Lecture 2: Molecular Design and Synthesis of Biomaterials I: Biodegradable Solid Polymeric Materials (continued)

Last time: chemistry and physical chemistry of degrading polymeric solids for biomaterials

Today: Theory of polymer erosion
Enzymatic degradation of synthetic biomaterials
Designing degradable materials

Reading: A. Gopferich, "Mechanisms of polymer degradation and erosion,' *Biomaterials* **17**, 103 (1996)
Ratner p. 243-259

Supplementary Reading: R.J. Young and P.A. Lovell, "Introduction to Polymers," ch. 4 *Polymer Structure* pp. 241-309 (crystallization of polymers, Tm, glass transition, etc.)

Surface vs. Bulk Hydrolysis: Göpferich's theory for polymer erosion[1-4]

Biodegradable solids may have differing *modes* of degradation:
Surface erosion – degradation from exterior only with little/no water penetration into bulk
Bulk erosion – water penetrates entire structure and degrades entire device simultaneously

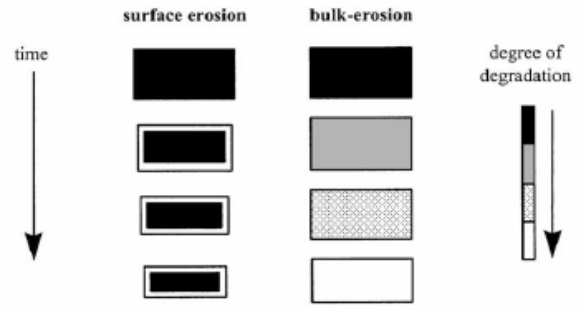


Fig. 1. Schematic illustration of the changes a polymer matrix undergoes during surface erosion and bulk erosion.

Polymers hydrolyzing by mechanisms II or III can be either surface or bulk eroding.[5-7]

Assuming that a polymer is water insoluble (initially) and that hydrolysis is the only mechanism of breakdown, the factors listed above all vary two rates of importance:
rate of water diffusion into polymer
rate of chain cleavage by water ions
The balance of these rates determines whether a polymer erodes from the surface in or by simultaneous degradation throughout the material:

Comparing velocities of water diffusion and chain cleavage:

Accounting for rate of water diffusion: Time required for water to diffuse a mean distance <x> into the solid polymer:

(1) $t_{diff} = \langle x \rangle^2 \pi / 4D_{H2O}$

D_{H2O} = effective diffusivity of water in polymer

See Atkins Phys. Chem p. 770 for derivation

Random walk:

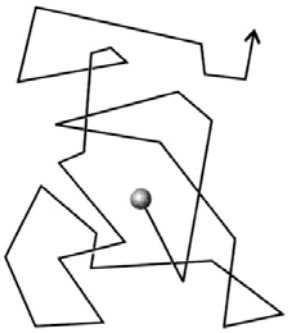


Fig. 10.18 One possible path of a random walk in three dimensions. In this general case, the step length is also a random variable.

(Atkins[8])

Mean distance from origin traveled by water molecule after time t = $\langle r \rangle = (2D_{H2O}t)^{1/2}$

Mean distance traveled in x direction = $\langle x \rangle = 2(D_{H2O}t_{diff}/\pi)^{1/2}$

EXPLAIN

Number of bonds in depth <x>:

(2) $n = \langle x \rangle (\text{bonds/cm}^3)^{1/3} = \langle x \rangle (N_{Av}\rho/M_0)^{1/3}$

N_{Av} = Avogadro's number

ρ = polymer density

M_0 = molecular weight of polymer repeat unit

Accounting for rate of chain cleavage (k): probability that a bonds breaks in the interval (0,t):

(3) $p(t) = ke^{-kt}$

where we have assumed that chain cleavage is a random event following Poisson kinetics

k = rate constant for bond hydrolysis

Therefore the mean lifetime of a single bond is given by:

(4) $$\langle t_c \rangle = \int_0^\infty t\, p(t)\, dt = \int_0^\infty t\, e^{-kt}\, dt = \frac{-1}{k}(kt+1)e^{-kt}\Big|_0^\infty = \frac{1}{k}$$

Time to degrade *n* bonds is a zero-order waiting time distributed according to a zero-order Erlang distribution:

(5) $\langle t_c(n) \rangle = (1/k)\Sigma[i=1 \text{ to } n]\ (1/i) \approx (1/k)\ln(n)$

$= (1/k)[\ln \langle x \rangle + (1/3)\ln(N_{Av}\rho/M_0)]$ (substituting (2))

Mechanism (surface vs. bulk) is controlled by ratio of time for diffusion to time for hydrolysis, a dimensionless parameter analogous to a Deborah number:

Erosion number = ε

(5) $\varepsilon \equiv t_{diff}/\langle t_c(n)\rangle = \langle x\rangle^2 k_c \pi/[4D_{H2O}\{\ln\langle x\rangle + (1/3)\ln(N_{Av}\rho/M_0)\}]$

- note <x> in denominator ln should have same units as ρ, i.e. cm if ρ is in g/cm^3

If <x> is replaced by the total thickness of a degrading sample, we can predict the mechanism of erosion:

$\varepsilon > 1$	bulk erosion
$\varepsilon = 1$	change in erosion mechanism
$\varepsilon < 1$	surface erosion

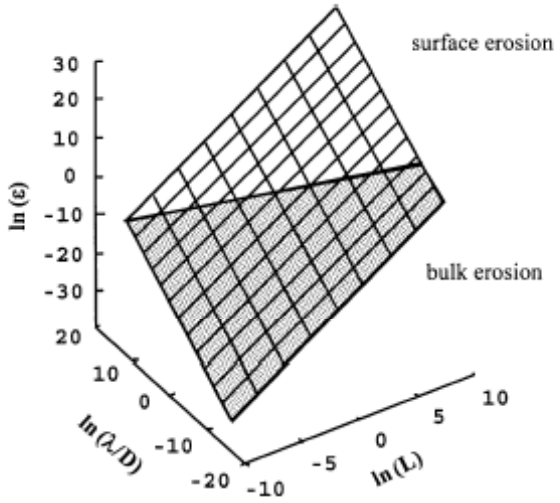
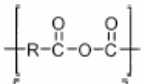
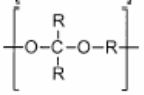
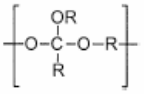
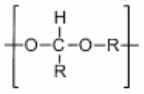
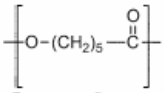
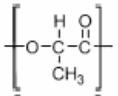


Fig. 2. Dependence of the erosion number, ε, on the diffusivity of water inside the polymer, D_{eff}, the dimensions of a polymer matrix, L, and the polymer bond reactivity, λ, calculated from equation 7. The white plane represents the area of surface erosion, the gray one the area of bulk erosion.

- mass loss is linear for surface-eroding devices only

Table 1
Estimated values of ε and $L_{critical}$ for selected degradable polymers

Chemical structure	Polymer	λ (s^{-1})	ε^a	$L_{critical}^b$
	Poly(anhydrides)	1.9×10^{-3} Ref. [30]	11,515	75 μm
	Poly(ketal)	6.4×10^{-5} Ref. [30]	387	0.4 mm
	Poly(ortho esters)	4.8×10^{-5} Ref. [30]	291	0.6 mm
	Poly(acetal)	2.7×10^{-8} Ref. [30]	0.16	2.4 cm
	Poly(ε-caprolactone)	9.7×10^{-8} Ref. [31]	0.1	1.3 cm
	Poly(α-hydroxy-esters)	$6.6 \times \cdot 10^{-9}$ Ref. [30]	4.0×10^{-2}	7.4 cm
	Poly(amides)	2.6×10^{-13} Ref. [30]	1.5×10^{-6}	13.4 m

[a] For a 1 cm thick device, $D = 10^{-8}\,cm^2\,s^{-1}$ (estimated from Ref. [32]) and $\ln\left[\sqrt[3]{\overline{M_n}/N_A(N-1)\rho}\right] = -16.5$.

[b] $D = 10^{-8}\,cm^2\,s^{-1}$ (estimated from Ref. [32]) and $\ln\left[\sqrt[3]{\overline{M_n}/N_A(N-1)\rho}\right] = -16.5$.

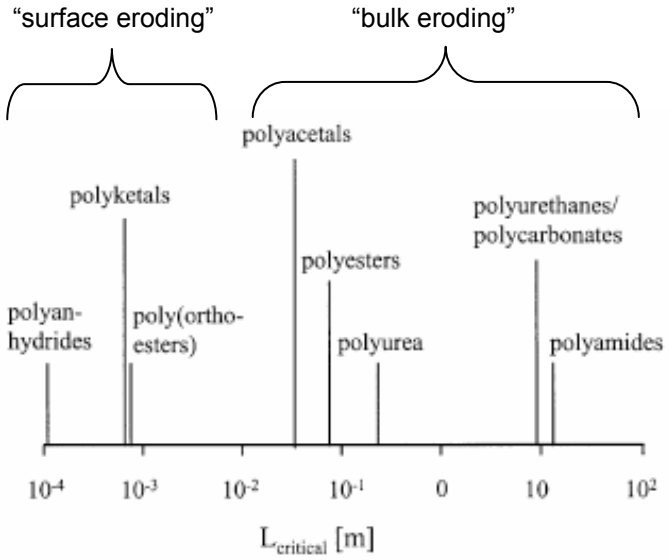


Fig. 3. Critical thickness, $L_{critical}$, that a polymer device has to exceed to undergo surface erosion (calculated from Eq. (7), data shown in Table 1).

Experimental demonstration of theory:

Transition of PLGA erosion from bulk to surface mode:
degraded at basic pH (>12)- increased k_c, thus decreasing $\varepsilon << 1$

Bulk (normal erosion at pH 7.4):

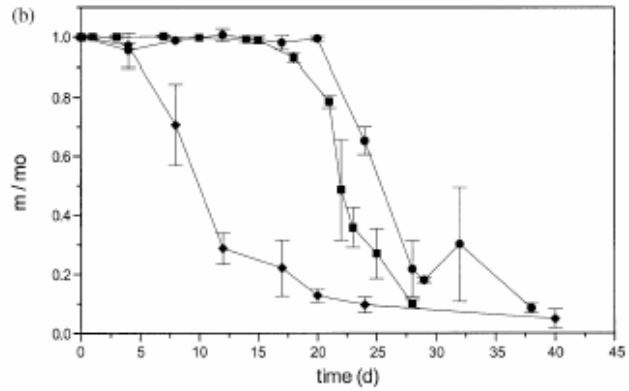


Fig. 4. Erosion profiles of poly(α-hydroxy esters) at pH 7.4: (a) $PLA_{50}11h$ (○) and PLA5017 (□), (b) $PLA_{25}GA_{50}8h$ (◆). $PLA_{25}GA_{50}14$ (●) and $PLA_{25}GA_{50}47h$ (■).

Surface (pH > 12):

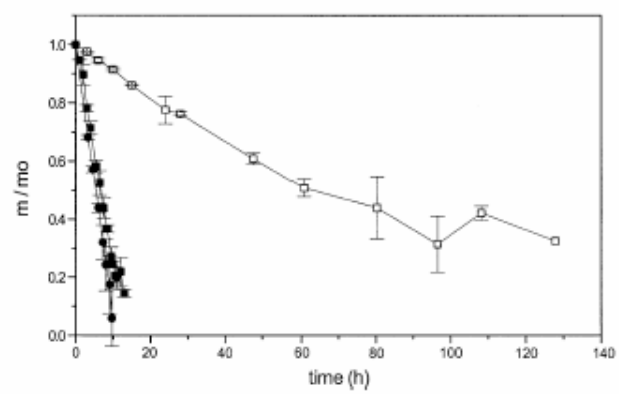


Fig. 9. Erosion of poly(α-hydroxy esters) at pH > 13: $PLA_{25}GA_{50}14$ (●) and $PLA_{50}17$ (□), $PLA_{25}GA_{50}47h$ (■).

SEM shown previously (Fig. 13) confirms transition to surface mode

Synthesizing biodegradable macromolecules to tailor properties

Approaches to molecular design

- Copolymerization
  - Control polymer hydrophobicity -> degradation rate
  - Control concentration of reactive groups
  - Alter biocompatibility
    - What are the degradation products? Acidity/basicity? Toxicity? Biological effects?

- Vary Tm, Tg[9], (mechanical properties)

(SLIDE)

Table 3. Properties of poly(CL-co-DXO), poly(VL-co-DXO), and poly(LLA-co-DXO)

Sample	% DXO in copolymer	T_g (DSC) [°C]	T_m (DSC) [°C]
CD50	50	−56.8	27.8
CD60	41	−57.8	27.2
CD70	29	−55.5	36.0
CD80	18	−61.0	42.8
CD90	8	−65.6	50.5
CD100	0	−65.9	57.6
VD70	33	−56.7	28.0
VD80	25	−56.1	37.7
VD90	7	−59.9	46.0
VD100	0	−63.4	57.5
LD70	28	23.1	154.1
LD85	13	41.1	170.8
LD100	0	58.5	183.8

Data adopted from [134]

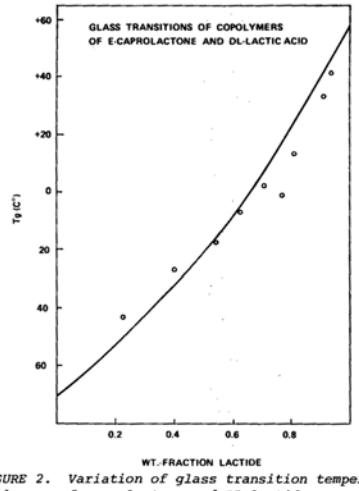


FIGURE 2. Variation of glass transition temperature (T_g) of copolymers of caprolactone and DL-lactide as a function of DL-lactide content. Solid line is calculated relationship, based on Fox equation (from Reference 8).

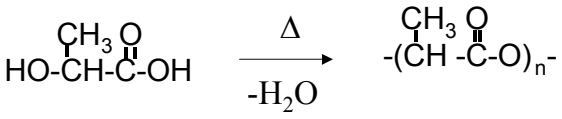
Polymer 36, 1009 (1995)

- Reactions on polymers/Polymer functionalization

Controlling Molecular Architecture

We won't undertake an exhaustive description, but some of the important methods to be aware of:

- Condensation polymerization
  - Not very efficient, produces low molecular weight polymers (usually ≤ 10K g/mole)



- Has been found useful for growing dendritic polymers:
  - Prepared using AB_2-type monomers

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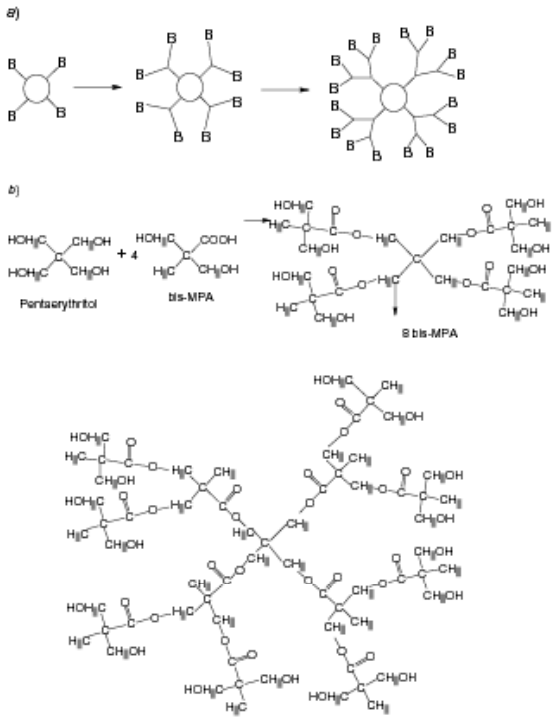
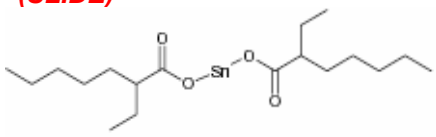


Scheme 22. *a*) The divergent growth approach for the preparation of dendritic polyesters. *b*) The divergent approach for the preparation of dendrimer having 16-hydroxy groups

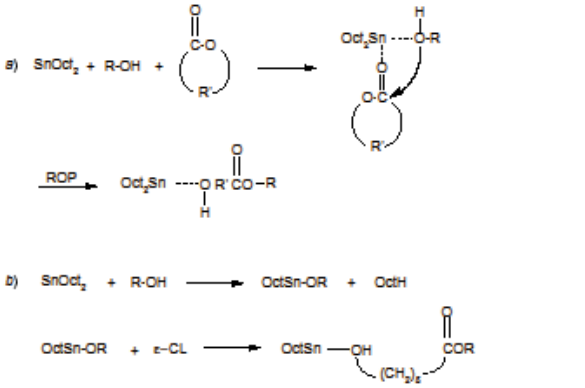
- Ring-opening polymerization
  - Catalysis by stannous octoate (tin 2-ethyl hexanoate, FDA-approved)
    - Useful for polyesters (PLA, PCL, PGA, and their copolymers)[10]
    - Polymerization initiates from alcohol co-initiator groups by a coordination-insertion mechanism:

(SLIDE)

Tin(II) 2-ethylhexanoate[11]:

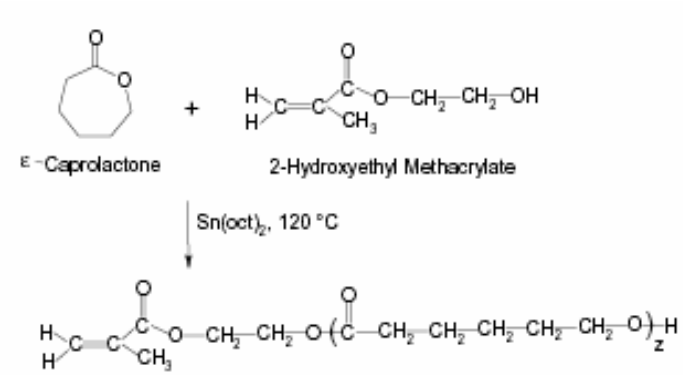


Proposed mechanisms: ***(on board)***



Scheme 6. The main ROP mechanism proposals with $Sn(Oct)_2$ as catalyst, *a*) complexation of a monomer and alcohol prior to ROP and *b*) formation of a tin-alkoxide before ROP of -CL

example insertion:



Scheme 17. α-Methacryloyl-ω-hydroxyl-poly(ε-caprolactone) macromonomer

- For lactide and glycolide, each ring monomer opens to 2 lactic acid/glycolic acid moieties:

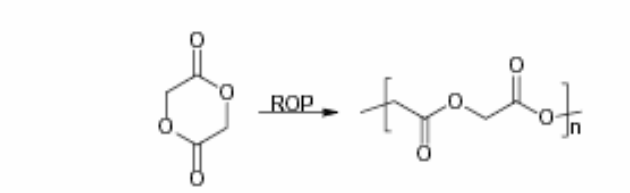
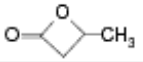
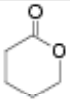
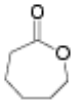
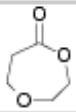
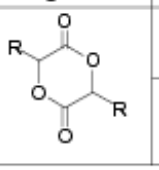


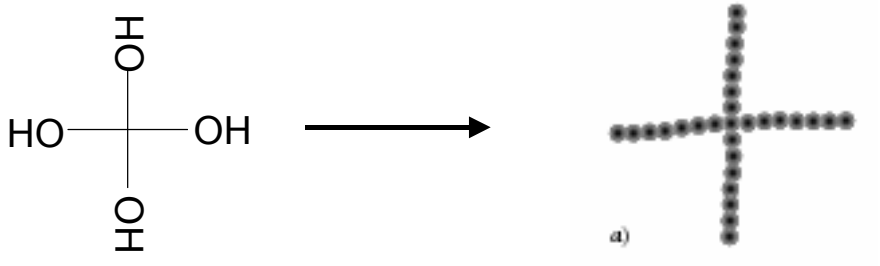
Fig. 8. The chemical structure of glycolide and the resulting repeating unit

A variety of similar catalysts can be used to polymerize lactone ring monomers: ***(SLIDE)***

Table 1. Structure and designation of various lactones

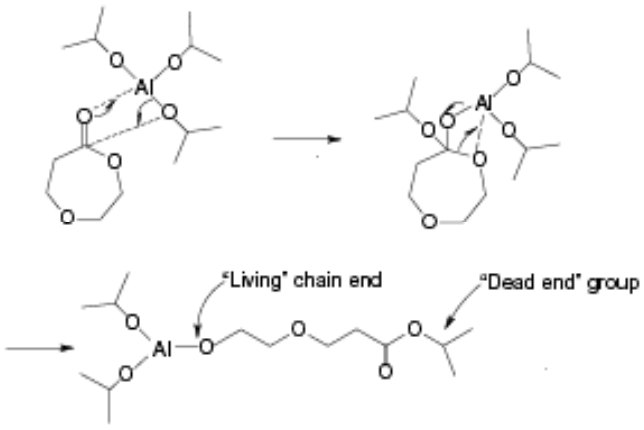
β-propiolactone		β-PL
γ-butyrolactone		γ-BL
β-butyrolactone		β-BL
δ-valerolactone		δ-VL
ε-caprolactone		ε-CL
1,5-dioxepan-2-one		DXO
R=H; glycolide		GA
$R=CH_3$; lactide		LA

- Multi-alcohol initiators permit synthesis of multi-armed polymers:



- Living ring-opening polymerization
  - Coordination-insertion catalysts: e.g. aluminum isopropoxide[10]

Provide control over molecular weight and MWD:



Scheme 15. Aluminum isopropoxide initiated polymerization of 1,5-dioxepan-2-one

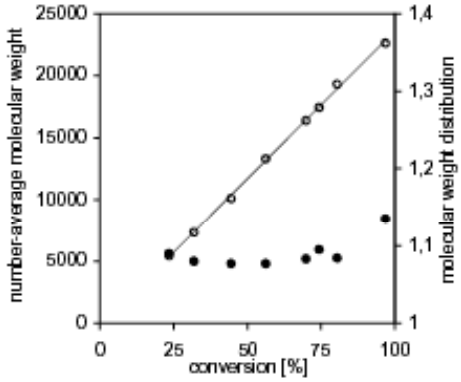


Fig. 2. The influence of L-LA monomer conversion on the number-average molecular weight (○) and the MWD (●). Polymerization conducted at 60 °C in chloroform with an initial monomer-to-initiator ratio of 100:1

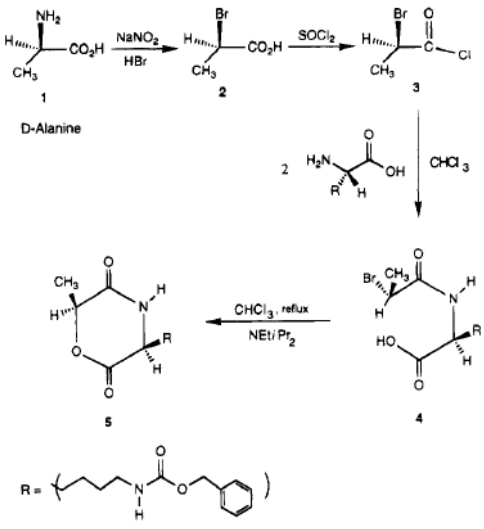
- Allows the synthesis of block copolymers:

Fig.5. A schematic presentation of an ABA tri-block copolymer with two A-blocks (gray circles with dark centers) and one B-block (gray circles with light centers)

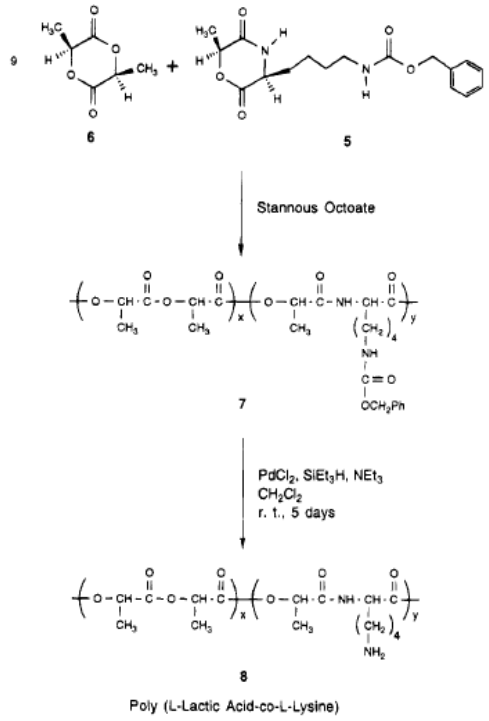
- Monomers polymerized sequentially, when block A is formed, monomer B is injected, etc. pendant peptide groups

- Copolymerization of ring peptides with biodegradable monomers

Scheme 1. Synthesis of 5, the Cyclic Dimer of L-Lactic Acid and Protected L-Lysine



Scheme 2. Synthesis of Poly(L-lactic acid-*co*-L-lysine)



e.g. Barrera et al[12-14]:

  - monomers must be synthesized from scratch
  - bulky substituents make for highly inefficient ring-opening polymerization[15]

Table 2. Effect of the Concentration of 5 on Polymerizations Conducted at 136 °C for 48 h Using a Catalyst to Monomer Ratio of 1/1000[a]

mole % 5[b]		yield			T_g	T_m
reaction	copolymer	(%)	M_n	M_w	(°C)	(°C)
0.0	0.0	85	132 000	223 000	61.6	169.4
5.3	2.6	71	14 500	36 700	57.5	155.3[c]
10.5	4.4	57	8 400	23 000	55.8	152.8[c]
27.7	10.6	20	12 300	15 000	52.4	none
100.0		0				

[a] All the molecular weight data were obtained on protected copolymers. [b] Determined by ^{1}H NMR. Incorporated of 10 mol % **5** actually yields only 5 mol % lysine since each molecule of **5** contains one lysine residue and one lactic acid residue. [c] Indicates 2 or more melting endotherms.

- Network polymerization
  - Photopolymerization of liquid precursors
    - E.g. polyanhydrides[16,17]
    - Allows formation of polymeric solids *in situ* from liquid precursors
      - Useful for dental restorations, bone fixation, tissue engineering
    - Curable through fiber optics or by shining light through tissue
    - UV or visible light initiators available

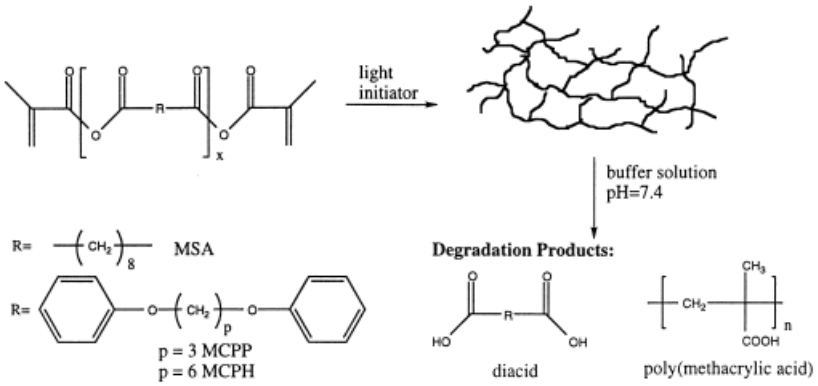


Fig. 1. Dimethacrylated anhydride monomers, methacrylated sebacic acid (MSA), methacrylated 1,3-*bis*(*p*-carboxyphenoxy) propane (MCPP) and methacrylated 1,6-*bis*(*p*-carboxyphenoxy) hexane (MCPH)), as well as a general polymerization and degradation scheme.

Benefit of rapid polymerization:

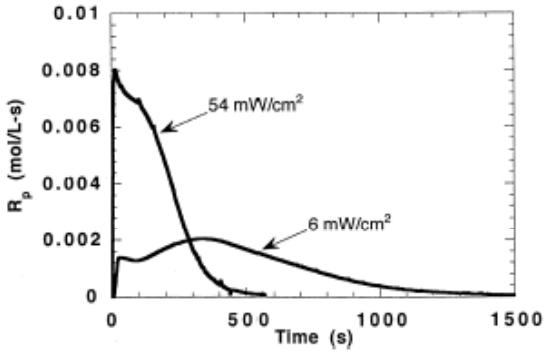


Fig. 3. Effect of light intensity on the rate of photopolymerization as a function of time for MSA polymerized with 0.5 wt% CQ and 0.5 wt% TEA.

network properties can be tuned at the molecular level by copolymerizing monofunctional monomers:

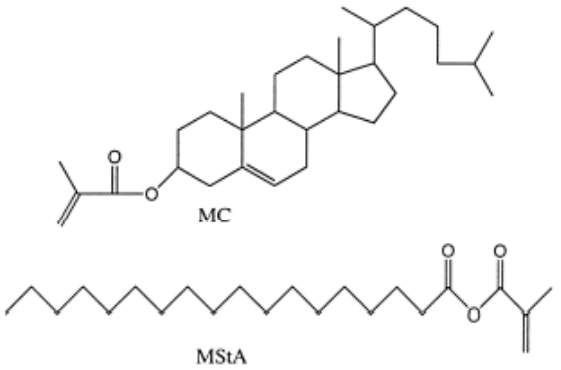


Fig. 2. Chemical structures of monovinyl monomers, methacrylated cholesterol (MC) and methacrylated stearic acid (MStA).

cholesterol a vital component of cell membranes; stearic acid a natural fatty acid

References

1. Gopferich, A. & Langer, R. Modeling of Polymer Erosion. *Macromolecules* **26**, 4105-4112 (1993).
2. Gopferich, A. Polymer bulk erosion. *Macromolecules* **30**, 2598-2604 (1997).
3. Gopferich, A. Mechanisms of polymer degradation and erosion. *Biomaterials* **17**, 103-14 (1996).
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