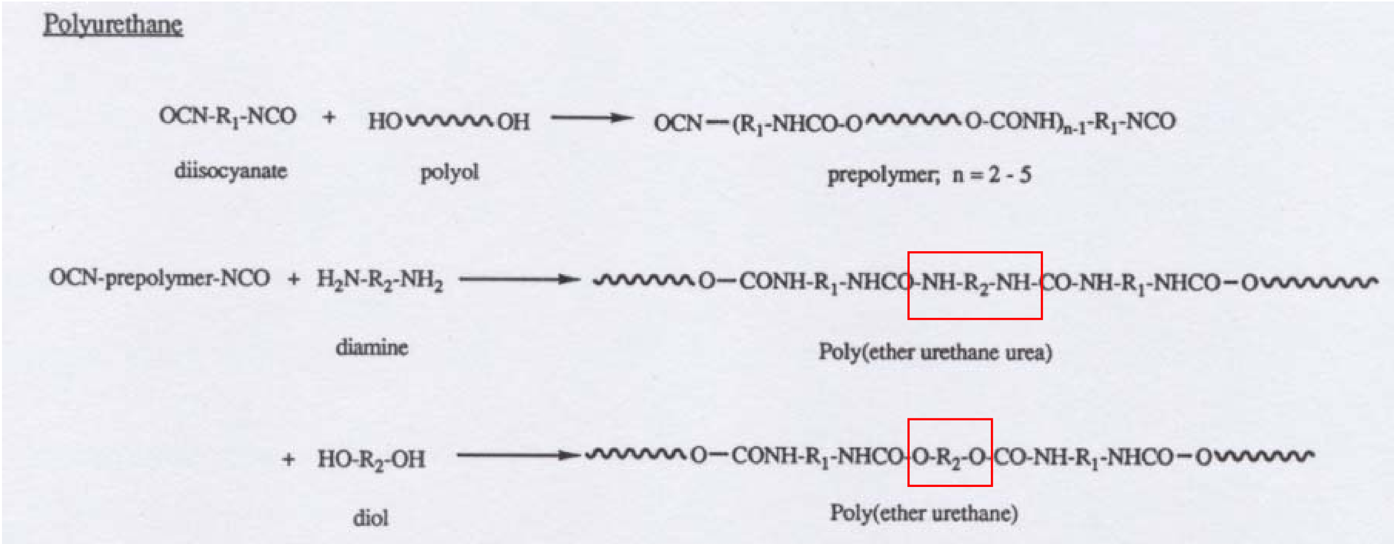


Copolymers

- PGL: random co-polymer, used in resorbable surgical sutures (gradual hydrolytic degradation of ester linkages in the polymer).



- Polyurethan: tough elastomers, stable to hydro-lysis;used in pace-maker insulation, vascular grafts.

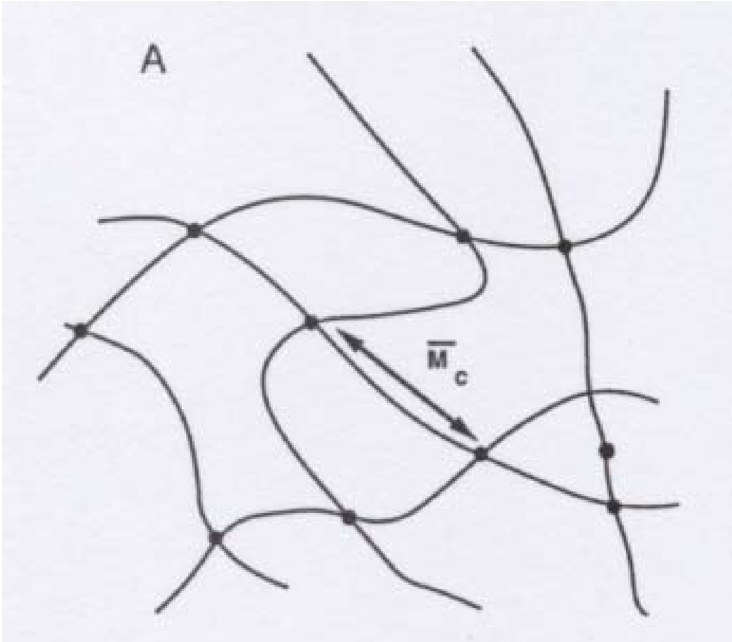


Hydrogels

- Hydrogels: water-swollen, cross-linked polymeric structures:
  - Homopolymers, copolymers, multipolymers, interpenetrating polymers
  - Neutral, anionic, cationic, ampholytic
  - Amorphous, semicrystalline, hydrogen-bonded, or complexation structures

- Prepared by swelling cross-linked structures in water or biological fluids.

- Cross-linking by:
  - Radiation reaction (gamma-rays, X-rays, UV-irradiation)
  - Chemical cross-linking



Hydrogels

- Highly swollen hydrogels:
  - Cellulose derivatives
  - Poly (vinyl alcohol)
  - PNVP (Poly (N-vinyl 2 pyrrolidone); soft contact lenses
  - Poly (ethylen glycol)

- Moderately swollen hydrogels:
  - PHEMA (poly (hydroxylethyl methacrylate))

    Is inert to normal biological processes, resistant to degradation, permeable to metabolites, not absorbed by the body, withstands heat sterilization, and can be prepared in a variety of shapes and forms.

Courtesy Rainer Zenz

Hydrogels

Highly biocompatible

- Blood-compatible biomaterials
- Contact lenses
- Artificial tendon material, kidney membranes, articular cartilage, artificial skin, vocal cord replacement materials
- Pharmaceutical applications:

  physiologically responsive drug release from swollen hydrogels (intelligent hydrogels).

Courtesy Rainer Zenz

Biodegradable Materials

biodgradation, bioerosion, bioabsorption, bioresorption...

- Eliminates additional surgery to remove an implant after it serves its function.
- Ideal when the „temporary presence“ of the implant is desired.
- Replaced by regenerated tissue as the implant degrades.

Courtesy Rainer Zenz

Biodegradable: Terminology

- Consensus conference of the European Society for Biomaterials:
  - Biodegradation: A biological agent (an enzyme, or cell) is responsible for degradation.
  - Bioerosion: contains both physical (such as dissolution) and chemical processes (such as backbone cleavage). E.g. a water-insoluble polymer that turns water-soluble under physiological conditions.
  - Bioresorption, Bioabsorption: Polymer or its degradation products removed by cellular activity (e.g. Phagocytosis).

Courtesy Rainer Zenz

Biodegradable Materials

- Degradation → short time application
  - Sutures
  - Drug delivery
  - Orthopedic fixation devices (requires exceptionally strong polymers)
  - Adhesion prevention (requires polymers that can form soft membranes of films)
  - Temporary vascular grafts (development stage, blood compatibility is a problem)

Biodegradable Materials

- Five main classes of degradable implants:
  - The temporary support device
  - The temporary tissue engineering scaffold
  - The temporary barrier
  - The drug delivery device
  - Multifunctional devices

Courtesy Rainer Zenz

Biodegradable: temporary support device

- Provides support until the tissue heals:
  - Weakened by disease, injury or surgery
  - Healing wound, broken bone, damaged blood vessel
  - Sutures, bone fixation devices, vascular grafts
- Rate of degradation:
  - Implant should degrade at the rate the tissue heals
- Sutures are most widely used:
  - Polyglycolic acid (PGA), Dexon®
  - Copolymers of PGA and PLA (polylactic acid) Vicryl®
  - Polydioxanone (PDS)

Courtesy Rainer Zenz

Biodegradable: temporary tissue engineering scaffold

- Artificial extracellular matrix providing space for cells to grow into and organize into functional tissue
- Rate of degradation:
  - Must maintain mechanical strength for support while new (bone) tissue forms. –Must not prohibit final tissue healing
- Structures most widely used:
  - Must be very porous
  - Feltlike material (knitted or woven fibers)
  - Foam or sponge like materials

Courtesy Rainer Zenz

Biodegradable: Barrier

- Prevent adhesion caused by clotting of blood in the extravasular tissue space.
  - Clotting → inflammation → fibrosis
  - Adhesion are common problems after cardiac, spinal and tendon surgery
  - Barrier in the form of thin membrane or film
- Another barrier use is artificial skin for treatment of burns

Courtesy Rainer Zenz

Biodegradable: Drug delivery

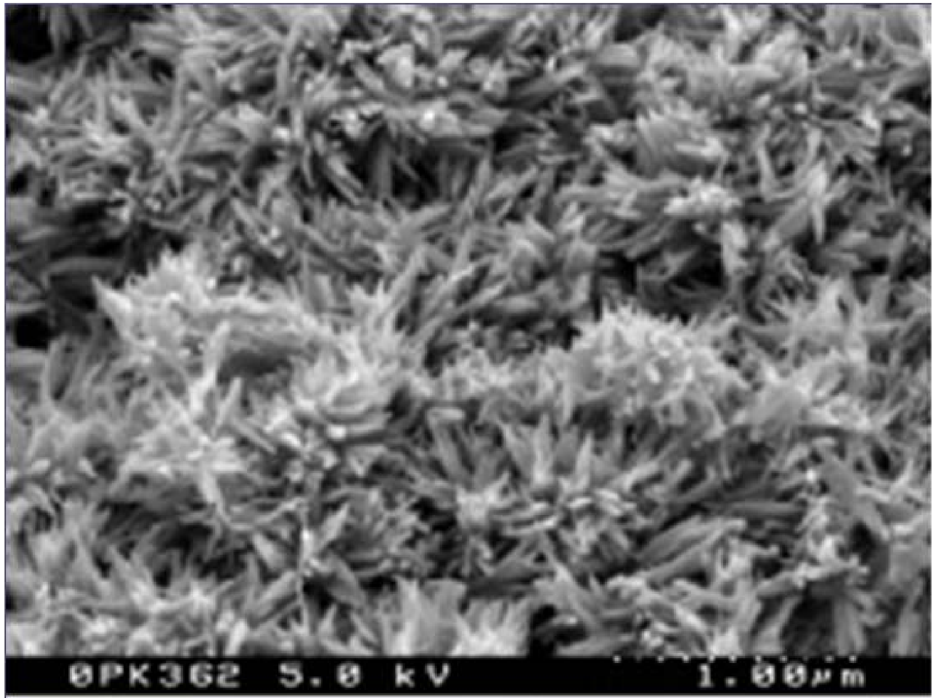
- Most widely investigated application
- PLA, PGA used frequently
- Polyanhydrides for administering chemotherapeutic agents to patients suffering from brain cancer.
- Encapsulated glucose oxidase (GOD) oxidizes glucose to gluconic acid (and H2O2) →local pH lowering →increased hydrogel poresize →insulin release

  Process: reversible

Biodegradable: Multifunctional devices

- Combination of several functions:

  Mechanical function + drug delivery:



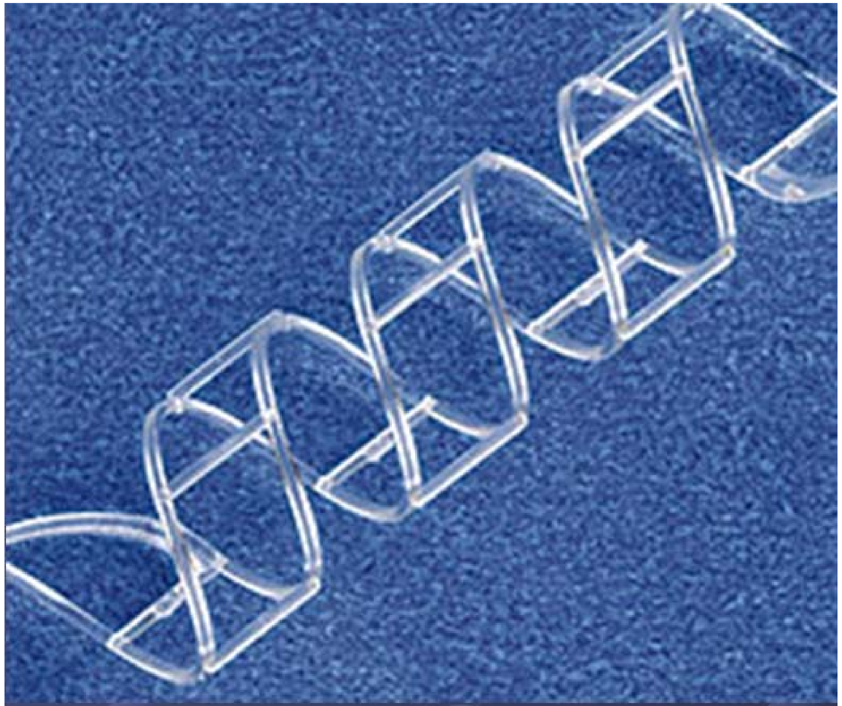
SEM image of biodegradable polyurethanes

Biodegradable bone nails and screws made of ultrahigh-strenght PLA and treated with BMP & TGF-β for stimulation of bone growth.

Courtesy Rainer Zenz

Biodegradable: Multifunctional devices

- Combination of several functions:
  - Mechanical support + drug delivery



Biodegradable intravascular stent molded from a blend of polylactide and trimethylene carbonate. Photo: Cordis Corp. Prototype

Biodegradable stents to prevent collapse and restenosis (reblocking) of arteries opened by balloon angioplasty and treated with anti-inflammatory or anti-thrombogenic agents.

Courtesy Rainer Zenz

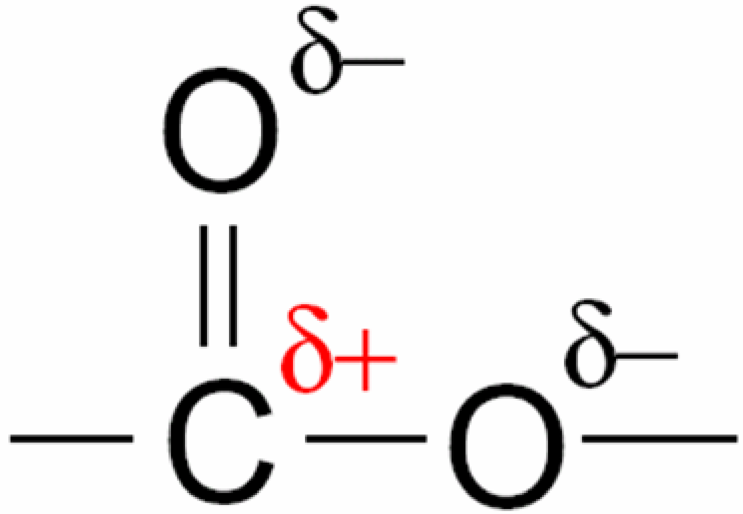
Biodegradable polymers

- Variety of available degradable polymers is limited due to stringent requirements:
  - Biocompatibility
  - Free from degradation related toxic products (e.g. monomers, stabilizers, polymerization initiators)
  - Few approved by FDA
  - PLA, PGA, PDS used routinely

Courtesy Rainer Zenz

Biodegradable polymers

- Most degradable polymers are polyesters.
- Ester is a covalent bond with polar nature; reactive.
- Can be broken down by hydrolysis.
- The C-O bond breaks.

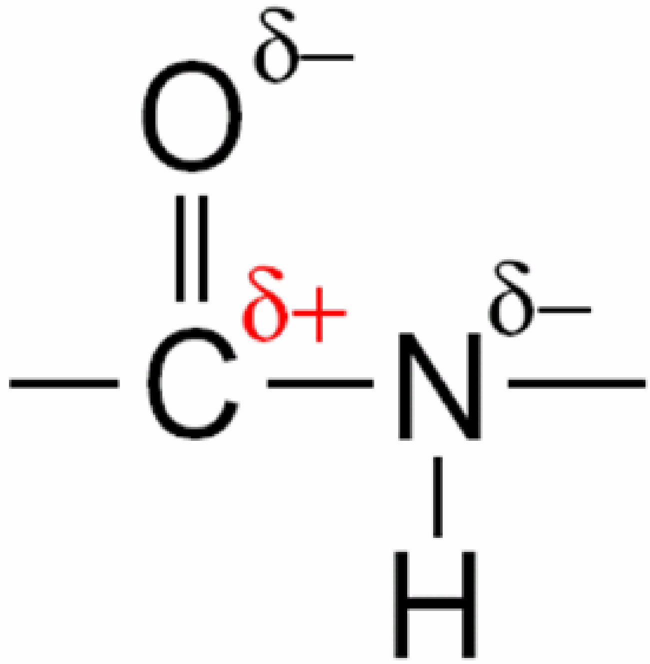


Ester bond

Courtesy Rainer Zenz

Biodegradable polymers

- Contain a **peptide (or amide)** link.
- Amide is a covalent bond with polar nature; reactive.
- Can be brocken down by hydrolysis.
- The C-N bond breaks.

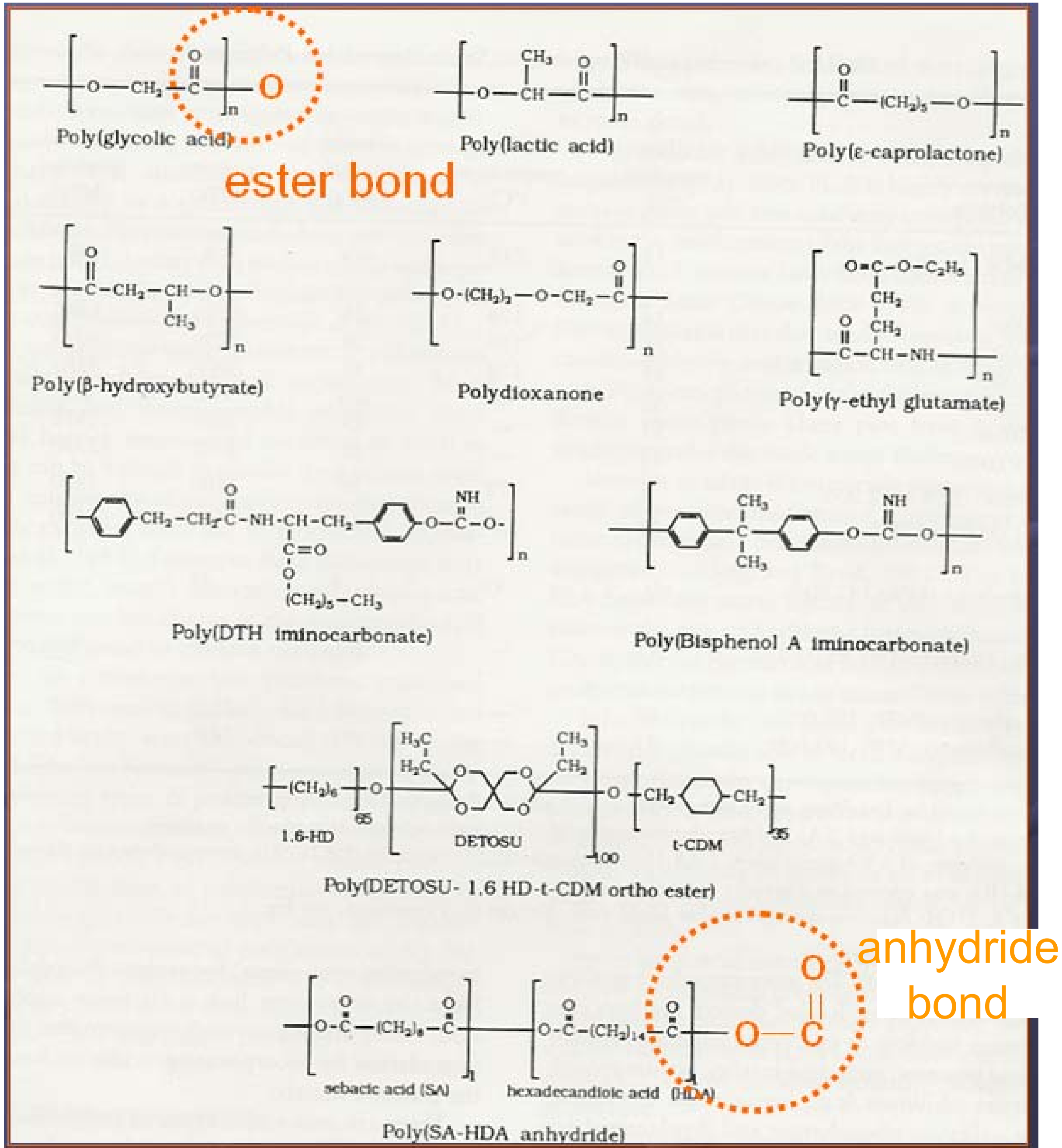


Amide bond

Courtesy Rainer Zenz

Biodegradable polymers

- PGA
  Poly (glycolic acid)
- PLA
  Poly (lactic acid)
- PDS
  Polydioxanone



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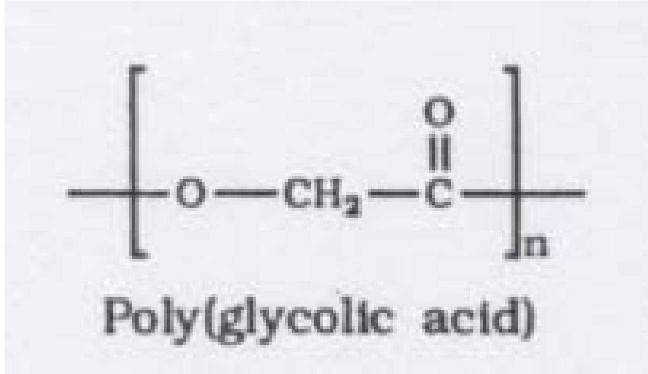
Biodegradable Polymers

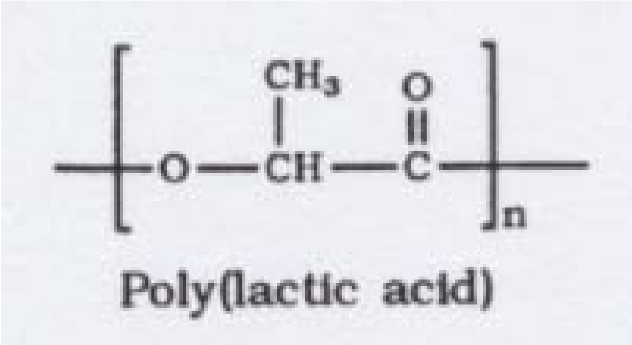
- PGA and PLA



  - Most widely used biodegradable polymers.
  - PGA is the simplest aliphatic polyester:
    - highly crystalline, high melting point, low solubility
    - appeared with the trade name Dexon.
    - Dexon sutures lose strength within 2-4 weeks (sooner than desired)
    - used as bone screws, Biofix®

Biodegradable Polymers

- PGA and PLA (cont.)



  - PLA
    - D,L-PLA amorphous polymer; used for drug delivery.
    - L-PLA semicrystalline; thus, mechanical applications such as sutures or orthopedic devices.

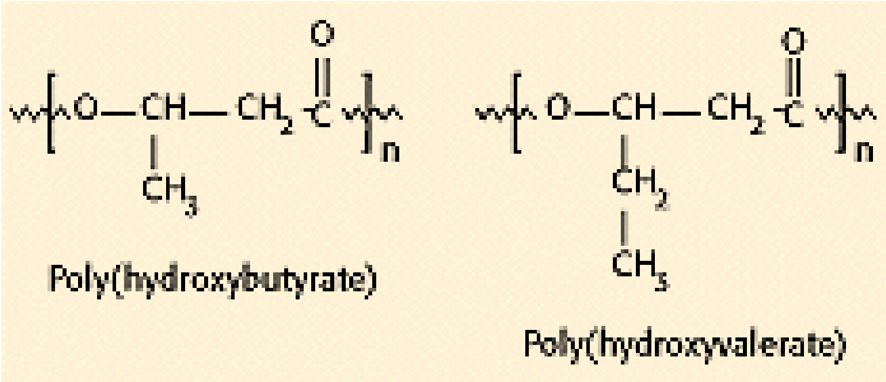
Biodegradable Polymers

- PGA and PLA (cont.)
  - Copolymers of PGA and PLA used to adapt material properties suitable for wider range of applications.
    - PLA is more hydrophobic than PGA.
    - Hydrophobicity of PLA limits water uptake of thin films to about 2% and reduces the rate of hydrolysis compared with PGA.
    - sutures with trade names:
      - Vicryl® and
      - Polyglactin 910®.

Courtesy Rainer Zenz

Biodegradable polymers

- PHB (polyhydroxybutyrate), PHV (polyhydroxyvalerate), and copolymers:

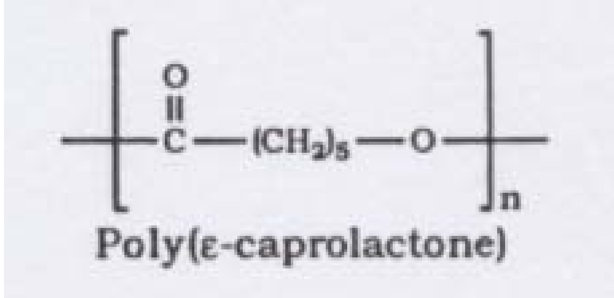


  - Polyesters synthesized and used by microorganisms for intracellular energy storage.
  - 70% PHB-30% PHV copolymer commercially available as Biopol®.
  - Rate of degradation controlled by varying copolymer composition.

Biodegradable Polymers

- PHB (polyhydroxybutyrate), PHV (polyhydroxyvalerate), and copolymers (cont.):
  - *in vivo* PHB degrades to hydroxybutyric acid which is a normal constituent of human blood ➔ biocompatible, nontoxic.
  - PHB homopolymer is highly crystalline and brittle.
  - copolymer of PHB with hydroxyvaleric acid is less crystalline, more flexible and more processible.
  - used in controlled drug release, suturing, artificial skin, and paramedical disposables.

Biodegradable Polymers



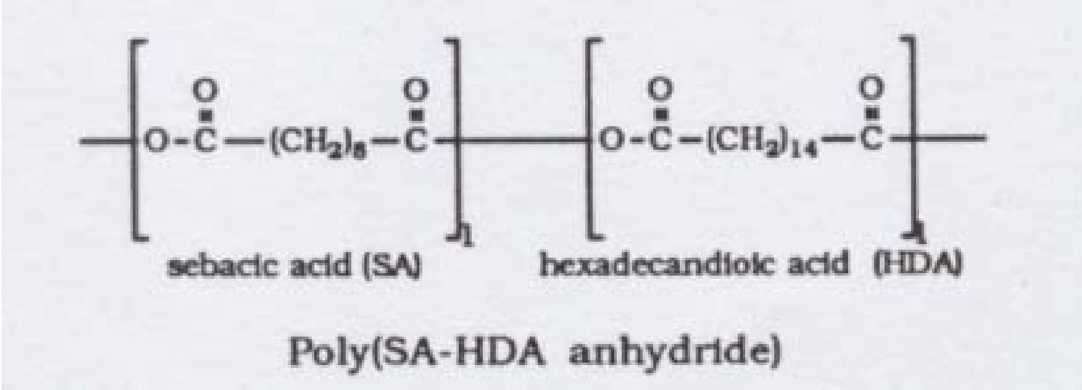
- Polycaprolactone:
  - semi-crystalline polymer
  - slower degradation rate than PLA
  - remains active as long as a year for drug delivery
  - Capronor®, implantable biodegradable contraceptive:
    - implanted under skin.
    - dissolve in the body and does not require removal.
    - degradation of the poly(ε-caprolactone) matrix occurs through bulk hydrolysis of ester linkages eventually to CO_2 and water.

Biodegradable Polymers

- Capronor®, implantable biodegradable contraceptive (cont.):
  - Capronor II consists of 2 rods of poly(ε-caprolactone) each containing 18 mg of levonorgestrel (gestagene, contraceptive).
  - Capronor III is a single capsule of copolymer (caprolactone and trimethylenecarbonate) filled with 32 mg of levonorgestrel.
  - The implant remains intact during the first year of use, thus could be removed if needed.
  - Over the second year, it biodegrades to carbon dioxide and water, which are absorbed by the body.

Biodegradable Polymers

- Polyanhydrides:



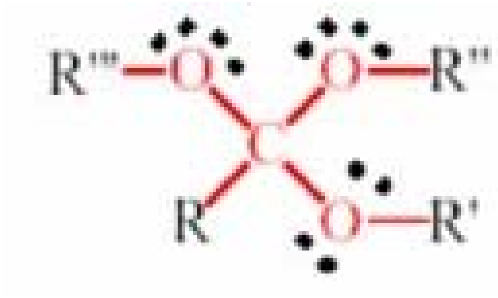
  - highly reactive and hydrolytically unstable.
  - degrade by surface degradation without the need for catalysts.
  - aliphatic (CH_2 in backbone and side chains) polyanhydrides degrade within days.
  - aromatic (benzene ring as the side chain) polyanhydrides degrade over several years.

Biodegradable Polymers

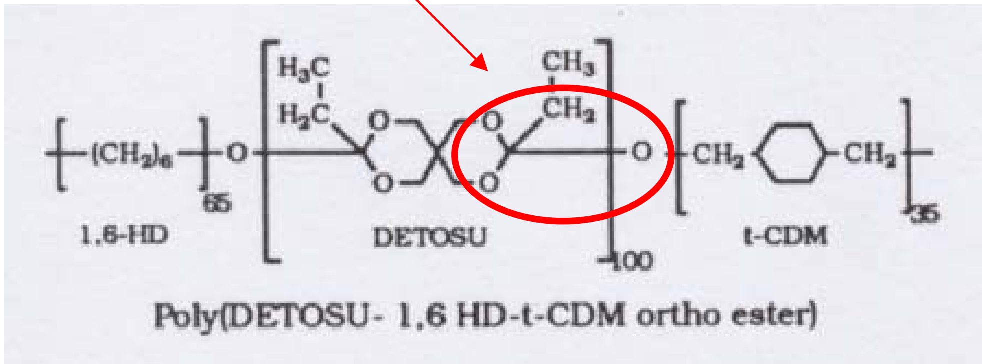
- Polyanhydrides (cont.):
  - aliphatic-aromatic copolymers can be used to tailor degradation rate.
  - excellent biocompatibility.
  - used in drug delivery.
  - drug loaded devices prepared by compression molding or microencapsulation.
  - insulin, bovine growth factors, angiogenesis inhibitors, enzymes,…

Biodegradable Polymers

- Polyorthoesters:



ortho ester



  - formulated so that degradation occurs by surface erosion.
  - drug release at a constant rate.

Biodegradable Polymers

- Polyaminoacids:
  - poly-L-lysine, polyglutamic acid.
  - Amino acid side-chains offer sites for drug attachment.
  - low-level systemic toxicity owing to their similarity to naturally occurring amino acids.
  - investigated as suture materials.
  - artificial skin substitutes.
  - limited applicability as biomaterials due to limited solubility and processibility.
  - polymers containing more than three or more amino acids may trigger antigenic response.

Courtesy Rainer Zenz

Biodegradable Polymers

- Polycyanoacrylates:
  - used as bioadhesives.
  - use as implantable material is limited due to significant inflammatory response.
- Polyphosphazenes:
  - inorganic polymer.
  - backbone consists of nitrogen-phosphorus bonds.
  - use for drug delivery under investigation.

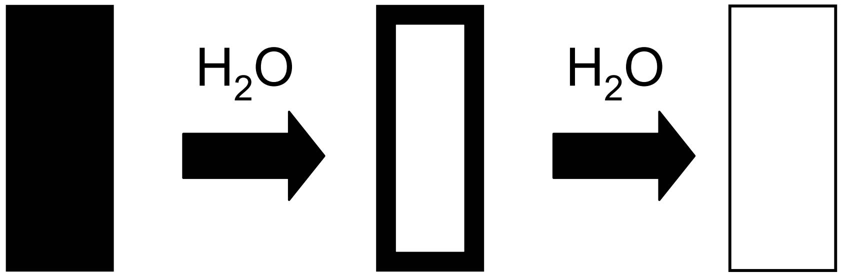
Biodegradable Polymers: Bioerosion

- Bioerosion cause:
  - changes in the appearance of the device
  - changes in the physicomechanical properties
  - swelling
  - deformation
  - structural disintegration
  - weight loss
  - loss of function

Biodegradable Polymers: Bioerosion

- Bioerosion is due to:
  - chemical degradation:
    - cleavage of backbone
    - cleavage of cross-links
    - side chains
  - physical processes (e.g. changes in pH)
- Two types of erosion:
  - bulk erosion
  - surface erosion

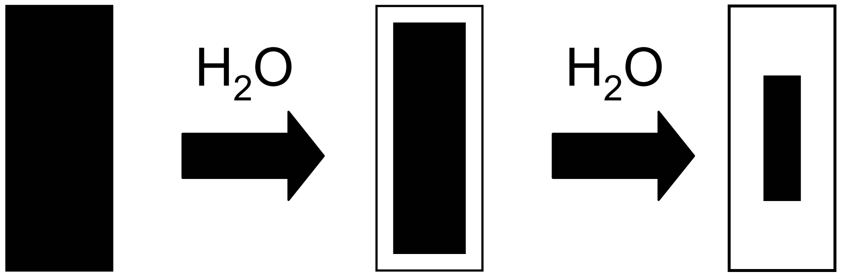
Biodegradable Polymers: Bioerosion



- bulk erosion:
  - water enters polymer
  - causes hydrolytic degradation
  - component hollowed out
  - finally crumbles (like sugar cube in water)
  - releases acid groups ➔ possible inflammation
  - characteristic of hydrophilic polymers

Courtesy Rainer Zenz

Biodegradable Polymers: Bioerosion



- surface erosion:
  - water penetration limited,
  - degradation occurs on the surface.
  - thinning of the component over time.
  - integrity is maintained over longer time when compared to bulk erosion.
  - hydrophobic polymers experience surface erosion since water intake limited.
  - acidic byproducts are released gradually ➔ acid burst less likely, lower chance of inflammation.
  - surface erosion can also occur via enzymatic degradation.

Courtesy Rainer Zenz

Biodegradable Polymers: Bioerosion

- Factors that determine rate of erosion:
  - chemical stability of the polymer backbone
    - erosion rate: anhydride > ester > amide
  - hydrophobicity of the monomer (addition of hydrophobic co-monomers reduce erosion rate).
  - morphology of polymer:
    - crystalline vs. amorphous:
      - crystallinity (high packing density): allows low water penetration; results in low erosion rate

Courtesy Rainer Zenz

Biodegradable Polymers: Bioerosion

- Factors that determine rate of erosion (cont.):
  - initial molecular weight of the polymer
  - fabrication process
  - presence of catalysts, additives or plasticizers
  - geometry of the implanted device (surface/volume ratio)
  - Polymer less permeable to water in glassy state:
    - T_g of the polymer should be greater than 37 °C to maintain resistance to hydrolysis under physiological conditions.

Courtesy Rainer Zenz

Biodegradable Polymers: Chemical Degradation

- Chemical degradation mediated by water, enzymes, microorganisms.

- Mechanisms of chemical degradation:
  - cleavage of cross-links between chains
  - cleavage of side chains
  - cleavage of polymer backbone
  - combination of above

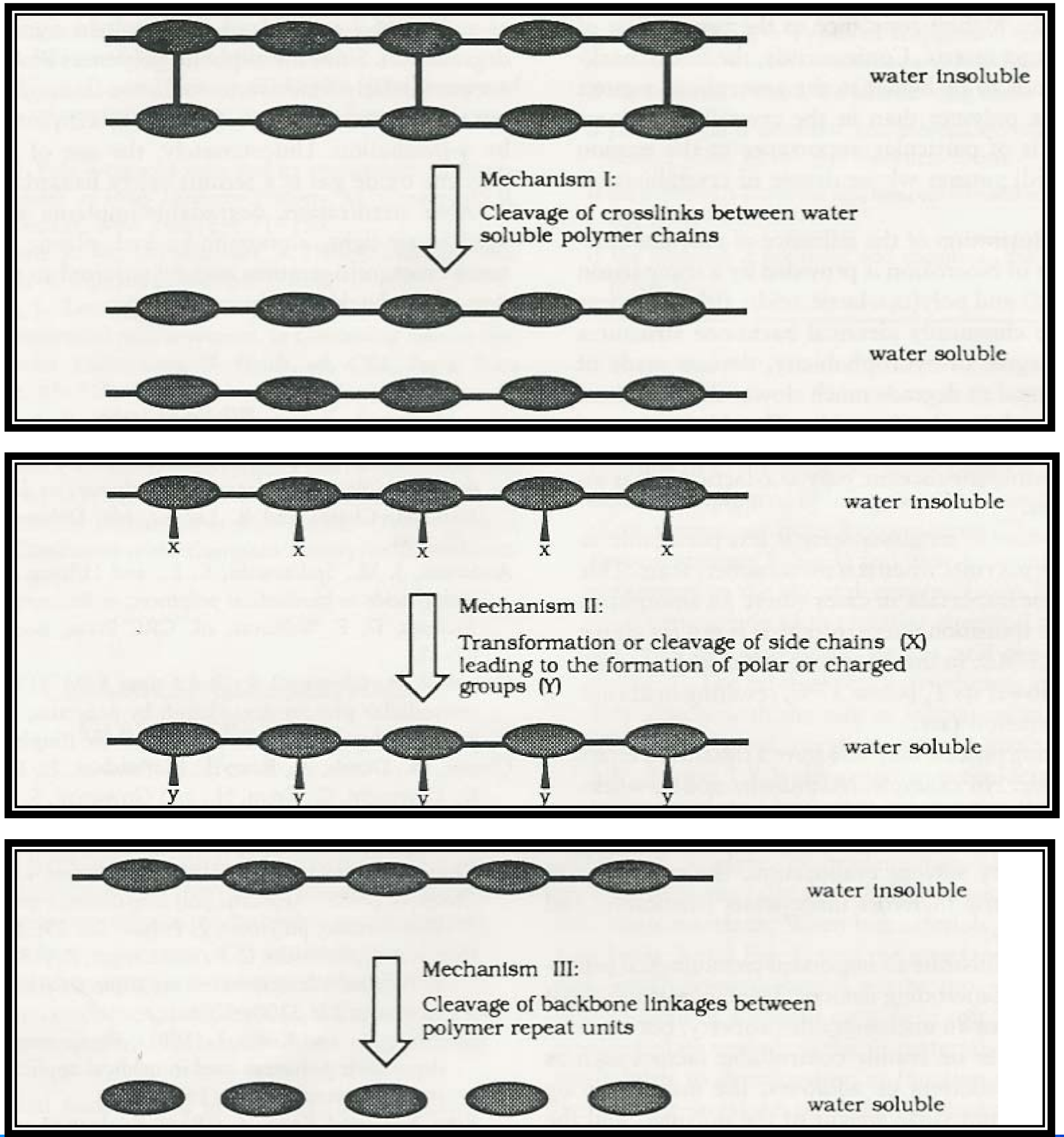
Courtesy Rainer Zenz

Biodegradable Polymers: Chemical Degradation

CLEAVAGE OF CROSSLINKS

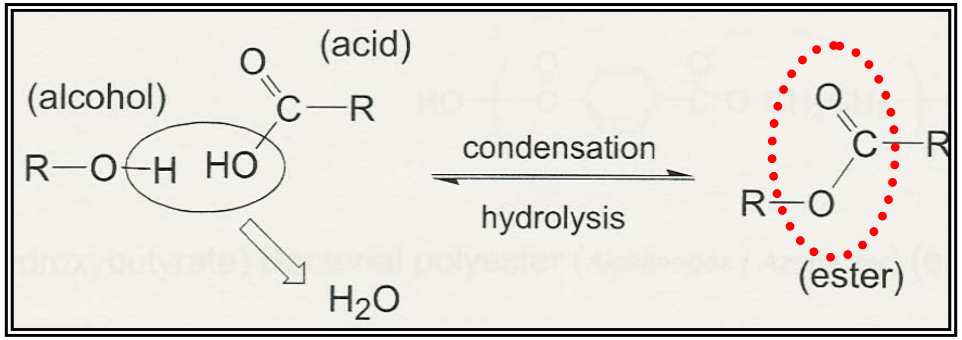
TRANSFORMATION OF SIDE CHAINS

CLEAVAGE OF BACKBONE



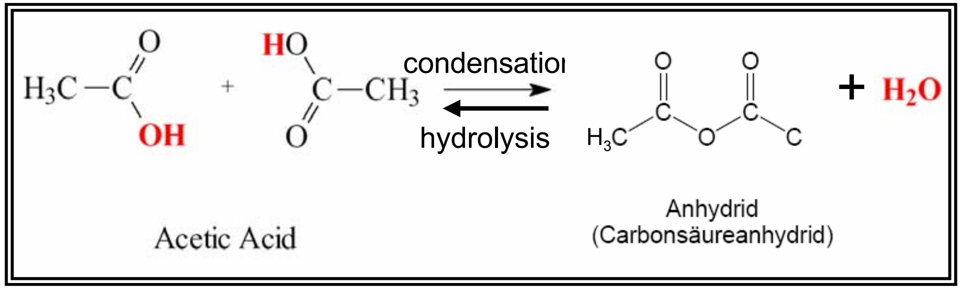
Hydrolysis of biodegradable polymers

- Breakdown of a molecule in the presence of water.



- Hydrolysis of the ester bond results in formation of an acid and an alcohol.

- Hydrolysis of the anhydride bond results in formation of two acids.



- Inverse of reaction to hydrolysis is condensation (remember condensation polymerization).

Biodegradable Polymers: Storage, Sterilization and Packaging

- minimize premature polymer degradation during fabrication and storage.
- moisture can seriously degrade, controlled atmosphere facilities required.
- Sterilization:
  - γ-irradiation or ethylene oxide
  - both methods degrade physical properties
  - choose lesser of two evils for a given polymer
  - γ-irradiation dose at 2-3 Mrad (standard level to reduce HIV,) can induce significant backbone damage
  - ethylene oxide (highly toxic)
  - Alternative: production under sterile conditions (ex: scaffold+cells)

- Packed in airtight, aluminum-backed, plastic foil pouches.
- Refrigeration may be necessary

Courtesy Rainer Zenz