

**Problem Set 1 Solution**

*Biodegradable Solid Polymers*

Issued: Day 1

Due: Day 4

5 points/problem (20 points total)

BE.462J/3.962J

Spring 2003

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1. The chemical structure of a new degradable polymer, poly(ethylene glycol)-b-polylysine-b-poly(D,L-lactide), is shown below.

a. Based on chemical structure alone, discuss your prediction of whether this material will degrade more quickly or more slowly than poly(L-lactide) *in vivo*.

*This material will likely degrade much more quickly than PLLA for several reasons:*

- i. It contains two highly hydrophilic blocks in the PEG and polylysine components, and both of these blocks can hydrogen bond with water, aiding water uptake in this polymer and allowing access of water to the ester bonds.*
- ii. The amine side chain may provide 'self-destroying' properties to the polymer by attacking the PLA block ester bonds.*
- iii. The polymer is likely non-crystalline unless the molecular weight of the individual blocks is quite large, which will make hydrolysis easier relative to semicrystalline PLLA.*
- iv. Polylysine maybe recognized by a peptidase or a protease and degraded in vivo. In general, it must be remembered that only L-amino acids and D-sugars are metabolized by the body. The 'non-physiological' amino acids and sugars are recognized by some special enzymes but those enzymes are rare. Generally, the physiological forms of amino acids and sugars are used for synthesizing biodegradable polymers.*

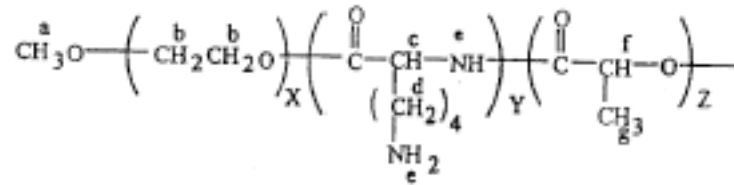
**Note:** Polyethylene glycol (PEG) contains ether (R-O-R') bonds and is therefore not degradable. The only mechanism for clearing body of any residual PEG is elimination which is dependent on the size (and consequently on the molecular weight) of the polymer chain.

b. Cite 2 physical data you would want to know to make a better prediction in part (a), and explain why these would aid in this estimate.

- i. Melting temperature(s) (if there are any)- account for possible crystallinity.*
- ii. Glass transition temperature(s) of the copolymer: lower T<sub>g</sub>, more mobility in chains and more rapid hydrolysis; higher T<sub>g</sub>, less mobility, slower hydrolysis.*

c. What will the end-point degradation products of this polymer be if it is degraded by incubation *in vitro* in phosphate buffered saline, pH 7.4 at 37°C? Would these products be different if the material were degraded *in vivo*?

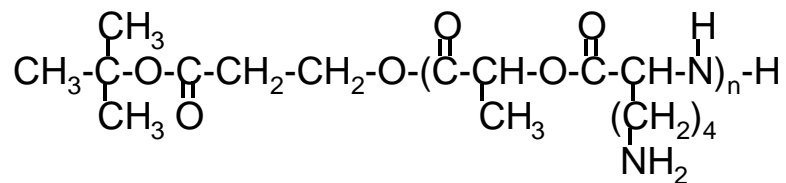
*In vitro*, the polymer will break down to poly(ethylene glycol), poly(L-lysine) (attached to one molecule of lactic acid at end) and lactic acid, due to hydrolysis of ester bonds in the polymer. The amide bonds are relatively stable under these conditions. *In vivo*, polylysine will also be degraded to amino acids by the action of proteases and peptidases.



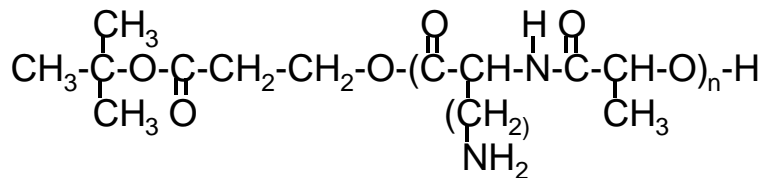
2. The generation of acidic or basic degradation products is a serious issue complicating the design of devices for *in vivo* application, even for well-established materials like poly(lactide-co-glycolide). Propose an approach to limit or eliminate the generation of a low pH within and near a PLGA device implant. Be creative! (limit ~1/2 page explanation).

Many solutions are possible, a few examples:

- i. Add an acid/base titrating compound (amine monomers) into the material
  - ii. Co-encapsulating lactate dehydrogenase (LDH). LDH will convert lactate into pyruvate – the end product of glycolysis and starting component of Citric acid cycle.
  - iii. Using salts like  $\text{Mg}(\text{OH})_2$ . The salt being basic will take up all the free protons from lactic acid generation and therefore act as a buffering agent.
3. Propose a route to synthesize the hydrolyzable polymer shown below. Show the structure of the monomers you would use and any initiators/catalysts.

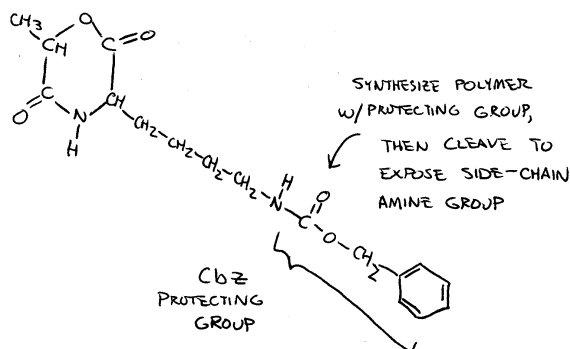


As discussed in class, this structure, exactly as drawn, is impossible to synthesize by any common chemical routes. Condensation polymerization of lactic acid and lysine can provide a random arrangement of lactic acid and lysine units in the polymer, but cannot provide a regular repeat –LA-LYS-LA-LYS-LA-LYS-etc. as shown, nor is it straightforward to cap one end of such polymers with a tert-butyl group as shown. The structure that was INTENDED to be shown is:

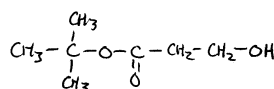


THIS structure CAN be synthesized using a ring-opening catalyst and a 6-membered ring monomer formed by lactic acid and lysine following the mechanism of ring-opening polymerization discussed in class:

THIS POLYMER CAN BE PRODUCED USING RING-OPENING CATALYSTS LIKE STANNOUS OCTOATE OR ALUMINUM ISOPROPOXIDE. THE MONOMER IS:



THE INITIATOR IS:



To prevent self-attack of the side chain amine of lysine on the backbone of the growing polymer chain, the side chain must be blocked by a protecting group of some type as shown above. Chain growth from the hydroxyl group of the initiator provides the endgroup structure followed by LA-LYS repeats.

4. In order to carry out studies of polymer hydrolysis on reasonable experimental timescales, a number of researchers have used elevated temperature to speed up degradation. Using the data given below, determine the degradation mechanism (surface or bulk erosion) for a sample of polycaprolactone ( $\rho = 1.146 \text{ g/cm}^3$ ) 0.02m thick degraded in water at 37°C and whether the mechanism is changed by degrading the sample at 85°. (Hint: assume both the hydrolysis rate constant and the diffusivity of water in the polymer have an Arrhenius form.)

At 37°C:  $k = 9.7 \times 10^{-8} \text{ s}^{-1}$        $D_{\text{H}_2\text{O}} = 10^{-8} \text{ cm}^2 \text{ s}^{-1}$

At 50°C:  $k = 5.4 \times 10^{-7} \text{ s}^{-1}$        $D_{\text{H}_2\text{O}} = 3.5 \times 10^{-8} \text{ cm}^2 \text{ s}^{-1}$

$k$  = rate constant of PCL bond hydrolysis

$D_{H_2O}$  = diffusivity of water in PCL

$$\epsilon = \frac{\langle x \rangle^2 k T}{4 D_{H_2O} \left[ \ln \langle x \rangle + \frac{1}{3} \ln \left( \frac{\rho_{H_2O} f}{M_0} \right) \right]}$$

Assumptions:

1.  $k$  and  $D$  follow Arrhenius equation
2.  $n$  is large for the above expression of  $\epsilon$ .

$$\epsilon = \frac{t_{diff}}{t_{react}}$$

$\Rightarrow \epsilon \gg 1$  (usually  $\geq 10$ ) Surface erosion ( $\because t_{diff} \gg t_{react}$ )

$\epsilon \ll 1$  (usually  $\leq 0.1$ ) bulk erosion ( $\because t_{diff} \ll t_{react}$ )

$$\langle x \rangle = 2 \text{ cm}$$

$$\rho_{H_2O} = 6.023 \times 10^{23}$$

$$f = 1.146 \text{ g/cm}^3$$

$$M_0 = 114.1 \text{ g/mole}$$

37°C:

$$\begin{aligned} \epsilon &= \frac{2^2 \times 9.7 \times 10^{-8} \times 3.14}{4 \times 10^{-8} \left[ \ln 2 + \frac{1}{3} \ln \left[ \frac{6.023 \times 10^{23} \times 1.146}{114.1} \right] \right]} \\ &= \frac{121.894}{4 \times 17.41} = 1.75 \end{aligned}$$

Since,  $\epsilon \sim 1$ , the degradation is a combination of surface and bulk erosion, i.e. transition phase.

k:

$$k = k_0 e^{-A/RT}$$

$$\Rightarrow \frac{k_1}{k_2} = e^{-\frac{A}{R} \left( \frac{1}{T_1} - \frac{1}{T_2} \right)}$$

$$\text{or } \ln \frac{k_1}{k_2} = -\frac{A}{R} \left( \frac{1}{T_1} - \frac{1}{T_2} \right)$$

$$\Rightarrow \ln \frac{9.7 \times 10^{-8}}{5.4 \times 10^{-7}} = -\frac{A}{R} \left( \frac{1}{310} - \frac{1}{323} \right)$$

$$\text{or } A = 109.94 \text{ kJ/mole}$$

$$k(85^\circ\text{C}) = k(37^\circ\text{C}) \cdot e^{-\frac{A}{R} \left( \frac{1}{358} - \frac{1}{310} \right)}$$
$$= 2.955 \times 10^{-5} \text{ s}^{-1}$$

D:

$$D = D_0 e^{-B/RT}$$

$$\Rightarrow \ln \frac{D_1}{D_2} = -\frac{B}{R} \left( \frac{1}{T_1} - \frac{1}{T_2} \right)$$

$$\Rightarrow \ln \frac{10^{-8}}{3.5 \times 10^{-9}} = -\frac{B}{8.314} \left( \frac{1}{310} - \frac{1}{323} \right)$$

$$\Rightarrow B = 80.223 \text{ kJ/mole}$$

$$D(85^\circ\text{C}) = 10^{-8} \cdot e^{-\frac{80.223}{8.314} \left( \frac{1}{358} - \frac{1}{310} \right)} \text{ cm}^2/\text{s}$$
$$= 6.49 \times 10^{-7} \text{ cm}^2/\text{s}$$

Using new values of  $k$  and  $D$  at  $85^\circ\text{C}$ ,

$$\begin{aligned} \epsilon &= \frac{2^2 \times 2.955 \times 10^{-5} \times 3.14}{4 \times 6.49 \times 10^{-7} \left[ \ln 2 + \frac{1}{3} \ln \left\{ \frac{6.023 \times 10^{23} \times 1.146}{114.1} \right\} \right]} \\ &= \frac{3.713 \times 10^{-4}}{4.52 \times 10^{-5}} \\ &= 8.215 \end{aligned}$$

Since,  $\epsilon(85^\circ\text{C}) \sim 10$ , ~~the~~ polymer may be assumed to degrade by surface erosion.

\* In general,  $\frac{k}{D} = \frac{k_0 e^{-A/RT}}{D_0 e^{-B/RT}} = \frac{k_0}{D_0} e^{-\frac{1}{RT}(A-B)}$

With an increase in temperature from  $37^\circ\text{C}$  to  $50^\circ\text{C}$ ,  $\frac{k}{D}$  increases.  
 $\Rightarrow (A-B) > 0$

$\Rightarrow$  For all values of  $T$ , as  $T \uparrow$ ,  $\frac{k}{D} \uparrow$ ,  $\epsilon \uparrow$ .

If mechanism at  $37^\circ\text{C}$  had been surface erosion, it would have remained unchanged at higher temperatures.

No calculations required in that case!