CHE 427/627

THE ORGANIC CHEMISTRY OF BIOLOGICAL MOLECULES

Fall 2014

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Required Texts: Carey and Giuliano, "Organic Chemistry" 8^{h} Edition
Study Guide for Carey, a set of molecular models

In Chemistry 427/627 we will continue to build on the foundational principles of organic chemistry established in CHE 275 and CHE 325 by examining the structure and reactivity of the compounds that constitute the building blocks of biological macromolecules: carbohydrates, amino acids, nucleic acids and lipids. For each group we will examine the structure, reactions and biosynthesis of representative compounds, and the laboratory synthesis and *in vitro* chemical derivatizations that lead to stereochemically-defined, richly functionalized organic intermediates. An understanding of the biological reactions of multifunctional compounds like carbohydrates and amino acids necessarily requires a command of the chemical events by which such compounds undergo regio- and stereoselective transformations and we will continue to develop proficiency in the mechanistic analysis of complex organic reactions. Use of biological subunits as templates for stereoselective organic synthesis will be used to introduce advanced topics in stereochemistry and spectroscopy. Special topics will include the chemistry of glycoproteins, glycolipids and other bioconjugates, techniques for sequencing peptides and oligonucleotides and the use of biological molecules as chiral auxiliaries for asymmetric reactions leading to new carbon-carbon bonds.

An understanding of the fundamentals of chemical bonding, structure and reactivity is required for this course, and enrollment is limited to those who have completed CHE 275 and CHE 325 or an equivalent two-semester organic chemistry sequence.

Problem Sets. Problem sets will be distributed on Monday of each week, and will consist of selected problems from the text in addition to supplemental problems. These problem sets will not be graded; their purpose is to serve as an ongoing assessment of your understanding of the subject matter and a mechanism to focus questions you may have about the lecture or reading material. In addition, these exercises represent a rough approximation of the scope and difficulty of problems you will encounter on the exams. Solutions to problem sets will be posted online at the course Blackboard website.

Problem Sessions: This semester we'll be experimenting with a flipped classroom format for our Friday sessions. In these sessions, I will introduce a new reaction or strategic concept, whereupon we'll use mechanism-based problems to develop a full understanding of the topic. The goal is to expose the

student to content not encountered in a typical organic sequence and to develop a mechanistic fluency that will allow students to extend their mastery of basic organic reactions to more complex systems.

Lecture Notes. PowerPoint supplementary material for lectures will be posted online weekly. *Note that these presentations are intended to supplement lecture discussions and provide students with copies of material that cannot be easily transcribed during a lecture (for example, spectra of organic compounds). These presentations will rarely contain the full content presented in a lecture.*

Reading. Reading assignments from the Carey-Guiliano text are listed in the accompanying course outline. Suggested review readings in the text, where relevant, are also noted. In addition, reading lists containing references to the primary chemical literature will be distributed periodically.

Examinations and Grading. Grades will be based on the results of three examinations and participation in the weekly problem sessions. Examinations 1 and 2 will be held on Thursday evenings from 5-6:30 PM. *Note that these times and dates are tentative and may change.* Exam 3 will be held during the assigned final exam period for CHE 427/627.

Exam 1: Oct 2 (Carbohydrates and Polysaccharides)

Exam 2: Nov 6 (Amino Acids and Proteins)

Exam 3: Finals week (Lipids and Nucleic Acids)

Office Hours. Office hours are available by appointment.

Academic Honesty: Complete academic honesty is expected of all students. Academic dishonesty, as defined by the SU Academic Integrity Policy (see http://academicintegrity.syr.edu), will result in both course sanctions and formal notification of the College of Arts & Sciences. In this course, students are allowed and encouraged to work and study together, but all examinations must reflect the work of the individual student and may not be copied from another student's work or any other source.

Disability Accommodation: Students with any sort of disability who may need special accommodations must see me two weeks before the first hour exam. In order to obtain authorized accommodations, students should be registered with the Office of Disability Services (ODS), 804 University Avenue, Room 309, 315-443-4498 and have an updated accommodation letter. Accommodations and related support services are not provided retroactively and, if granted, will not be changed during the semester.

Religious Observances: Syracuse University recognizes the diversity of faiths represented among the campus community and protects the rights of students, faculty, and staff to observe religious holy days according to their tradition (http://supolicies.syr.edu/emp_ben/religious_observance.htm). Students who anticipate that work requirements that may be missed due to a religious observance must notify the instructor by September 8. The online notification process is available through MySlice/Student Services/Enrollment/My Religious Observances until the end of the second week of class.

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Course Outline and Text Reading Assignments

Week 1. Carbohydrates: Structure and Stereochemistry

Classification of carbohydrates. Fisher projections and the D,L notation. The furanose and pyranose forms of carbohydrates. Haworth projections. Mutarotation and the anomeric effect. Ketoses. Deoxysugars and amino sugars.

Reading: Chapter 23.1-23.13 Review: Chapters 7.7, 7.11, 7.12 (Fisher projections). Also review the chemistry of alcohols in Chapters 4, 8, 14, 15.

Problem Session: Carbonyl Interconversions

Week 2. Reactions of Carbohydrates I

The anomeric effect. Epimerization and isomerization: ketoses. Deoxysugars and amino sugars. Acid-catalyzed glycosidation. Formation of polysaccharides.

Reading: Chapter 23.14-23.17. Review: Chapter 17 (aldehydes and ketones).

Week 3. Reactions of Carbohydrates II

Oxidation and reduction of sugars. Alkylation and acylation of carbohydrate hydroxyl groups. Thioketalization. Nucleophillic additions to simple sugars. Hydroxyl group masking strategies: silylation and ketalization. Synthesis of deoxysugars.

Reading: Chapter 23.18-23.23. Review alcohol/carbonyl redox chemistry: Chapter 15.2, 15.9

Problem Session: Conjugate Addition Reactions

Week 4. Carbohydrates in Organic Synthesis

Preparation of chiral building blocks from sugars. Multistriatin. Chiral templates for polyketide synthesis from D-glucose. Homologation and degradation reactions of monsaccharides. Survey of naturally-occurring oligosaccharides. Glycosidation and regiocontrolled synthesis of disaccharides.

Reading: Review Chapter 16.9-6.14 (epoxidation).

Problem Session: Acyl Anion Equivalents

Week 5. Laboratory Synthesis of Carbohydrates

Strategies for solid phase synthesis of oligosaccharides. Synthesis of monsaccharides: Diels-Alder synthesis of chiral glycals. The Ferrier rearrangement. Synthesis of optically active carbohydrates from epoxides. Metabolism of carbohydrates: glycolysis.

Reading: Chapter 23.24-23.25.

FIRST HOUR EXAM

Week 6. Amino Acids

Classification and stereochemistry of amino acids. Structure and occurrence of the standard amino acids. Review of amine and carboxylic acid chemistry.

Reading: Chapter 25.1-25.2. Review: Chapters 18 (carboxylic acids), 21 (amines).

Problem Session: Chelation Controlled Addition to C=O

Week 7. The Chemistry of α-Amino Acids.

Acid-base chemistry of α-amino acids. Chemical transformations: acylation and alkylation. Diazotization of the amino group: synthesis of α-hydroxy acids. Reduction of amino acids. Preparation of chiral building blocks from amino acids. Chiral auxiliaries for asymmetric synthesis: preparation and alkylation of chiral oxazolidinones. Alkylation of chiral enamines.

Reading: Chapter 25.3, 25.5.

Problem Session: Vinylogous Functional Groups

Week 8. Synthesis of Amino Acids

Pyridoxal-mediated biosynthesis of amino acids. Transamination and decarboxylation. Strategies for synthesis of α-amino acids. The Strecker synthesis. Asymmetric syntheses of amino acids via nitrogenation, alkylation and reduction. Chemical and enzymatic resolution of amino acids.

Reading: Chapter 25.4, 25.6.

Problem Session: Sigmatropic Rearrangements, Part I

Week 9. Polypeptides and Proteins

Review of amide chemistry. Primary structure of polypeptides. Post translational modification of side-chain residues. Non-specific and site-selective hydrolysis reactions. N-Terminal degradation of proteins: the Edmans and Sanger reactions. Automated peptide sequencing.

Reading: Chapter 25.7-25.13. Review: amide chemistry, Chapter 19.14-19.17

Problem Session: Sigmatropic Rearrangements, Part II

Week 10. Protein Synthesis

Laboratory synthesis of proteins: strategies for solution and solid phase peptide bond formation. Protecting groups for the N-terminus, C-terminus and side-chain residues. Secondary and tertiary structure of proteins: protein folding.

Reading: Chapter 25.14-25.23

SECOND HOUR EXAM

Week 11. Nucleic Acids

Purines and pyrimidines. Nucleotides and nucleosides: structure and nomenclature. Synthesis and biosynthesis of nucleosides and nucleotides. Bioenergetics: ATP and ADP.

Reading: Chapter 26.1-26.7

Week 12. Nucleic Acids and Oligonucleotides

Nucleic acids: nomenclature. Secondary structure of DNA: the double helix. Tertiary DNA structure: supercoils. Biosynthesis of oligonucleotides. Solid phase synthesis of DNA via the phosphoramidite and H-phosphonate methods. RNA synthesis. Restriction enzymes and DNA sequencing.

Reading: Chapter 26.7-26.16

Week 13. Lipids

Fats, oils, waxes and fatty acids. Triacyl glycerols. Acetyl CoA and thioesters. Biosynthesis of fatty acids. Phospholipids. Saponification of triglycerides. Reactions of fatty acids. Fatty acid biosynthesis and catabolism.

Reading: Chapter 24.1-24.5.

Week 14. Terpenes and Steroids

The isoprene rule. Terpenes and sesquiterpenes. Steroids: structure and stereochemistry. Steroidal vitamins and hormones. Biosynthesis of terpenoid natural products. Prostaglandins. Synthesis of prostaglandins from carbohydrates.

Reading: Chapter 24.6-24.16.

Week 15. Bioconjugates

If time permits, we will discuss the special chemistry and biochemistry of glycoproteins, glycolipids and other "mixed" macromolecules.

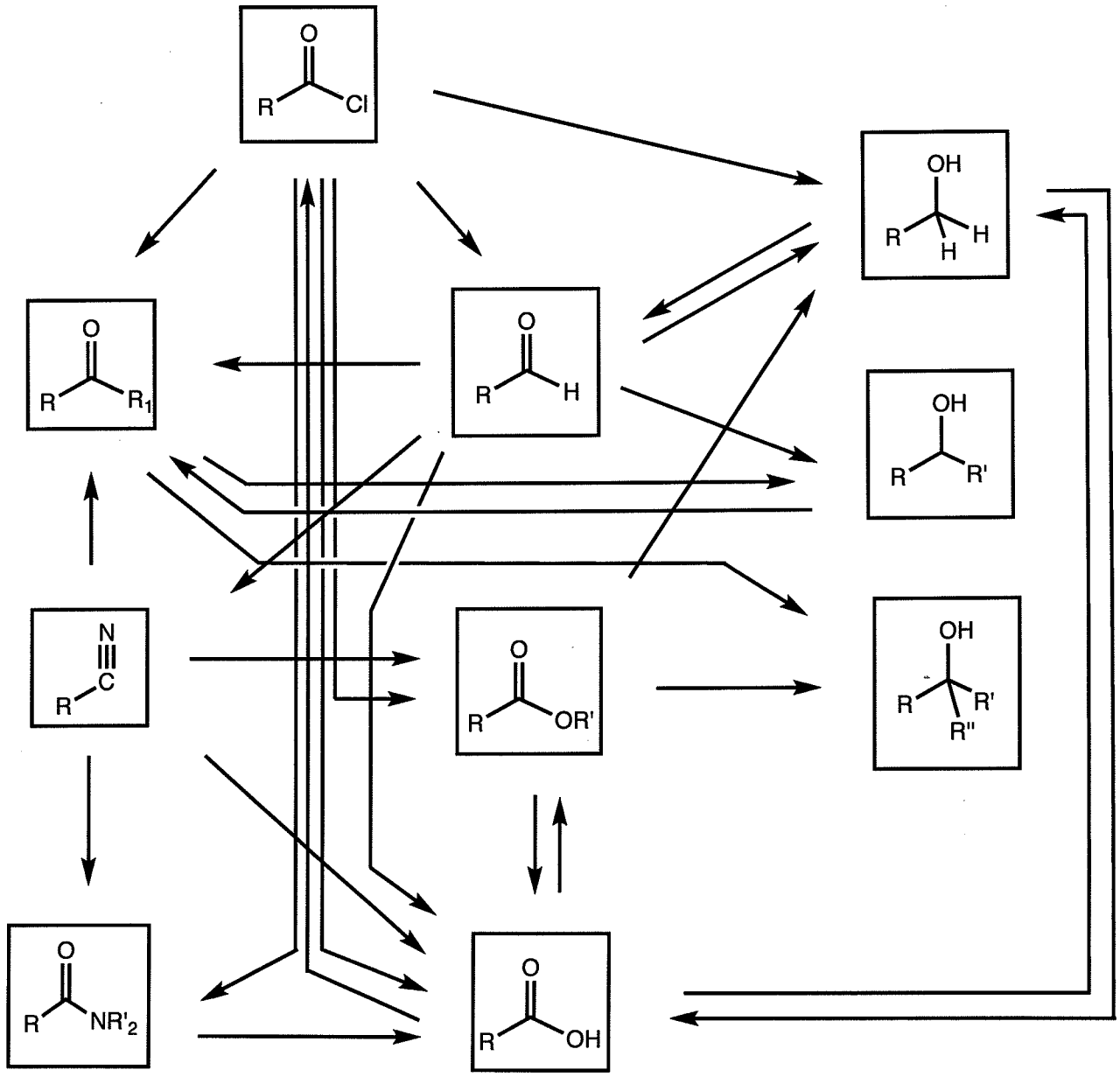
THIRD HOUR EXAM

Problem Set 1

1) Send an email to jkallmer@syr.edu from the account at which *you* prefer to receive email. On the subject line of the email, put "Problem Sessions"; in the body of the message, tell me about your MWF availability before *and* after our class and suggest a couple of different times for office hours.

2) Carey, Chapter 23, 23.26, 23.27, 23.28, 23.29, 23.30, 23.32.

3) Carbonyl transformations and alcohol-carbonyl interconversions are reactions of critical importance in biological chemistry, so let's take an opportunity to review. Provide reaction conditions (or a short synthetic sequence) which could be used to carry out the indicated transformations. *While you're in the neighborhood, take a moment to review the mechanisms of these carboxylate interconversions.*



Seems like a lot of work, but familiarity with these conversions will pay huge dividends in this class and in life. You *know* I'm right.