20.462J/3.962J Molecular Principles of Biomaterials

Summary of course objective:

Develop a firm understanding of the **fundamental materials science & engineering principles** underlying synthetic/engineered materials used in **biology, biotechnology, and biomedical** applications--focusing on a subset of problems that can be quantitatively understood (and that we have time to cover!)

Image removed for copyright reasons.
Please see:

Fig. 1(a) in Richardson T. P., M. C. Peters, A. B. Ennett, and D. J. Mooney. "Polymeric System for Dual Growth Factor Delivery." *Nature Biotechnology* 19, no. 11 (2001): 1029-34.

Prelude to degradable solid polymers: *In vivo* applications of Biomaterials

<u>'active' lifetime:</u>

8-10 yrs

≤ 1 year

≤ 6 months

Hours - days

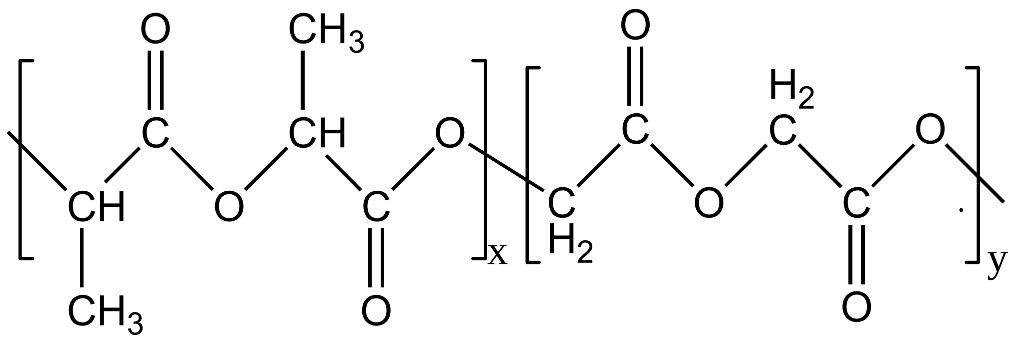
- Implants
  - Artificial hips, artifical heart, pacemaker, etc.
- Tissue engineering, cell therapy
  - Delivery of cells
  - Scaffolds for *in vivo* tissue guidance
- Drug delivery
  - Injected or implanted devices
- Biosensors
  - *In situ* measurements of pH, analyte concentrations, etc.

If a material is to be utilized *in vivo*, what characteristics must it have in addition to fulfilling device requirements?

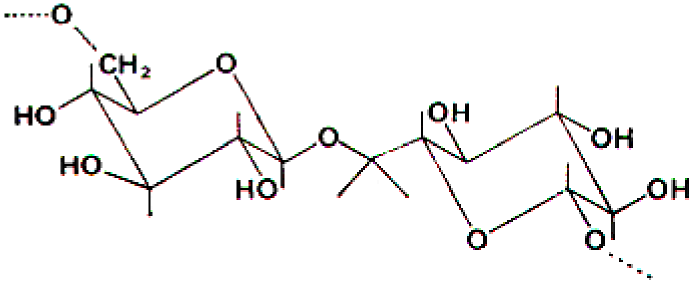
CBS News | **FDA** Rejects **Silicone Implants** | January 8, 2004 09:38 **...**

"Long-term safety, the concern that prompted the removal from the market 11 years ago, was clearly not demonstrated," Whalen wrote.

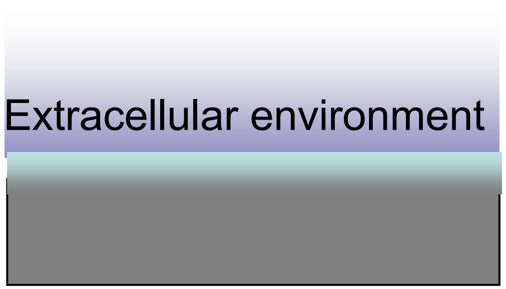
3 classes of materials used in vivo:
(1) biodegradable materials

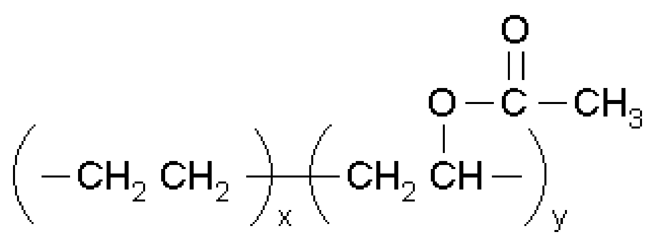


(2) Bioeliminable Materials



(3) Permanent/retrievable materials





Poly(ethylene-co-vinyl acetate) (PEVAc)

Biodegradable solid polymers

- our definition of ‘biodegradable’ for this course:

- Why use biodegradable materials?

hydrolysis-susceptible bonds

Pathways of solid polymer degradation

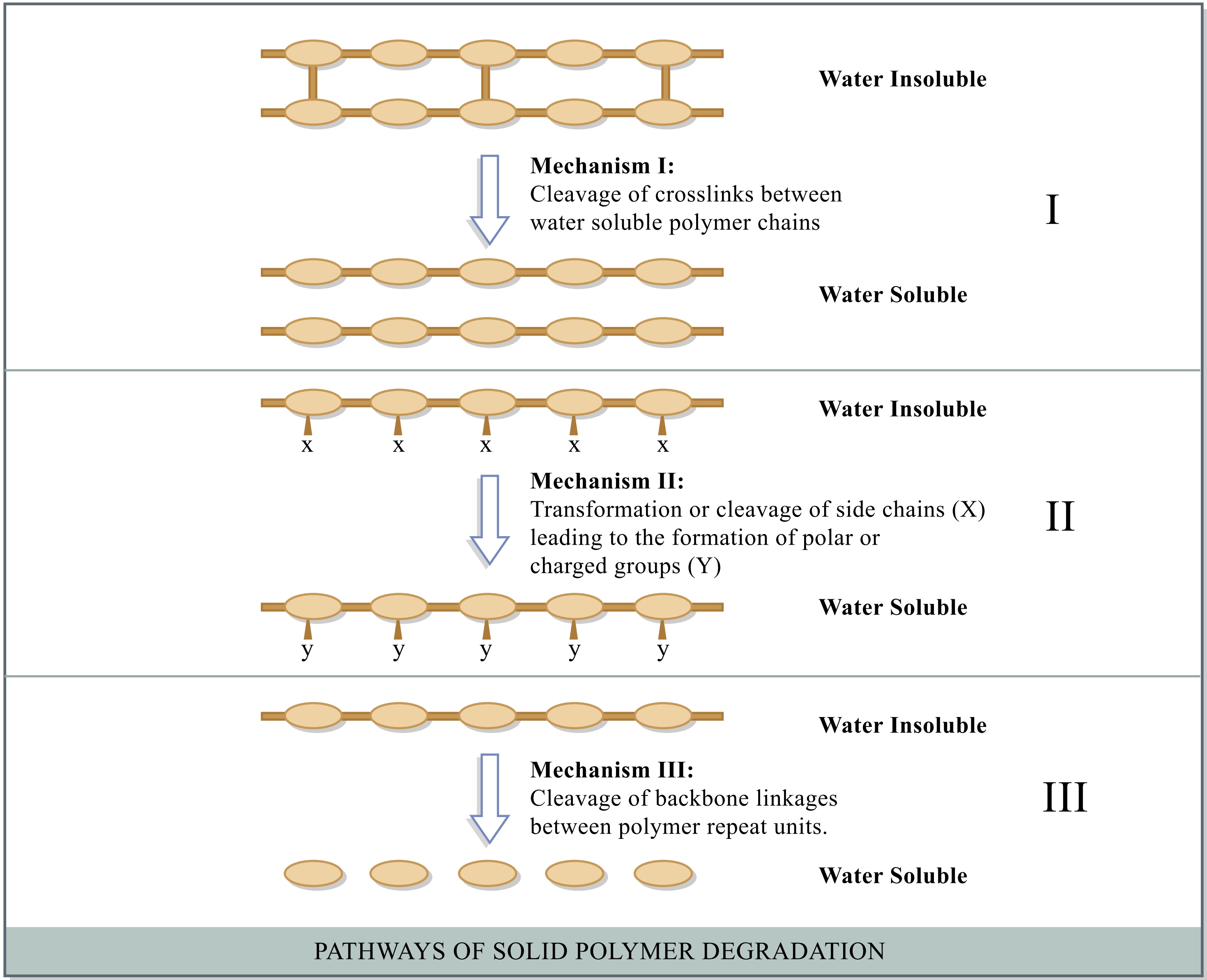
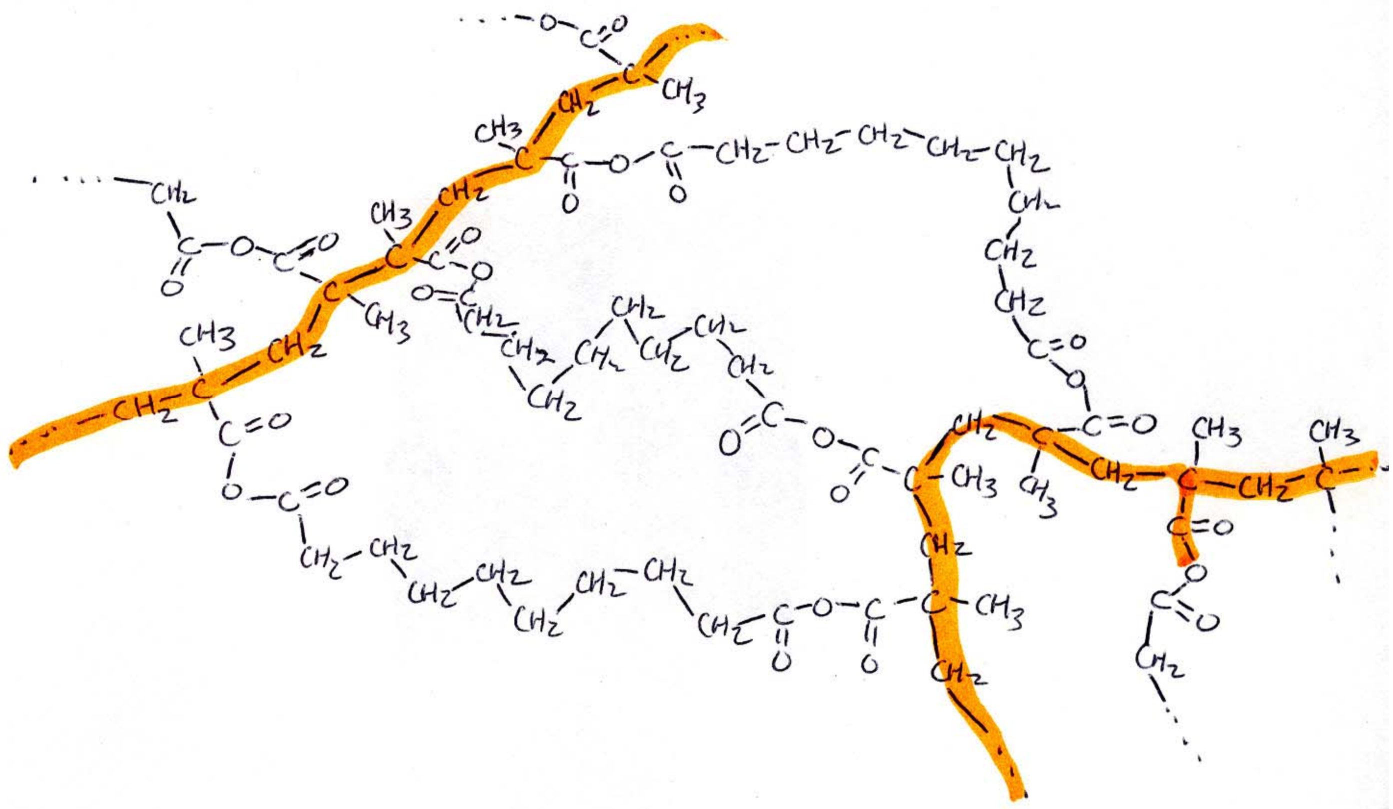


Figure by MIT OCW.

Mechanism I example: polyanhydride networks



Burkoth A. K., and K. S. Anseth. "A Review of Photocrosslinked Polyanhydrides: In Situ Forming Degradable Networks." *Biomaterials* 21, no. 23 (December 2000): 2395-404.

Mechanism II

- Poly(methyl vinyl ether-co-maleic anhydride)

- Poly(alkyl cyanoacrylates)

Mechanism III

- Example: Polyphosphazenes:

Medically-applied degradable polymers are chosen for metabolizable or excretable final breakdown products

- PLGA
- Poly(caprolactone) (PCL)
- Poly(hydroxybutyrate)

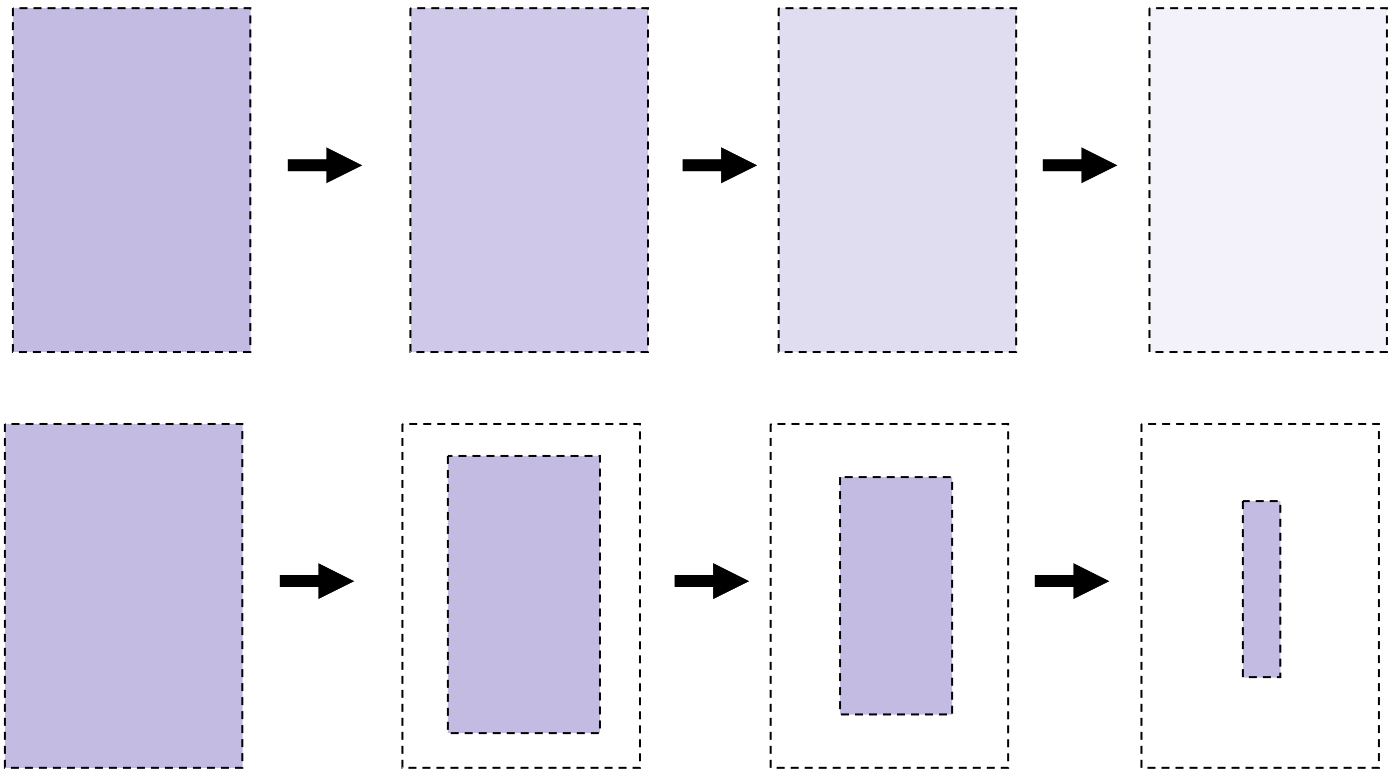
What doesn’t work?

- Degradation too slow
- Breakdown products not clearable

Physical chemistry of hydrolysis

structure influences mechanism of erosion as well as overall rate

- Mechanisms of dissolution:



Bulk vs. surface erosion

Bulk erosion

Images removed for copyright reasons.

Please see:

Fig. 8(b) in Lu, L., C. A. Garcia, and A. G. Mikos. “In Vitro Degradation of Thin Poly(DL-lactic-co-glycolic acid) Films. *J Bio Med Mater Res* 46 (1999): 236-44.

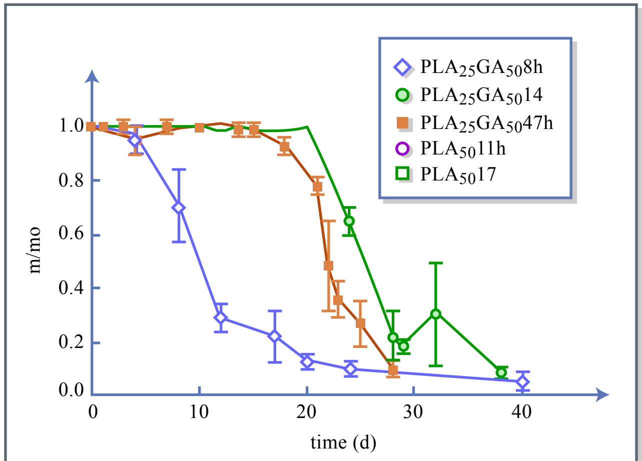
Fig. 6(d) in Agrawal, C. M., and K. A. Athanasiou. “Technique to Control pH In Vicinity of Biodegrading PLA-PGA Implants.” *J Biomed Mater Res* 38 (1997): 105-14.

Surface erosion

Images of surface erosion removed due to copyright restrictions.

Dissolution during hydrolysis

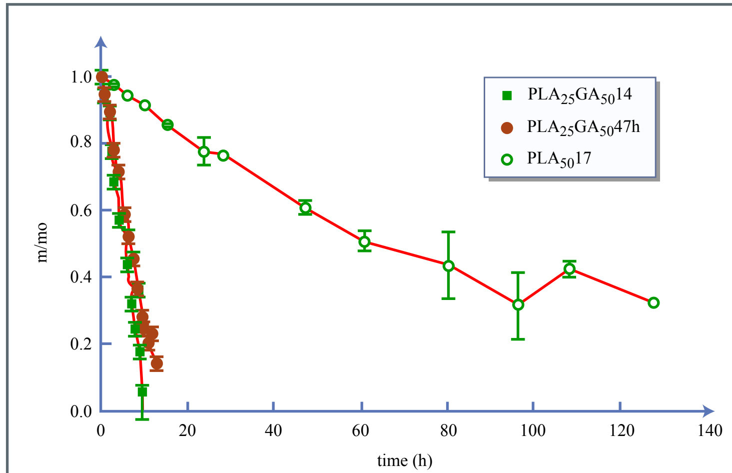
Bulk erosion:



Erosion profiles of poly(α-hydroxy esters) at pH 7.4.

Figure by MIT OCW.

Surface erosion:



Erosion of poly(α-hydroxy esters) at pH > 13

Figure by MIT OCW.

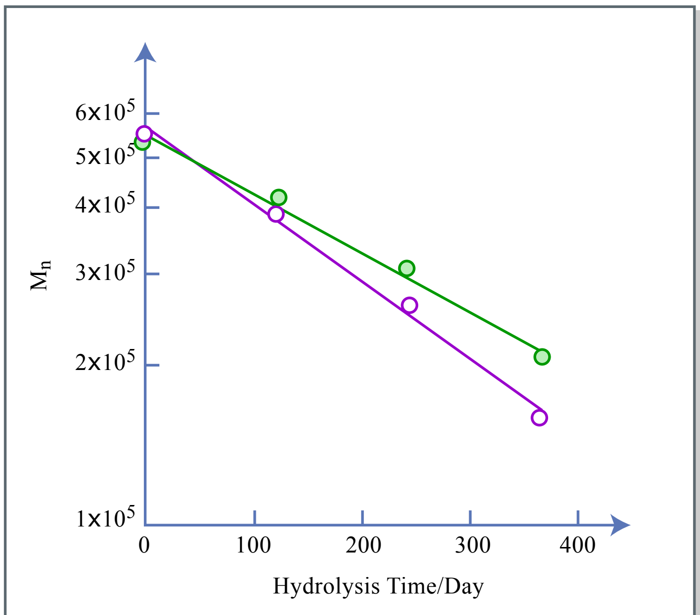
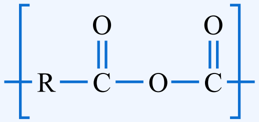
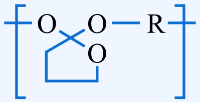
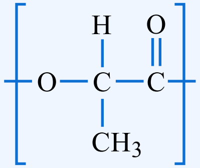
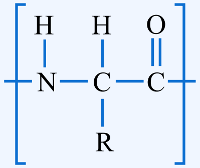


Figure by MIT OCW.

Role of molecular structure in hydrolysis rate:

Role of molecular structure in hydrolysis rate:

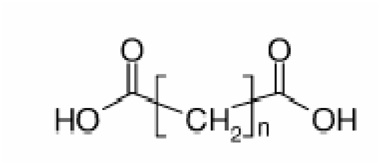
(1) Relative bond stability:

	Polymer Class	Half-life
	poly(anhydrides)	0.1 h
	poly(ortho esters)	4 h
	poly(esters)	3.3 yrs
	poly(amides)	83000 yrs

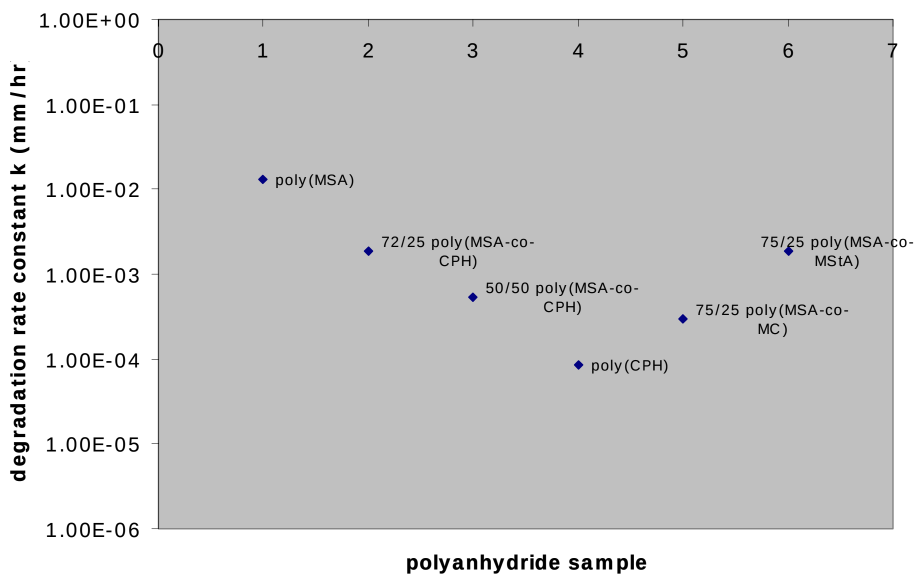
Classes of Hydrolysable Bonds with Half-Lives

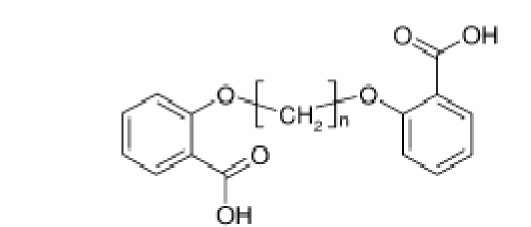
Figure by MIT OCW.

(2) Effect of polymer hydrophobicity on solid polymer erosion rate



Sebacic acid





n = 6 : 1,6-bis(o-carboxyphenoxy)hexane (o-CPH)

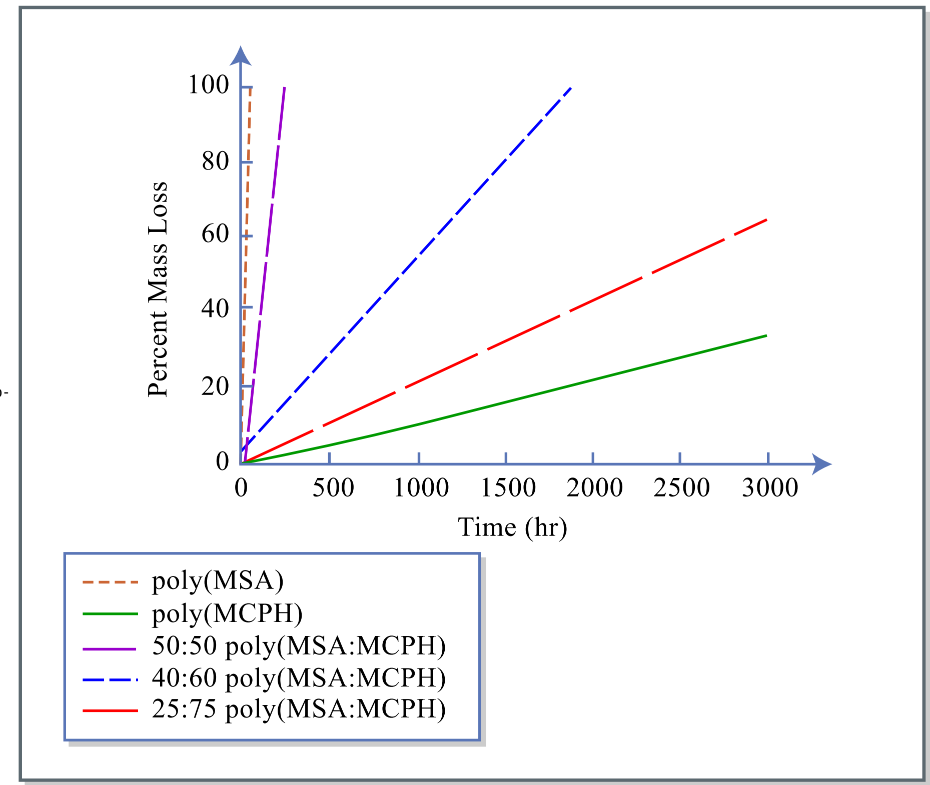


Figure by MIT OCW.

(3) Steric effects controlling polymer hydrolysis rates

- Local structure

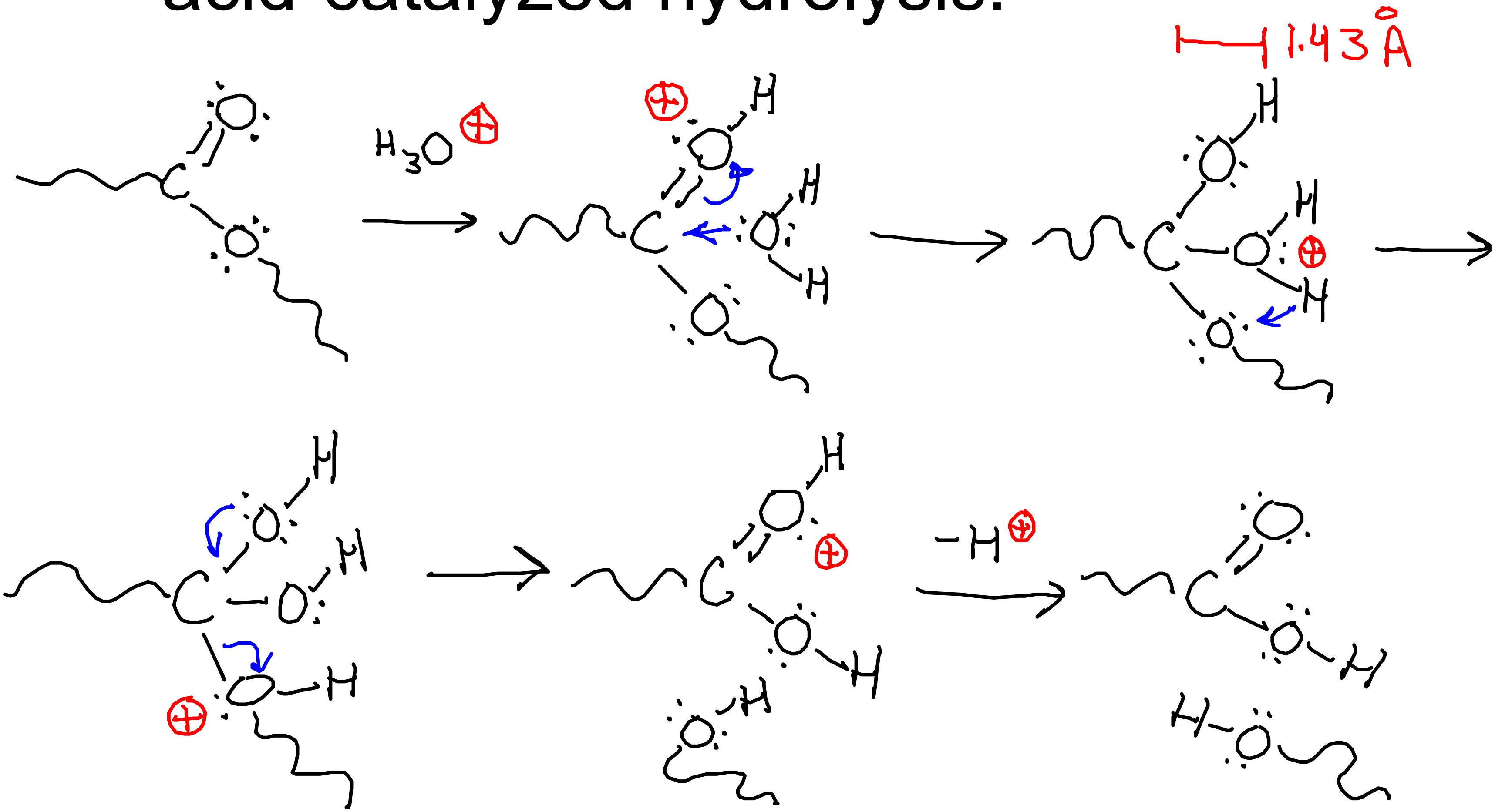
- Glass transition (Tg)

(4) Production of autocatalytic products

- Polyesters:

Mechanisms of hydrolysis: polyesters

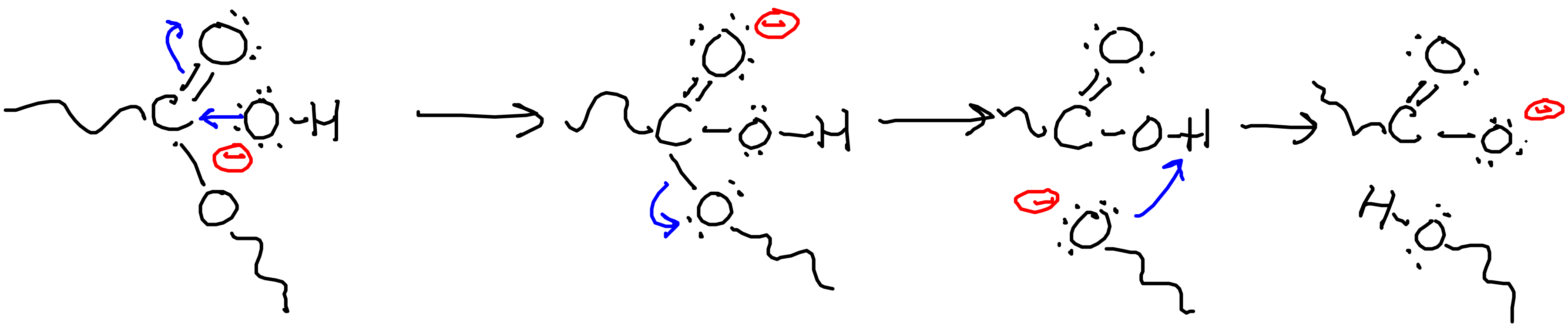
- acid-catalyzed hydrolysis:



Mechanisms of hydrolysis: polyesters

- Base-catalyzed hydrolysis:

(saponification)



Nucleophilic substitution at acyl carbon

Physical properties

Semicrystalline polymers boxed

Polymer	Glass Transition (°C)	Melting Temperature (°C)	Tensile Strength (MPa)	Tensile Modulus (MPa)	Flexural Modulus (MPa)	Elongation Yield (%)	Elongation Break (%)
Poly(glycolic acid) (MW: 50,000)	35	210	n/a	n/a	n/a	n/a	n/a
Poly(lactic acids)							
L-PLA (MW: 50,000)	54	170	28	1200	1400	3.7	6.0
L-PLA (MW: 100,000)	58	159	50	2700	3000	2.6	3.3
L-PLA (MW: 300,000)	59	178	48	3000	3250	1.8	2.0
D, L-PLA (MW: 20,000)	50	–	n/a	n/a	n/a	n/a	n/a
D, L-PLA (MW: 107,000)	51	–	29	1900	1950	4.0	6.0
D, L-PLA (MW: 550,000)	53	–	35	2400	2350	3.5	5.0
Poly(β-hydroxybutyrate) (MW: 422,000)	1	171	36	2500	2850	2.2	2.5
Poly(ε-caprolactone) (MW: 44,000)	-62	57	16	400	500	7.0	80
Polyanhydrides[b]							
Poly(SA-HDA anhydride) (MW: 142,000)	n/a	49	4	45	n/a	14	85
Poly(ortho esters)[c]							
DETOSU: t-CDM:1,6-HD (MW: 99,700)	55	–	20	820	950	4.1	220
Polyiminocarbonates[d]							
Poly(BPA iminocarbonate) (MW: 105,000)	69	–	50	2150	2400	3.5	4.0
Poly(DTH iminocarbonate) (MW: 103,000)	55	–	40	1630	n/a	3.5	7.0

[a]Based on data published by Engelberg and Kohn (1991). n/a = not available, (–) = not applicable. [b]A 1:1 copolymer of sebacic acid (SA) and hexadecanedioic acid (HDA) was selected as a specific example. [c]A 100:35:65 copolymer of 3, 9-bis(ethylidene 2, 4, 8, 10-tetraoxaspiro [5,5] undecane) (DETOSU), *trans*-cyclohexane dimethanol (t-CDM) and 1, 6-hexanediol (1,6-HD) was selected as a specific example. [d]BPA: Bisphenol A; DTH: desaminotyrosyl-tyrosine hexyl ester.

Mechanical Properties of Some Degradable Polymers[a]

Figure by MIT OCW.

Further Reading

1. Maheshwari, G., Brown, G., Lauffenburger, D. A., Wells, A. & Griffith, L. G. Cell adhesion and motility depend on nanoscale RGD clustering. *J Cell Sci* **113 (Pt 10)**, 1677-86 (2000).
2. Richardson, T. P., Peters, M. C., Ennett, A. B. & Mooney, D. J. Polymeric system for dual growth factor delivery. *Nat Biotechnol* **19**, 1029-34 (2001).
3. Griffith, L. G. & Naughton, G. Tissue engineering--current challenges and expanding opportunities. *Science* **295**, 1009-14 (2002).
4. Drumheller, P. D. & Hubbell, J. A. Polymer networks with grafted cell adhesion peptides for highly biospecific cell adhesive substrates. *Anal Biochem* **222**, 380-8 (1994).
5. Burkoth, A. K. & Anseth, K. S. A review of photocrosslinked polyanhydrides: in situ forming degradable networks. *Biomaterials* **21**, 2395-404 (2000).
6. Burkoth, A. K., Burdick, J. & Anseth, K. S. Surface and bulk modifications to photocrosslinked polyanhydrides to control degradation behavior. *J Biomed Mater Res* **51**, 352-9 (2000).
7. Muggli, D. S., Burkoth, A. K. & Anseth, K. S. Crosslinked polyanhydrides for use in orthopedic applications: degradation behavior and mechanics. *J Biomed Mater Res* **46**, 271-8 (1999).
8. Heller, J. & Baker, R. W. in *Controlled Release of Bioactive Materials* (ed. Baker, R. W.) 1-17 (Academic Press, New York, 1980).
9. Solomons, T. W. G. *Organic Chemistry* (John Wiley, New York, NY, 1988).
10. Albertsson, A. C. & Varma, I. K. in *Degradable Aliphatic Polyesters* 1-40 (2002).
11. Winet, H. & Bao, J. Y. Fibroblast growth factor-2 alters the effect of eroding polylactide-polyglycolide on osteogenesis in the bone chamber. *J Biomed Mater Res* **40**, 567-76 (1998).
12. Lu, L., Stamatas, G. N. & Mikos, A. G. Controlled release of transforming growth factor beta1 from biodegradable polymer microparticles. *J Biomed Mater Res* **50**, 440-51 (2000).
13. Edlund, U. & Albertsson, A.-C. Degradable polymer microspheres for controlled drug delivery. *Advances in Polymer Science* **157**, 67-112 (2002).
14. Merkli, A., Tabatabay, C., Gurny, R. & Heller, J. Biodegradable polymers for the controlled release of ocular drugs. *Progress in Polymer Science (Oxford)* **23**, 563-580 (1998).
15. Einmahl, S. et al. A viscous bioerodible poly(ortho ester) as a new biomaterial for intraocular application. *J Biomed Mater Res* **50**, 566-73 (2000).
16. Einmahl, S. et al. Therapeutic applications of viscous and injectable poly(ortho esters). *Adv Drug Deliv Rev* **53**, 45-73 (2001).
17. Caliceti, P., Veronese, F. M. & Lora, S. Polyphosphazene microspheres for insulin delivery. *Int J Pharm* **211**, 57-65 (2000).
18. Agrawal, C. M. & Athanasiou, K. A. Technique to control pH in vicinity of biodegrading PLA-PGA implants. *J Biomed Mater Res* **38**, 105-14 (1997).
19. Lu, L., Garcia, C. A. & Mikos, A. G. In vitro degradation of thin poly(DL-lactic-co-glycolic acid) films. *J Biomed Mater Res* **46**, 236-44 (1999).
20. Tsuji, H. & Nakahara, K. Poly(L-lactide). IX. Hydrolysis in acid media. *Journal of Applied Polymer Science* **86**, 186-194 (2002).
21. Park, T. G. Degradation of poly(D,L-lactic acid) microspheres: effect of molecular weight. *Journal of Applied Polymer Science* **30**, 161-173 (1994).
22. Hoogsteen, W., Postema, A. R., Pennings, A. J. & ten Brinke, G. Crystal structure, conformation, and morphology or solution-spun poly(L-lactide) fibers. *Macromolecules* **23**, 634-642 (1990).
23. Zong, X. H. et al. Structure and morphology changes in absorbable poly(glycolide) and poly(glycolide-co-lactide) during in vitro degradation. *Macromolecules* **32**, 8107-8114 (1999).
24. Lim, Y. B., Choi, Y. H. & Park, J. S. A self-destroying polycationic polymer: Biodegradable poly(4-hydroxy-L-proline ester). *J. Am. Chem. Soc.* **121**, 5633-5639 (1999).
25. Lim, Y. B., Kim, C.-H., Kim, K., Kim, S. W. & Park, J. S. Development of a safe gene delivery system using biodegradable polymer, poly[alpha-(4-aminobutyl)-L-glycolic acid]. *J. Am. Chem. Soc.* **122**, 6524-6525 (2000).
26. Younes, H. & Cohn, D. Phase separation in poly(ethylene glycol)/poly(lactic acid) blends. *Eur. Polym. J.* **24**, 763-773 (1988).
27. Nijenhuis, A. J., Colstee, E., Grijpma, D. W. & Pennings, A. J. High molecular weight poly(L-lactide) and poly(ethylene oxide) blends: Thermal characterization and physical properties. *Polymer* **37**, 5849-5857 (1996).