



Time and place: Class will tentatively meet in WIDT 330. The **first lecture will be Monday, January 5 from 4:00 – 4:50 PM in WIDT330**. We will choose the permanent class time during the first lecture. Per department policy, class time will be determined based on student and instructor schedules, with special emphasis on accommodating graduate teaching assistant schedules.

Office Hours: To be announced once class time is finalized

Text: There is no required textbook for this class. However, you should have access to a general biochemistry textbook (Lehninger, Voet and Voet, Garrett and Grisham, etc) for review of fundamental principles. The course material will rely to a large extent on recent papers and review articles which will be available through WebCT (see below). The following resource texts are of relevance to course materials and will be available at the SciTech Library Reserve desk and/or on WebCT:

Creighton, T.E. Proteins: Structures and Molecular Properties. Freeman, 1993.
Fersht, A. Enzyme Structure and Mechanism. Freeman, 1985.
Fersht, A. Structure and mechanism in protein science, Freeman, 1999
Walsh, C.T. Enzyme Reaction Mechanisms. Freeman, 1979.

WebCT I will be using Blackboard for the management of Chem. 6730. All resource materials (class standings, current exam keys, problem set solutions, material from previous years, lecture overheads, and other material relevant to the course) will be posted on Blackboard. The reserve materials will be provided to you as downloadable PDF files, which require AcrobatReader. To log on to Blackboard, go to the web address: bb.usu.edu. Your **USERNAME** is your BANNER login and your default **PASSWORD** is your BANNER password. Blackboard has many useful features (your assignment scores, a chat room, bulletin board, e-mail, etc.) and you should take the time to explore them from within our course page. I will provide more instructions on using Blackboard in class.

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|---|--|-------------------------|------------|---|------------|-----------------------|-----------|-------------------|-------------------|
| Computer resources | We will be using PC-based computer programs in this class: SigmaPlot and PyMol or WebLab ViewerPro. | | | | | | | | |
| Prerequisites: | A full year of undergraduate Organic Chemistry; a comprehensive upper division undergraduate course in Biochemistry (comparable to Biochem 5700 at USU), physical chemistry or physical biochemistry recommended but not mandatory. | | | | | | | | |
| Course Withdrawal: | Withdrawal from the course after Jan. 26 will result in a “W” notation being placed on your transcript. No withdrawal is permitted after March 30. | | | | | | | | |
| Provisions: | The administration of Chem 6730 will adhere strictly to the regulations outlined in the Spring Semester Schedule of Classes, pp. 102-110. Per recent instructions from the Dean’s office, no assignments will be accepted or graded from students not formally enrolled in the course. Students not enrolled in the course may sit in only with instructor approval. | | | | | | | | |
| Course Content: | Chemistry 6730 is one of four core courses in advanced biochemistry for qualified students in chemistry, biochemistry, and biological sciences. The four courses are taught independent of each other and can be taken in any sequence. The focus of this course is enzyme catalysis, mechanism, and kinetics. On the following page is a <u>tentative</u> (subject to some change) outline of the topics to be covered in the class meetings. | | | | | | | | |
| Problems: | Three problem sets, worth 50 points each, will be distributed during the course of the semester. | | | | | | | | |
| Exams: | Three midterm exams will be given on the dates indicated on the course schedule. The final examination (midterm 3) is not comprehensive and covers only material presented after midterm 2. The exam format will be a mixture of short answer, short essay, and problem solving. | | | | | | | | |
| Quizzes | Short quizzes, covering material from prior lectures, will be given at the beginning of lecture on random dates. Missed quizzes can be made up if you had a valid reason for missing class (illness, travel, etc) and may require documentation for the absence, at my discretion. | | | | | | | | |
| Grading: | <table> <tr> <td>Three hourly exams.....</td> <td>300 points</td> </tr> <tr> <td>Three problem sets @ 50 points each</td> <td>150 points</td> </tr> <tr> <td>In class quizzes.....</td> <td>30 points</td> </tr> <tr> <td>Total.....</td> <td>480 points</td> </tr> </table> | Three hourly exams..... | 300 points | Three problem sets @ 50 points each | 150 points | In class quizzes..... | 30 points | Total..... | 480 points |
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| Three problem sets @ 50 points each | 150 points | | | | | | | | |
| In class quizzes..... | 30 points | | | | | | | | |
| Total..... | 480 points | | | | | | | | |

In accordance with the Americans with Disabilities Act, reasonable accommodations will be provided for all persons with disabilities in order to ensure equal participation in Chem 570. In cooperation with the Disability Resource Center, reasonable accommodation will be provided for students with disabilities. Please meet with the instructor during the first week of class to make arrangements. Alternative format print materials, large print, audio, diskette or Braille, will be available through the Disability Resource Center.

Class Schedule, Chemistry 6730, Spring Semester 2007

Lectures are arranged here as if taught on a 50 minute MWF format. We may, instead, meet for two 75 minute lectures in a TR format, depending on the final decision of the class. In that case, three lectures here will equal two lectures on the TR format. We may also decide to meet three times a week for 75 minutes each on a MWF schedule, in which case we will finish 2/3 of the way through the semester (around March 23).

| Week | Day | Date | Lecture | Topic | Text chapter | Handout |
|------|------|------|---------|--|------------------------------------|---|
| 1 | Mon. | 1/5 | 1 | Course organization and introduction | Creighton Chap. 9; Walsh Chap. 1-2 | Kornberg 10 commandments ; Cleland, Steady State Kinetics |
| | Wed. | 1/7 | 2 | methods to study enzymes | | |
| | Fri. | 1/9 | 3 | Enzyme Kinetics | | |
| 2 | Mon. | 1/12 | | Enzyme Kinetics (cont.) | | |
| | Mon. | 1/14 | 4 | (cont.) | | |
| | Wed. | 1/16 | 5 | Principles of rate acceleration | | |
| 3 | Mon. | 1/19 | 6 | No class- Martin Luther King Jr. Day | Creighton Chap. 9 | Fersht TIBS article |
| | Wed. | 1/21 | 7 | (cont.) | | |
| | Fri. | 1/23 | 8 | binding energy: tyrosyl-tRNA synthetase | | |
| 4 | Mon. | 1/26 | 9 | binding energy: tyrosyl-tRNA synthetase (cont.) | Fersht Chap. 7 & 9; Walsh Chap. 3 | Mechanism based inactivators of serine proteases |
| | Wed. | 1/28 | 10 | methods to study intermediates and mechanism: serine proteases | | |
| | Fri. | 1/30 | 11 | | | |
| 5 | Mon. | 2/2 | 12 | (cont.) | Walsh Chap. 6 & 7 | |
| | Wed. | 2/4 | 13 | phosphoryl group transfer | | |
| | Fri. | 2/6 | 14 | (cont.) | | |
| 6 | Mon. | 2/9 | 15 | (cont.) | Fersht Chap. 8; Walsh Chap. 4 | |
| | Wed. | 2/11 | | Midterm 1 | | |
| | Fri. | 2/13 | 16 | No class, Ensign at NIH study section | | |
| 7 | Tue. | 2/17 | | C-C bond; aldols, claisens, chiral methyls | | Floss Chiral methyls |
| | Wed. | 2/18 | 17 | (cont.) | | |
| | Fri. | 2/20 | 18 | (cont.) | | |
| 8 | Mon. | 2/23 | 19 | pyridoxal phosphate-requiring enzymes | | Kirsch PLP enzymes |
| | Wed. | 2/25 | 20 | (cont.) | | |
| | Fri. | 2/27 | 21 | thiamine pyrophosphate-requiring enzymes | | |
| 9 | Mon. | 3/2 | 22 | (cont.) | Walsh Chap. 10 | Knowles Biotin; Rose and Middlefort PIX |
| | Wed. | 3/4 | 23 | biotin-requiring enzymes | | |
| | Fri. | 3/6 | 24 | (cont.) | | |
| | Mon. | 3/9 | | | | |
| | Wed. | 3/11 | | Spring break—no class | | |
| | Fri. | 3/13 | | | | |

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|----|------|------|----|---|--|
| 10 | Mon. | 3/16 | 25 | NADH/NAD-requiring enzymes | Walsh Chap. 11 & 12 |
| | Wed. | 3/18 | 26 | (cont.) | |
| | Fri. | 3/20 | 27 | Midterm 2 | |
| 11 | Mon. | 3/23 | 28 | flavoproteins: dehydrogenase, oxidases | Pai NADPH disulfide oxidoreductase |
| | Wed. | 3/25 | 29 | (cont.) | |
| | Fri. | 3/27 | | (cont.) | |
| 12 | Mon. | 3/30 | 30 | metalloenzymes: overview | |
| | Wed. | 4/1 | 31 | (cont.) | |
| | Fri. | 4/3 | 32 | C1 transfer reactions: SAM, folates, cobalamin | |
| 13 | Mon. | 4/6 | 33 | (cont.) | Ludwig and Matthews B12 |
| | Wed. | 4/8 | 34 | (cont.) | |
| | Fri. | 4/10 | 35 | methionine synthases | |
| 14 | Mon. | 4/13 | 36 | methionine synthases (cont.) | Cleland et al Rubisco |
| | Wed. | 4/15 | 37 | Rubisco | |
| | Fri. | 4/17 | 38 | (cont.) | |
| 15 | Mon. | 4/20 | 39 | special topics (time allowing) | |
| | | 4/22 | 40 | special topics (time allowing) | |
| | | 4/24 | | special topics (time allowing) | |

TBA

Final Exam (not comprehensive)

Chemistry 6730 Learning Objectives

- (1) Understand, define, and apply the following principles of enzyme catalysis:
 - binding energy
 - nucleophilic catalysis
 - electrophilic catalysis
 - proximity/orientation
 - effective molarity
 - transition state stabilization
 - general acid/base catalysis
 - covalent catalysis
 - chemical/kinetic competence

- (2) Understand, define, and apply the following terms related to enzyme kinetics:
 - V_{\max} , K_m , k_{cat}
 - Determine V_{\max} , K_m graphically, interconvert V_{\max} , k_{cat}
 - Haldane relationship
 - sequential, ping-pong reactions
 - competitive, noncompetitive, uncompetitive inhibitors
 - allosteric effectors
 - slow-binding inhibitors, mechanism-based inactivators

- (3) Understand the principles of nonlinear regression analysis of kinetic data. Use appropriate software to fit experimental kinetic data to the appropriate Michaelis-Menten models for single and two substrate reactions to determine the kinetic mechanism and derive kinetic constants.

- (4) Be able to download “.pdb” files from the Protein DataBank, and render and manipulate the files using the computer software PyMol. Manipulate “.pdb” files to focus on structural details of a portion of an enzyme of interest, e.g. the enzyme active site, and ligand binding therein.

- (5) Understand the roles of active-site amino acid residues in stabilizing ES, EI, and transition state complexes, and understand how the contributions can be deduced experimentally.

- (6) Outline the mechanism of peptide bond hydrolysis catalyzed by serine proteases. Explain the function of the "catalytic triad" of serine proteases using the current models.

- (7) Explain the information the following experiments provided concerning the mechanism of chymotrypsin:
 - (a) burst kinetics
 - (b) p-nitrophenyltrimethyl acetate as substrate
 - (c) cryoenzymology
 - (d) aminoacyl-ester vs. aminoacyl-amide substrates
 - (e) substrate partitioning
 - (f) affinity label(s)
 - (g) group specific agent(s)
 - (h) mechanism-based inactivator(s)
 - (i) site-directed mutagenesis

- (8) Explain the stereochemical consequences of dissociative vs. associative phosphoryl group transfer reactions and of in-line vs. adjacent phosphoryl transfer.

- (9) Explain how the stereochemical outcome of RNA hydrolysis by ribonuclease A was determined.
- (10) Understand and explain biological strategies for increasing the acidity of protons on α -carbons for a biological aldol condensation reactions.
- (11) Outline a representative biological claisen condensation reaction. How does the strategy of carbanion stabilization differ from the aldol condensation?
- (12) Show how TPP can be used in a transketolation reaction.
- (13) Understand the functions of the following coenzymes in enzymatic reactions ,and interpret experimental results leading to the elucidation of their functions.
PLP, TPP, biotin, flavins, SAM, biopterin, cobalamin, flavins, lipoamide
- (14) Draw mechanisms for representative transamination, racemization, decarboxylation, and elimination reactions catalyzed by PLP-dependent enzymes.
- (15) What factors contribute to the increased acidity of the C-2 hydrogen of TPP?
- (16) Draw mechanisms for oxidative and nonoxidative decarboxylation reactions.
- (17) What methods exist to discriminate between "concerted" and step-wise" mechanisms involving reactions where three "substrates" react (e.g. biotin carboxylase, glutamine synthetase, carbamoyl phosphate synthetase). Why or why not might these methods reveal useful information?
- (18) Discuss the pros and cons of " CO_2 " vs. " HCO_3^- " as substrates for biological carboxylation reactions.
- (19) Provide specific enzymatic examples that illustrate redox, masked redox, and nonredox roles for NAD(P)(H).
- (20) Explain the chemical basis for the primary hydrogen isotope effect
- (21) What is a prochiral center?
- (22) Compare the mechanisms of alpha-hydroxyacid dehydrogenation by NAD^+ - and FAD-dependent dehydrogenases
- (23) Nucleophilic and electrophilic activation of O_2 are two strategies employed by different flavin-dependent monooxygenases. Give an example of each, and draw the mechanism for each enzyme.
- (24) What is the "NIH shift" and where is it seen? What mechanism(s) have been proposed to explain this shift?