

Chemistry 41c Midterm Review Sheet – Spring Quarter 2013

Chapter 18 topics:

Pages 831-848. Review aspects of electron bookkeeping (oxidation state, d^n count, and valence electron count), focus on the fundamental processes (ligand dissociation-association & ligand substitution; oxidative addition; reductive elimination; ligand insertion; beta-elimination). Focus on the Heck reaction and mechanism as a representative transition-metal-catalyzed reaction.

Chapter 19 topics:

Spectroscopic signatures of aldehydes and ketones (1H/13C/IR/MS).

Review 41a/b methods for synthesizing aldehydes and ketones.

The oxidation series (R-OH, RCHO, RCOOH, etc.). Assignment of oxidation states of carbon in organic compounds.

Lithium aluminum hydride (LAH) reduction of aldehydes and ketones. Mechanism of reaction. Sodium borohydride reduction of aldehydes and ketones. Mechanism of reaction. Compare different experimental conditions and “reducing power” for LAH vs. NaBH4. The small lithium ion as a privileged Lewis acid (seen time and again throughout 3rd quarter material).

Orbital implications of nucleophilic addition reactions involving C=O bonds, and the reasons for the relative reactivity differences of aldehydes vs. ketones. The concept of substrate control in hydride additions to, for example, cyclohexanone.

Acetals and ketals and their hemi- forms. Be able to identify these functional groups. Know the mechanism of formation/hydrolysis for an acetal. The Dean-Stark trap for shifting acetal formation reactions ‘to the right.’ Be aware of the utility of acetals and ketals as protecting groups in organic synthesis.

The addition of amines to aldehydes and ketones: mechanisms for imine and enamine formation. You should be familiar with the related chemistry of oximes and hydrazones.

The addition of HCN to aldehydes and ketones. Mechanism of cyanohydrin formation and synthetic utility of products.

Hydrated aldehydes and ketones—occurrence, mechanism of formation, and equilibrium content.

Preparation and reaction of Grignard reagents with aldehydes and ketones. Mechanism of reaction and work-up step; functional group compatibility issues to consider when using Grignards.

Reduction of ketones and aldehydes via the Wolff-Kishner reaction.

The Wittig reaction. Mechanism of reaction, definition of ylide, betaine, oxaphosphatane. The Horner-Wadsworth-Emmons Modification.

Chapters 20/21 topics:

Review the properties and spectroscopic properties ($^1\text{H}/^{13}\text{C}$ NMR/IR) of carboxylic acids and their derivatives as presented in class.

Acidity. Have in mind a chemically relevant definition of pK_a , one that is derived from the Henderson-Hasselbalch equation. Review the general factors which affect acidity.

Preparation of carboxylic acids. Review the synthetic methods (from 41a/b) and know the scope and mechanisms of reaction for the two new methods we discussed: (i) carbonation of a Grignard reagent and (ii) acid/base hydrolyses of nitriles.

Review the general mechanism of nucleophilic addition/elimination reactions involving carbonyl groups of various types. Review the factors we have used to rate the relative reactivity of acyl compounds.

Preparation and reactions of acid chlorides. Focus your attention on the thionyl chloride method for preparing acid chlorides, and take note of their applications in synthesis.

Preparation and reactions of acid anhydrides.

Esters and lactones: mechanism of the Fischer esterification (carboxylic acid + catalytic acid/ROH); ester syntheses using $\text{S}_{\text{N}}2$ chemistry, including diazomethane; ester syntheses using activated carbonyl groups (anhydrides or acid chlorides). Mechanism of basic saponification or acid hydrolysis of esters, use of isotopes to support mechanism of reaction. Be familiar with the term transesterification. Lactones-- know the relevant nomenclature, properties, and reactions.

Amides and lactams: methods for the synthesis of amides from activated carbonyl groups (anhydrides or acid chlorides). Hydrolysis of amides: know the acid and base mechanisms, compare these hydrolyses with the ester case in terms of ease of hydrolysis. Lactams--nomenclature, properties, occurrence, and reactions.

Be familiar with the decarboxylation reactions of carboxylic acid derivatives.

We focused ample mechanistic attention on hydride reduction reactions involving carboxylic acids and their derivatives. Acid chlorides and their reduction to aldehydes [via $\text{LiAlH}(\text{OtBu})_3$] or to the alcohol [via LAH]. Esters and their reduction to the component alcohols [via LAH but not NaBH_4]. Amides and nitriles and their LAH reduction to the amine, without rupture of the C-N bond and in contrast to C-O rupture in the ester case [via LAH]. Though not discussed in class, acids are reduced to the alcohols via a similar mechanistic pathway [via LAH].

We also discussed mechanistic details for a number of C-C bond-forming reactions with carboxylic acids and (mainly) their derivatives. These included Grignard reactions with esters to form alcohols, as well as a series of methods for converting acids to ketones (using methyl ketones as a test case): (i) cuprates with acid chlorides, discussed in the context of the failed Grignard process with acid chlorides, (ii) Grignard reagents with Weinreb amides, and (iii) alkyllithiums (2 equivalents) with acids.

Chapter 22 topics:

Acidity of the α -hydrogen of carbonyl compounds; know the pKa's of acetone, a generic ester, and a generic β -dicarbonyl. Why are these hydrogens acidic? What does an enolate ion look like, from an orbital perspective?

Keto-enol tautomerism; rationalize the preferred keto form on the basis of select bond strengths.

Why do certain optically active aldehydes and ketones racemize easily?

Be familiar with the base-promoted α -halogenation of aldehydes and ketones, the haloform reaction (mechanism), and the HVZ reaction (mechanism exempted under Article 11 of the 1998 Mechanism Reduction Act). What is the synthetic utility of these reactions?

Lithium enolates via LDA treatment. Thermodynamic and kinetic enolates. Alkylation of lithium enolates.

Direct alkylation of esters and nitriles using lithium diisopropylamide (LDA).

The acetoacetic ester synthesis of substituted acetones. Know the step-by-step mechanism of reaction. Break it up into the four steps: 1. Deprotonation, 2a. Alkylation #1 (know limitations), 2b. Alkylation #2 (can be same or different from #1), 3. Saponification (hydrolysis) of the ester under basic conditions, 4. Acidification with heating to decarboxylate (lose CO₂). Be aware that the acetoacetic ester anions can also be acylated, and that their dianions can be alkylated.

The malonic ester synthesis of substituted acetic acids. Know the step-by-step mechanism of reaction. Break it up into the four steps: 1. Deprotonation, 2a. Alkylation #1 (know limitations), 2b. Alkylation #2 (can be same or different from #1), 3. Saponification (hydrolysis) of the esters under basic conditions, 4. Acidification with heating to decarboxylate (lose CO₂).

The Claisen and Dieckmann condensations as methods for constructing β -keto esters. Mechanism of reaction (condense two molecules of ethyl propionate, commenting on factors which favor product formation. There are two: one of experimental design, one inherent to the molecular system).

Understand the crossed Claisen condensation.

The aldol reaction. Know the mechanism of the general reaction, focusing on three issues: (i) the “forward” direction, completely reversible, to yield a β -hydroxy ketone or aldehyde, (ii) the “reverse” direction, or retro-aldol (usually from β -hydroxy ketones, but judicious use of the Soxhlet thimble can serve as a work-around in some hydroxide-promoted cases), and (iii) irreversible dehydration of aldol addition products to yield conjugated systems (this happens at higher temperatures as well as for products whose elimination of H₂O results in conjugated systems). Intramolecular aldol reactions give a ring as a product. Acid-catalyzed variant of the aldol reaction: mechanism of reaction.

Extend your mechanistic insights to examples of crossed and directed aldol reactions, including those involving lithium enolates, generated by the strong hindered base lithium diisopropylamide.

Definition of 1,2 vs. 1,4 addition to α , β unsaturated systems; mechanism of 1,4 attack; conjugate addition; Michael addition; mechanism of the Robinson annulation.