Exam 2 **BE.462J/3.962J**
Model Solutions **Spring 2003**

(80 points total possible)

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1. (10 points) Explain the phenomenon of pH-sensitive swelling in polyelectrolyte hydrogels. Why does the swelling depend on pH? Why does it depend upon ionic strength of the solution?

The dependence of polyelectrolyte gel swelling on pH and ionic strength can be understood by considering the case of gels containing acid ionizable groups. The fraction of ionized groups is determined by pH: at elevated pH, protons are released from the acid groups, creating a fixed charge on the polymer chain. These protons recombine with the excess OH^- present in the basic solution. The charge on the polymer chain is compensated by entry into the gel of a cation from outside, along with another hydroxyl ion- causing an increase in the concentration of cations within the gel. Swelling is driven by water entering the gel in response to the concentration gradient of cations (also termed osmotic pressure): at equilibrium, the system seeks to have an equal concentration of electrolyte everywhere. Thus water enters the gel in an attempt to dilute the electrolyte back to the concentration that exists outside the gel. Ionic strength clearly influences this process since a higher concentration of electrolyte ions in the gel at the start will reduce the number that need to be 'recruited' into the gel to compensate the ionizing polymer chains, and reduce the magnitude of the concentration gradient in free ions created. (Thus, the higher the ionic strength, the lower the concentration gradient of electrolyte formed when the gel is charged, and the lower the amount of osmotic pressure-driven water influx and swelling). Due to charge compensation (cations enter the gel to 'shield' the acidic group charge) and the rapid decay of electrostatic force with distance, the electrostatic repulsion between charged groups does not play a significant role in controlling swelling except for conditions of extremely high charge density in low ionic strength solutions. An analogous description of events can be considered for the case of swelling in polybasic hydrogels.

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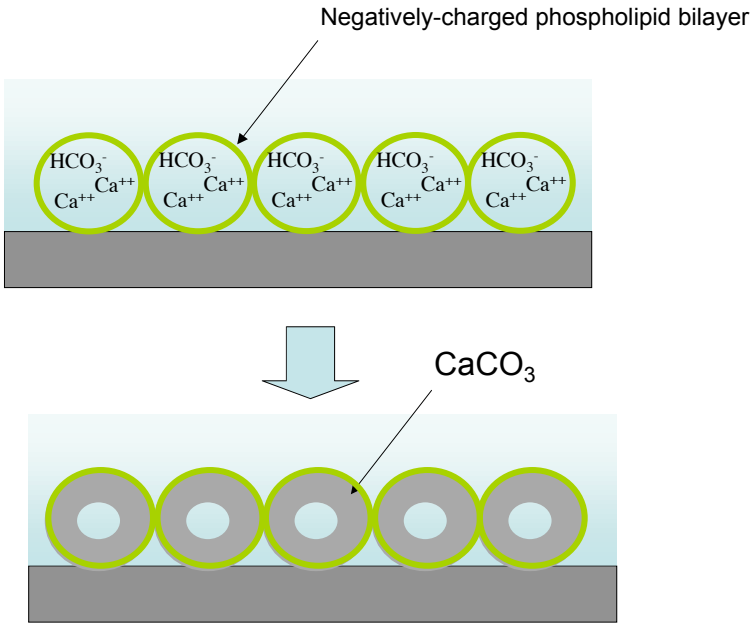
2. (10 points) Why do polyelectrolyte gels of smaller dimensions (smaller total volume) show faster swelling/deswelling to equilibrium than gels of larger volume comprised of the same polymer chains and the same mesh size?

Because polyelectrolyte gel swelling/deswelling is driven by the flux of ions either into or out of the gel, the time to reach equilibrium is governed by diffusion of these cations and anions. Ions have a shorter diffusion distance to reach every point in a gel with smaller total volume, thus the response time is much faster. Increasing the size of a gel increases the time for ions to diffuse to the center and equilibrate the system in response to a change in pH, thus the swelling rate scales as $(\text{size of gel})^{-2}$.

3. (10 points) Biomaterials scientists are seeking to mimic the formation of complex inorganic structures using vesicular mineralization approaches. In a recent approach, phospholipids that form bilayer vesicles were loaded with calcium bicarbonate and deposited into a close-packed array on a substrate to form an organized calcium carbonate structure (illustrated by the cartoon). Describe two ways in which biological systems gain further control over this type of process, which are not replicated in this 'biomimetic' process. Explain how one or both of these additional mechanisms could be incorporated into a synthetic materials synthesis, and how the inorganic structure, nucleation and/or growth would be affected.



Biology utilizes a number of intricate methods to gain control over inorganic microstructures:

- *control over supersaturation within vesicles via ion pumps that can move electrolytes against concentration gradients*
- *control over pH using proton pumps*
- *control of vesicle size and physical arrangement, including super-assembly of multiple vesicle structures via microtubules and actin cytoskeletal elements*
- *control over crystallization using organic templates that can select crystal polymorphs and crystal orientation*

As an example of utilizing two of these principles, one might seek to use a patterned surface (e.g. self-assembled monolayer prepared by photolithography or microcontact printing) that electrostatically dictates the arrangment of oppositely-charged vesicles. Nucleation and growth within vesicles could be tuned by the introduction of ion pump proteins into the vesicle membranes (this can be achieved by generating recombinant proteins in bacteria, purifying the proteins in bacterial membranes, then fusing bacterial membranes with the synthetic phospholipids used in the materials synthesis.)

4. (20 points) Suppose a given inorganic crystal can take on 3 different crystal structures (A, B, and C) under atmospheric conditions. At 37°C and 1 atm pressure, A is kinetically most favored, followed by crystal structure B, and C is the least favored crystal structure. Show schematically how an organic surface modifies the free energy barriers to nucleation of an inorganic crystal for the following situations:

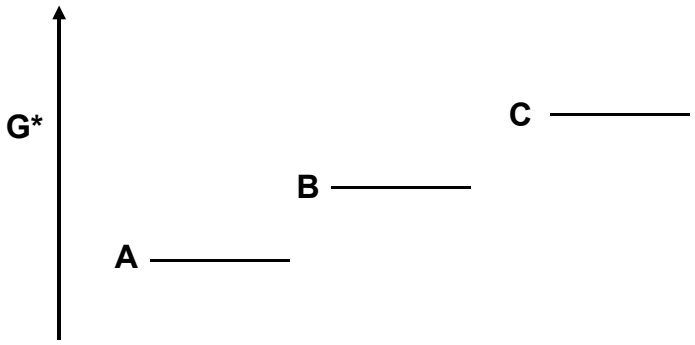
a. First sketch the relative energy barriers described for A, B, and C at 37°C 1 atm.

b. Sketch the relative energy barriers if an organic surface is present that lowers the free energy barrier to nucleation of all 3 structures but does not change the relative kinetics of formation of the 3 polymorphs.

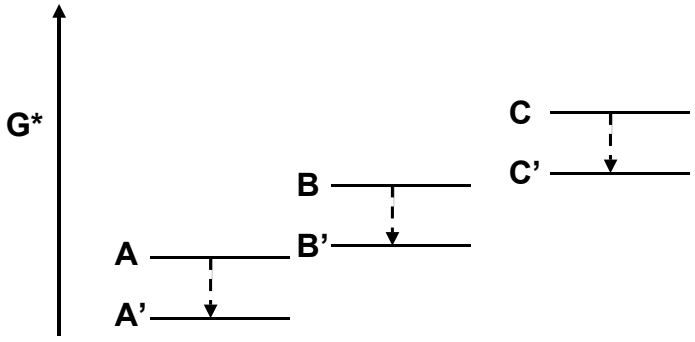
c. Sketch the relative energy barriers if the organic surface selectively nucleates crystal structure B and inhibits the formation of crystal structure A, and has no effect on the nucleation rate of structure C.

d. Describe 3 features of an organic surface that mediate selective nucleation of a particular crystal structure and crystal orientation.

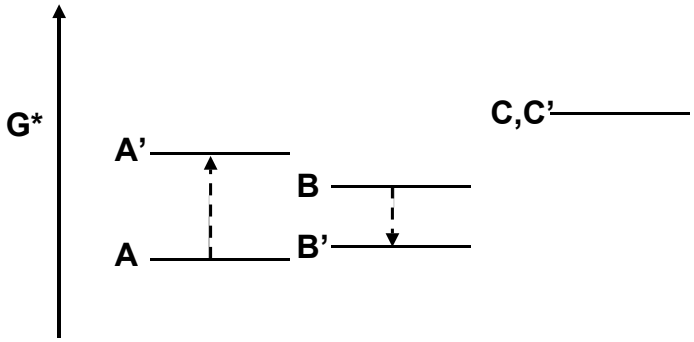
a.



b.



c. Note that in each of these diagrams, we are not given enough information to identify the magnitude of the changes in G (barrier free energy), only the direction.*



d. Numerous aspects of an organic surface can serve to provide a 'templating' function:

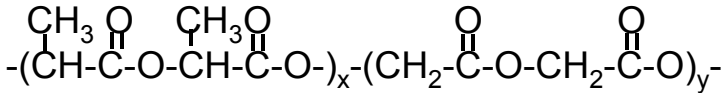
a. Complementarity in spatial distribution of charges

b. *Matching of the dimensions of the organic repeat structure to the lattice of the inorganic crystal*

c. *Complementary in defect sites*

d. *Matching bonding chemistry*

5. (10 points) A poly(lactide-co-glycolide) scaffold for tissue engineering is being studied for use as a scaffold for tissue engineering of bone. (The structure of PLGA is given below as a reminder.) In preliminary tests, the degradation rates of flat films of PLGA were measured at 37°C in simulated body fluid (SBF), a phosphate-buffered saline solution (0.1 M sodium phosphate, 0.1 M NaCl pH 7.4) that also contains a high level of calcium (50 mM) to mimic the extracellular environment of bone tissue. Surprisingly, chemical analysis of the surfaces after 1 week of immersion in SBF revealed deposition of hydroxyapatite (HA) crystals on the polymer surface. The crystals formed have a preferential orientation that places a calcium-rich plane of the HA structure aligned parallel to the surface. As this could be a very beneficial outcome for engineering a structure that integrates with bone, additional experiments were carried out by incubating fresh surfaces in the presence of serum-containing medium (which contains phosphate and calcium in concentrations comparable to SBF, in addition to proteins from extracellular fluid) used for the growth of osteoblasts (bone-producing cells). After even 4 weeks at 37°C, no HA deposition is observed on these surfaces, and breakdown of the polymer film is nearly complete. Provide an explanation for the oriented deposition of HA in the first case and the complete lack of deposition in the second.

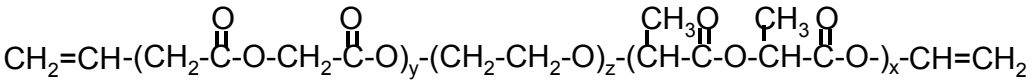


Incubation of PLGA surfaces in a calcium and phosphate-containing buffer makes the formation of HA possible. Nucleation of HA may be driven by the formation of a high density of carboxylic acids on the polymer surface as the PLGA chains are hydrolyzed. The presentation of complementary negative charges favors nucleation of a Ca^{++}-rich plane of HA. Ordering of the crystal structure may further be aided by the presence of crystalline regions of the polymer at the surface- providing an ordered lattice for templating (crystallization of typically amorphous compositions of PLGA becomes possible once hydrolysis begins). Crystallization of HA at the polymer surface may provide protection of the surface from further hydrolysis and stabilize the surface structure. When incubated in serum-containing medium, the rapid adsorption of a disordered and heterogeneous protein layer to the surface may block access to hydrolyzed chain ends and compete with the inorganic ions for binding to these groups, thus eliminating the nonspecific templating effect of the polymer structure.

6. (20 points) A covalent hydrogel network is designed for controlled release of a protein drug by photopolymerizing the macromonomer shown below. Also given below are the equations for gel mesh size and the diffusion coefficient for a drug entrapped within a hydrogel.

   a. Describe in words how you expect the diffusion constant for drug transport through the gel to vary with time. State which terms in the equations below will be functions of time, which direction their values will change with time, and why.

   b. Will this gel be sensitive to pH? Explain.



$$\xi = \frac{\left(\bar{r}_0^2\right)^{1/2}}{C_{2,s}^{1/3}} = Q^{1/3}\left(\bar{r}_0^2\right)^{1/2} = C_n^{1/2} Q^{1/3} N^{1/2} l$$

$$D_{gel} = D_0\left(1 - \frac{r}{\xi}\right)^{\frac{1}{(Q-1)}}$$

a. The diffusion constant for transport of a protein through the network will increase with time, due to the increase in the swelling ratio Q and mesh size ξ with time:

   a. Hydrolysis of the ester linkages in the network will cause the molecular weight between cross-links (M_c) to increase. (As cross-links are severed, the distance traveled along the chains between intact cross-links increases). This change in network structure will drive the swelling ratio, Q, to increase with time as hydrolysis proceeds. The swelling ratio is also driven to increase due to the in situ formation of charged groups as hydrolysis proceeds: each chain break introduces a carboxylic acid in the network that remains a part of the network until the cross-link severs in a second position to free the oligomers from the structure. At neutral pH, these groups will largely be ionized, driving further swelling by the process analyzed in problem 1.

   b. Mesh size increases with time due to the increase in Q outlined above, and the increase in N- the number of repeat units between cross-links as hydrolysis proceeds. Eventually, it is possible for the diffusion constant to plateau at the free solution diffusion rate D_0, if the mesh size becomes >> drug size.

b. This gel becomes increasingly pH-sensitive as hydrolysis proceeds and carboxylic acid groups are generated in the structure. Protonation-deprotonation of these groups will significantly affect swelling of the gel as a function of pH.