Chemistry 565, 665/Biochemistry 665: Fall, 2019

Instructor: Tom Record (3214 BSB) Email: mtrecord@wisc.edu Tel: 262-5332

Office Hrs (3221 BSB): Mondays 12 – 1 and/or 2:30 - 3:25 PM.
Also after lecture or by appointment

Updated Catalog Statement for 565/665:
Chemical thermodynamics and chemical kinetics, applied to biochemical processes in aqueous solution. Expected background: Chem 327 or 329; Math 222; Physics 201 or 207; Biocore 303 or Biochem 501 or 507 (or concurrent registration) or consent of instructor.

Specific Learning Outcomes:

565/665 develops the principles of chemical thermodynamics and chemical kinetics and applies these principles to understand the energetics and mechanisms of biochemical processes in aqueous solution. Processes include chemical reactions (enzyme catalyzed) and noncovalent interactions, including the self-assembly interactions which form functional structures of proteins, nucleic acids, carbohydrates, lipids and their complexes, and the ligand-binding interactions which regulate them.

This material is useful both at a practical level (in understanding the chemical basis of methods for the separation, purification, and characterization of biological molecules) and at a conceptual level (in understanding the thermodynamic and mechanistic principles of biopolymer processes). Although starting with the basics of thermodynamics and kinetics, 565/665 progresses to a level suitable as background for more advanced graduate courses or literature work in biophysical areas including protein and nucleic acid stability and interactions, enzyme catalysis and bioenergetics.

Books and Readings

There is **no required textbook** for 556/665, which is taught from handouts (chapters, papers, problem sets and examples) for which there is a one-time charge of $30.

Klotz and Rosenberg (a "recommended" book on reserve in Steenbock and Chemistry libraries; see below) is a very readable introduction to Chemical Thermodynamics at the level of this course, and a useful reference for the first month of 565/665.

Supplementary Readings (Not Required for Purchase; in Chemistry and Steenbock Libraries)

1) Reference for fundamentals of thermodynamics:

I. Klotz and R. Rosenberg, Chemical Thermodynamics (Benjamin-Cummings). (Numerous editions; any of them is OK.) Chapters 1-11 and 14 provide a detailed and very readable treatment of fundamentals of thermodynamics, at the math level of 565/665, and are very useful outside reading for the first month of the class.

2) Other Reference Books (Not Required for Purchase)

Textbooks:
J. Kuriyan, B. Konforti, D. Wemmer, The Molecules of Life; Physical and Chemical Principles (Garland, 2013). KKW is an advanced undergrad-beginning grad text from UC Berkeley that combines structural biology with chemical thermodynamics and kinetics at the level of 565/665. (The cover is a nice illustration of the attempt to combine these topics.)
K. Dill and S. Bromberg (2010 or 2003) Molecular Driving Forces (Garland). Excellent coverage of biophysical and polymer physical chemistry, from a statistical thermodynamic perspective. Moderately high math level.
Other books:
T. Creighton, Proteins: Structure, Molecular Properties (2011; Freeman)
V. Bloomfield, D, Crothers and I. Tinoco, (2000) Nucleic Acids (USB);
also (1974) Physical Chemistry of Nucleic Acids (Harper Row)
C. Tanford (1980) Hydrophobic Effect; John Wiley & Sons.
K. van Holde, W. C. Johnson, P. S. Ho, Physical Biochemistry, Prentice-Hall

Course organization:

1. **Lectures, handout materials and the weekly problem sets** define the course content. You should prepare for class by working through the relevant parts of the handout chapters, sample problems and/or papers. Questions and discussion are encouraged in all class meetings (lecture and discussion).

   Notes taken by a TA are posted on line so you can check yours, but are not a substitute for attending and participating. Extra copies of handouts are available in a file drawer on the right as you enter the department office (near Mills St. entrance)

2. **Discussion section meetings** on Thursdays discuss methods of problem solving, work sample problems, and discuss current lecture material. It is important to prepare for discussion section and to participate actively in discussion; the "optional" listing for these sections means only that no quizzes are given.

   In the **first section meeting** please give your TA a **check for $30** made out to Department of Chemistry (or cash, in an envelope with your name on it) to cover the cost of the handouts for the semester.

3. **Problem sets** are assigned weekly, and should be **brought to class** and turned in **before class** on the due date, usually Friday. Lateness will reduce your grade. Please don't put problem sets in our mailboxes.

   C**onscientious work on all the problem sets, and submitting them on time, is very important for many reasons** (e.g. understanding the material, getting a good grade; see #5 below). Problem set questions are at the level of exam questions. **Demonstration of effort on all problem sets is expected.**

4. **It is a very good idea to form a study group** to discuss the lecture material, to solve practice problems, and to develop strategies for solving the assigned problems. But copying answers from others or from previous years' handouts is not acceptable. **No credit will be given for work which is not your own.**

5. **Exams**: The three exams are given as proctored problem sets. You may bring to the exam the printed chapters and handouts, as well as your handwritten notes and problem set answers, but not other textbooks or photocopied parts thereof, reference materials, and/or old exams. Any single-purpose calculator can be used, but no other electronic devices are permitted and must be inaccessible during the exam. Exams are cumulative, but will cover primarily the material since the cut-off date for the previous exam.

Exam dates are **Thursday Oct. 10, Thursday Nov. 14, and Thursday Dec. 19**.

The first two exams will be from **7:15-9:15 PM**; the third exam will be in our assigned final exam time slot from **7:45 - 9:45 AM.** No makeup exams are given. Please let me know of any academic conflicts with these exam dates during the first week of the course.

6. **Grading**: Each exam counts 33% of the course grade.

The assigned problem sets contribute in several ways toward your grade:

a) if in any third of the course, your problem set average is higher than your grade on the corresponding exam, the problem sets will count 25% and the exam 75% of your grade for that portion of the course;

b) if the raw exam scores are curved upwards, you must have shown conscientious effort on **all 4** of the corresponding problem sets to receive the curved score, and

c) conscientious effort on the problem sets and active participation in all aspects of the course will help your grade in borderline final-grade situations, while **lack of effort on the problem sets will reduce your grade**.

7. **Advice on the Problem Sets**: It is important that you attempt to work all the problem sets and turn in your work on time. It is equally important that you be able to do this efficiently, without spending too much time on false starts. Consequently you should plan to start working the problems early in the week in which they are due. Ask for help after class or in office hours if you are confused. Bring your attempts with you. **We will not discuss solutions of problems with people who have not thought about them and attempted to work them.**

8) Approximate exam grade conversion scale:

87 and above: AB, A
75-86: BC, B
65-74: C
55-64: D

9) General Learning Outcomes: Development of Core Competencies Sought by Graduate Schools, Medical Schools and Employers

Science Competency: Apply knowledge and skill in the natural sciences to solve problems related to molecular or macroscopic systems.

***Thinking, Reasoning Competencies*:**

Critical Thinking: Use logic and reasoning to identify the strengths and weaknesses of alternative solutions, conclusions, or approaches to problems.

Quantitative Reasoning: Apply quantitative reasoning and appropriate mathematics to describe or explain phenomena in the natural world.

Scientific Inquiry: Apply knowledge of the scientific process to integrate and synthesize information, solve problems and formulate research questions and hypotheses; be facile in the language of the sciences and use it to participate in the discourse of science and explain how scientific knowledge is discovered and validated.

Written Communication: Effectively convey information to others using written words and sentences.

Interpersonal Competencies

Social Skills: Demonstrate awareness of others' needs, goals, feelings, and the ways social and behavioral cues affect peoples' interactions and behaviors; adjust behaviors appropriately in response to these cues; and treats others with respect.

Teamwork: Work collaboratively with others to achieve shared goals; share information & knowledge with others and provide feedback; put team goals ahead of individual goals.

Oral Communication: Effectively convey information to others using spoken words and sentences; listen effectively; recognize potential communication barriers and adjust approach or clarify information as needed.

Intrapersonal Competencies

Ethical Responsibility to Self and Others: Behave in an honest and ethical manner; cultivate personal and academic integrity; adhere to ethical principles and follow rules and procedures; resist peer pressure to engage in unethical behavior and encourage others to behave in honest and ethical ways; and develop and demonstrate ethical and moral reasoning.

Reliability and Dependability: Consistently fulfill obligations in a timely and satisfactory manner; take responsibility for personal actions and performance.

Resilience and Adaptability: Demonstrate tolerance of stressful or changing environments or situations and adapts effectively to them; be persistent, even under difficult situations; recover from setbacks.

Capacity for Improvement: Set goals for continuous improvement and for learning new concepts and skills; engage in reflective practice for improvement; solicit and respond appropriately to feedback.

Fall, 2019 Syllabus **Instructor: Tom Record**

Biophysical Chemistry 565/665

Thermodynamics, Kinetics of Biochemical Processes

A) Introduction to Biopolymer Processes and to **Applications of Chemical Thermodynamics and Chemical Kinetics to Biopolymer Processes**

(1-2 lectures: Read **Overview, Introduction, Ch. 1** of Handouts)

B) Fundamentals of Chemical Thermodynamics of Systems and Processes
(Ch 1-7; ~12 lectures) Starting with the Laws of Thermodynamics, we progress rapidly to free energy and chemical potential. Chemical potential differences are the driving force for moving molecules in processes, from one solution environment or phase to another and from reactant to product in a chemical reaction or noncovalent interaction.

1) **Preliminaries**:

Math of State Functions, Exact, Inexact Differentials, Partial Derivatives
(**Ch. 1 Appendix**; see also Klotz & Rosenberg (KR) Ch. 2);
Work, Heat; Reversible, Irreversible Processes (**Ch. 2**; see also KR Ch. 3).

2) **First Law (Ch. 2**):
Energy, Enthalpy, Heat Capacity of Systems; Changes in these Functions in Processes (see also KR Ch. 3-6).

3) **Second Law (Ch. 3**;**)**:
Physical and Mathematical Properties of Entropy (see also KR Ch. 7)

4) **Free Energy and Work (Ch. 4,5)**:
Criteria for a Spontaneous Process and for Equilibrium at Constant T and P; Summary of State Functions; Maxwell Relations; Calculations of Entropy, Free Energy Changes for Simple Processes (see also KR Ch 8)

5) **Mixing** as a Spontaneous Process; Ideal Gas Mixtures (**Ch 5**; see also KR Ch 14).

6) Thermodynamics of **Mixtures** (**Ch. 6**).:
Extensive, Intensive Quantities; Molar and Partial Molar Quantities; Multi-Component Systems, Mixtures; Characterizing Contributions of Different Components to the Thermodynamic Properties of a Mixture

7) **Chemical Potential** (Partial Molar Gibbs Free Energy) (**Ch. 6, 7**)

8) **Applications** of Chemical Potential to Analyze Fundamental Processes: **Chemical Reaction and Chemical Equilibrium** in a Gas-Phase Molecular Mixture;
Phase Change and Phase Equilibrium in a Pure System where Molecular Mixing is Not Involved **(Ch. 7)**

C) Thermodynamics of Solutions (~5 lectures; **Ch. 8**)

1) **Ideal Solutions** (**Random Liquid Mixtures**), Mole Fraction Concentration Scale; **Nonideal (i.e. Nonrandom) Solutions**, Activity Coefficients. Nonrandomness arises from unequal interactions and/or unequal volumes of the species in the mixture; both are described by activity coefficients.

2) **Very Dilute** (also called "Ideal Dilute") **Nonideal Solutions**; Thermodynamic Characterization of Solute-Solvent Interactions and Solute-Solute Interactions. Here the only nonrandomness is from hydration of the solute; the hydrated solutes form a random mixture with the solvent.

3) **Solvent, Solute Chemical Potentials**; Molar and Molal Concentration Scales.

4) **Electrolyte Solutions** (Dissociation; Hydration of Ions; Local Deviations from Electroneutrality (Non-random Mixing) in Salt and Biopolymer Solutions; Nonideality from Long-range Coulombic Interactions of ions at very low concentrations, especially for polyions).

Exam 1 on this material (first 4 problems sets): Thursday, October 10, 7:15 PM

D) Applications of Chemical Potential to Analyze Biochemical Processes and Equilibria in Solution (~10 lectures; **Ch 9-12**; see also KR 9, 10)

1) **Processes and Equilibria Involving Solvent** in Solution **(Ch. 9):**
Colligative Properties of Solutions (FP depression, BP elevation, VP lowering, Osmotic Pressure). Analysis of **Osmosis and Reverse Osmosis**. Living Cells as Osmotic Systems

2) **Processes and Equilibria Involving Solutes** in Solution **(Ch 10):**
a) **Biochemical Covalent Reactions** (**ATP hydrolysis** is the best characterized example) and **Noncovalent Binding/Association Interactions**. One remarkable feature of these processes is how sensitive they are to solution variables like pH and concentrations of ligands, solutes and salt. Hence their equilibrium "constants" aren't constant when these solution variables change.

b) **Solubility, Phase Partitioning, Polymer-Polymer Phase Separation, Liquid Droplet Formation (Ch. 11):** Underlying process is transfer of a solute from one environment to another. Very important in all aspects of biochemistry (from preparative to conceptual).

c) **Transfer of Hydrocarbon Solutes** to Water from a Nonaqueous Phase as a Model for the **Hydrophobic Effect (Ch. 11)** Burying hydrocarbon surface is a major driving force for protein processes including folding, subunit assembly, and binding.

d) **Thermodynamics of Forming Ions** from Uncharged Solutes in Water **(Ch. 10, 11).**

E) Macromolecular Recognition, Self-assembly and Other Noncovalent Biopolymer Processes in Water (Ch. 12):
Micelle Formation
Nucleic Acid Helix Formation and Folding
Protein Folding, Protein-Ligand and Protein-Protein Interactions
Roles of the Hydrophobic Effect, Base Stacking and other Noncovalent Interactions

F) Ligand Binding to Biopolymers; Regulation of Processes by Ligands (Ch. 13) (~10 lectures)

1) **Noncooperative and Cooperative Binding Isotherms** for Ligand-Biopolymer Interactions
2) **Experimental Thermodynamics** of Ligand Binding: Equilibrium Dialysis, Spectroscopic and Calorimetric Methods
3) **Analysis** of Ligand Binding and Ligand Effects using **Binding Polynomials; Ligand Binding Statistics**.

4) **Regulation by Ligands** of Processes and Equilibria of Biopolymers.
5) **Applications**: O_2 Binding to Mb and Hb, *Lac* Repressor-*lac* Operator Interactions: Well-characterized examples of binding interactions which are regulated by other (allosteric, competitive) binding interactions). Cooperativity of ligand binding from coupled conformational changes or other coupled processes.

After 4 problem sets, Exam 2 covers this material (up to Section F4): Thursday, November 14, 7:15 PM

G) Interactions of Proteins, Nucleic Acids with Solutes, Salts from the Hofmeister series and Polymers (Excluded volume agents); Effects of these Solutes, Salts and Polymers on Protein and Nucleic Acid Processes (**Ch. 14, 15**; ~4 lectures)
Solutes and Salts form Series in how they interact with proteins and nucleic acids and affect their processes: the progressions below are (left to right) from solutes that interact favorably with proteins and nucleobases and destabilize their assemblies to ones that don't.
Solute series: Urea, formamide, glycerol, proline, glycine betaine, TMAO
Hofmeister (noncoulombic) **Salt Ion Series**:

Anions: SCN^-, I^-, ClO_4^-, Br^-, Cl^-, $Acetate^-$, F^-, $Glutamate^-$, SO_4^{2-}, HPO_4^{2-}

Cations: GuH^+, NH_4^+, K^+, Na^+, alkylated NR_4

Monomer to Polymer Series: Ethylene glycol ($HOCH_2CH_2OH$) to Polyethylene Glycol ($HOCH_2(CH_2OCH_2)_nCH_2OH$)

H) Chemical Kinetics and Mechanisms of Biopolymer Processes (~16 lectures; **Ch 16-19**) Kinetics and thermodynamics are complementary disciplines; kinetics provides information about key aspects of processes that are not significant for thermodynamics (how fast they occur; their path or mechanism). Unlike thermodynamics, kinetics has few fundamental principles and little predictive power; in particular you can't predict the kinetics or mechanism of a process from its balanced chemical equation. An understanding of thermodynamics is needed to interpret kinetic data.

1) Elementary (Single-Step) Reactions (Ch 16-17)
a) Rate Laws, Rate Equations (First Order, Second Order; Irreversible, Reversible; Relaxation Analysis (**Ch. 16**).
b) Diffusion-Collision Step in Second Order Reactions in Solution (Diffusion Limit, Facilitated Diffusion; **Ch. 17**).
c) Chemical Limitations to Elementary Reaction Rates: Enthalpic, Entropic Contributions to Activation Free Energy Barriers of Elementary Reactions (**Ch. 17**)

2) Reactions with Intermediates (Ch 18)
a) Mechanisms
b) Analysis using Steady State or Rapid Equilibrium Approximations

3) Kinetics and Mechanisms of Enzyme-Catalyzed Reactions (Ch 19):
Noncooperative Enzymes, Biophysical Basis of Catalysis, Catalytic Antibodies, Cooperative Enzymes, Regulation of Catalytic Activity by Ligand Concentration

4) Examples: Kinetics and Mechanisms of Protein Folding, Nucleic Acid Helix Formation, Protein-Protein and Protein-Nucleic Acid Interactions

After 3 problem sets, Exam 3 covers this material (primarily from section F5 on): Friday, December 19, 7:45 – 9:45 AM