

## Chapters 8-9. Ouellette, 2/e. Chemistry X402.

Ch 8. Alcohols and phenols.

Ch 9. Ethers and epoxides. (Sect 1-3 only)

### **Skip:**

Ch 8 Sect 5.

Ch 9 Sect 4-8.

The “Overview of skipped sections”, below, also briefly describes Ch 7, which we entirely skip.

Ch 8 is the first of a set of chapters that examines (primarily) the O-containing functional groups, in order of increasing oxidation state. You may want to review Sect 2.4, on redox reactions. The topic of O-containing functional groups continues in Ch 9, 10, 12.

⇒ **Attached:** three separate pages, each summarizing some aspects of these “oxygen” chapters.

⇒ **Practice quizzes** posted at the web site...

- Alcohols and ethers, which should be considered “basic” (though some of the questions are fairly challenging).
- Oxidation and reduction, listed for Ch 12, will help you with these concepts. It is “general”, and can be done at any time between now and Ch 12.
- A review quiz, which broadly covers all chapters up to this point (i.e., Ch 9); this may be good preparation for Test 2.

**Essays.** None are formally assigned. However, the essay on Toxicity of Alcohols, p 230, is very interesting and has considerable practical implications. Don’t worry about the biochemical mechanisms for now; we will explore them later in the course.

### **Chapter 8 notes**

Sect 1. Be sure to make a clear distinction between the “OH” groups of inorganic hydroxides (i.e., the OH<sup>-</sup> ion), alcohols, phenols and acids (Ch 12).

Sect 2. As you read the nomenclature rules here, note how they are mostly familiar. You need a new suffix, -ol for alcohols, and new priority rules -- but the basic plan is the same as with alkanes and alkenes.

In rule 4 (p 220), but-3-en-1-ol is an alternative name. (IUPAC encourages putting the number closer to what it specifies, but use of this convention is still weak.)

The classification of alcohols as primary etc is based on the C atom to which the -OH is attached. Reminder... See my web page on Primary etc for an overview of all of the meanings of these terms.

Sect 3. When considering the H-bonding properties of a compound, be careful to distinguish whether the molecule can serve as both an H-bond donor and acceptor, or merely an acceptor. Compounds in the latter class (such as ethers, aldehydes and ketones) can H-bond with water and thus (if small) have significant solubility. However, since they cannot H-bond with themselves, they have low BP. This idea will recur during upcoming chapters.

Sect 4. Says that acidity of alcohols is similar to that of water. However, it may not be clear what the acidity of water is. Distinguish  $K_a$  for water and  $K_w$ .  $K_w$  is based on the standard equilibrium constant expression, and the  $[H_2O(l)]$  term is omitted. However, when comparing water as an acid to other acids, omitting that term is “unfair”. So, the  $K_a$  expression includes the  $[H_2O]$  term, just as any  $K_a$  expression includes the unionized acid HA (Sect 2.7).  $K_a$  for water =  $K_w/[H_2O] = (10^{-14} M^2)/(56 M) = 1.8 \times 10^{-16} M$ . This gives  $pK_a = 15.7$ .

Review, as needed:

- Sect 2.3 on acid-base reactions.
- Sect 2.6 on chemical equilibrium, including how to write K expressions.
- Sect 2.7 on acid-base equilibria, including how to write and compare  $K_a$ .

Don't worry about this section beyond the basic point that alcohols are normally considered neutral compounds. However, we will talk about acids and bases in later chapters, so if you are rusty, this might be a good place to get started with refreshing these topics.

Sect 6. You should know the basic reaction, but mechanism is an “advanced” topic.

Sect 8. Much of this section is “advanced”. Top priority is to see some approaches for making alcohols. Some of these are the reverse of reactions of alkenes (Ch 4), and some are the reverse of reactions of aldehydes/ketones (Ch 10).

Ouellette introduces the use of chemicals such as  $NaBH_4$  as reducing agents. One can think of these as “hydrogen carriers”. Instead of using  $H_2$  as the reducing agent, we use  $NaBH_4$ . The biological hydrogen carriers are chemicals such as NADH, introduced at the bottom of p 232. When we discuss metabolism, we will explore the role of NADH and other carriers for various chemical groups. “Carriers” is an important conceptual point in biochem.

In the sub-section on indirect hydration (p 233), the main point is to see the variety of reactions possible. One can “add water to an alkene” following Markovnikov's rule by doing it one way, and can do it anti-Markovnikov by using a different procedure. You need not remember either procedure, but you should be aware that many things are possible beyond the few reactions that we emphasize.

For the more “advanced” student, this section also introduces some complications that organic chemists need to deal with...

- Competing reactions. More than one reaction may occur under a particular set of conditions.
- Reversibility. Your desired reaction, reactant  $\rightarrow$  product, may “prefer” to go the other way; sometimes one can adjust conditions to help deal with this.

- Intra-molecular preferences. A reagent may react with more than one group in your starting material, and it may react with them unequally; this may be “good” or “bad”. It is because of all these complications that organic chemists need to know many ways to make alcohols. It serves our purposes as an introduction to understand that alcohols can be made by hydrating alkenes or reducing carbonyl groups. But trying to actually make a specific alcohol in the real world requires dealing with all the complications; the more detailed variations one knows, the better your chances of finding a way to do your reaction effectively and efficiently.

In biochem, many of these complications are dealt with by the enzymes. That is, the enzymes don't merely accelerate reactions; they control which reactions actually occur. More in the Metabolism chapter.

Sect 9. A key difference between the behavior of alcohols and phenols is the acidity of phenols. But note that simple phenol is a quite weak acid.

Sect 10. We will mention S compounds only briefly, but will return to them when we discuss amino acids and proteins (Ch 15). The thiol  $\rightleftharpoons$  disulfide interconversion (p 240, shown there only as the oxidation) is important in protein structure, because the amino acid cysteine is a thiol (p 438). You should also be generally aware of the odor of S compounds. (Do you want me to bring a demo?)

Reaction summary. Reactions #2-5 are most important; formally, we could think of these as two pairs of reverse reactions. (Can you show that?) For #5, you should know generally that alcohols can be made by hydration of alkenes, but don't worry about the specific tricks.

A couple of important reactions are missing from his summary: acidity of phenols, thiol-disulfide interconversion.

### **Chapter 9 notes**

We will cover only Sect 1-3, and will cover these only briefly. Our main goal is to establish what ethers are, so you are aware of them. We will note their general chemical inertness, which makes them useful solvents.

Ignore the stuff on naming of cyclic ethers, p 250.

A common lab chemical is “petroleum ether” (or “pet ether”). This is not an ether, in the proper sense. It is a fraction of low-boiling alkanes from petroleum, mainly pentanes and hexanes (lighter than gasoline). I suspect it is called “ether” because its boiling point and flammability (hence hazardousness) are similar to those of the common ether, diethyl ether. However, the solvent properties are somewhat different (why?), and the two usually should not be interchanged.

Reaction summary. Skip; we are skipping all sections on reactions of ethers.

### Suggested problems

Ch 8. Models # 1, 2. Main exercises: # 1-16, 27-29, 31-36, 47-52. Again, doing some of the more advanced questions on reactions, open book, is good practice for those who are going on, even if you then don't worry about this material when preparing for our tests.

Ch 9. Models # 2, 4, 5, 7. For the main exercises, only #1-16 are on the assigned sections. #11-14 deal with issues of general importance.

- For #11... Question asks about dioxane. The structure of 1,4-dioxane -- the common dioxane -- is on p 253.
- For #16... See p 252.

### Overview of skipped sections

Ch 7; skipped entirely. Broad issue is classifying organic reactions into types. Two types are substitution and elimination. We discussed electrophilic substitutions in Ch 5. Ch 7 focuses on nucleophilic substitutions; the C of a C-X bond is  $\delta^+$ , thus is susceptible to attack by a nucleophile. Both nucleophilic substitutions and eliminations are further subdivided, based on kinetic and mechanistic criteria, into type 1 and type 2. One of the Computer Resources listed below illustrates these reaction types. Good organic chemistry!

Ch 8 Sect 5. Substitution reactions, where, for example, an -OH is replaced with -Cl. These are nucleophilic substitutions. They fall into two mechanistic subclasses,  $S_N1$  and  $S_N2$ . This all depends on Ch 7, which we skip. But if you read this section, start with the general overall description that the reaction is a substitution.

Ch 9 Sect 4-8. As noted at the top, for Ch 9 we will cover only Sect 1-3. That is, we will introduce ethers and look at their physical properties. However, we will skip Sect 4-8, on chemical properties. As a generality, ethers are fairly inert -- more like alkanes. They are often used as solvents because of their inertness. Epoxides (cyclic ethers with a strained 3-membered ring) are an exception, but we omit them. One class of epoxides was noted in an earlier (non-assigned) essay, p 158. Metabolism of aromatic compounds may proceed through an arene oxide, which is essentially an epoxide. These reactive intermediates may be involved in carcinogenesis. More on this in the (non-assigned) essay on p 260.

### Further reading

More about Old MacDonald's second career? D Ryan, J Chem Educ 74:782, 7/97.

S Niwa et al, A one-step conversion of benzene to phenol with a palladium membrane. Science 295:105, 1/4/02. Phenol is one of the major aromatic compounds of industrial interest, but its synthesis is still a challenge. Here they discuss how phenol is made, and suggest a new synthesis. A key aspect of their procedure is keeping the  $O_2$  and  $H_2$  separate -- on opposite sides of the membrane -- to avoid explosion.

D Chandler, Hydrophobicity: Two faces of water. *Nature* 417:491, 5/30/02. A “Concept” essay. “Oil and water molecules actually attract each other, but not nearly as strongly as water attracts itself.”

M C Stensmyr et al, Pollination: Rotting smell of dead-horse arum florets. *Nature* 420:625, 12/12/02. A story of mimicry. The flowers smell like dead horses in order to attract the flies that pollinate them. The odor is due to S-compounds, such as dimethylsulfide,  $\text{CH}_3\text{SCH}_3$ . Also see Todd et al (2007).

K Kamata et al, Efficient epoxidation of olefins with  $\geq 99\%$  selectivity and use of hydrogen peroxide. *Science* 300:964, 5/9/03. An example of an attempt to develop a “green” (environmentally friendly) industrial process. The reaction type here is one that we skip (formation of epoxides, Sect 9.7); nevertheless, browsing this article can give you an idea of how attempts are being made to take into account broader environmental concerns.

J Koller et al, Ancient materials: Analysis of a pharaonic embalming tar. *Nature* 425:784, 10/23/03. There has been debate about whether the oils used were from juniper trees or from cedar trees. Here they do chemical analysis of some 3500 year old embalming material. It contains a variety of terpenoids (Ch 4) and phenolics. Overall, the composition is more consistent with the use of cedar oil.

J E Sadler, Medicine: K is for koagulation. *Nature* 427:493, 2/5/04. News. Vitamin K is involved in blood clotting. It helps to modify blood clotting proteins, and is itself reversibly modified during this process. The modified form of vitamin K is an epoxide, hence the inclusion of this item here for Ch 9. The common anti-clotting drug (and rat poison) warfarin (coumadin) works by inhibiting the regeneration of the active vitamin K from the epoxide -- a reduction process. In the work discussed here, they identify the gene for this vitamin K epoxide reductase, based in part on work with humans (and rats) that are resistant to warfarin.

C Manach et al, Polyphenols: food sources and bioavailability. *Am J Clin Nutr* 79:727-47, 5/04. Polyphenols may be useful as anti-oxidants. This review article surveys the types of polyphenols found in foods, discusses their amounts and various pharmacological issues that would affect their active concentration in the body. However, don't expect much in the way of conclusions about the actual usefulness of these compounds; it is a murky field! The article seems well written, but it is quite long. I suggest you start with the Abstract and the Conclusions, then browse the rest. Those interested in nutritional issues and in metabolism of drugs and toxins may also find this article of interest. There is more about polyphenols, including the red wine constituent resveratrol, on the web page of Further reading: Medical topics.

R E Casey & F A Pittman, Intermolecular forces as a key to understanding the environmental fate of organic xenobiotics. *J Chem Educ* 82:260, 2/05. This article discusses how molecules of different polarities, hence different solubilities in water, have different fates in the environment. The discussion is targeted to an introductory course in environmental science, and should be appropriate for students at our level.

I Paterson & E A Anderson, Chemistry: The renaissance of natural products as drug candidates. *Science* 310:451, 10/21/05. General. Discusses the interconnected roles of discovery of natural products and organic synthesis in drug development.

- 1) S Gramser, The party gene.
- 2) R Dalton, Saving the agave.
- 3) A Witze, The grapes of rock.

*Nature* 438:1068, 1070 & 1073, 12/22/05. A series of articles in a feature section "Alcohol and science". #1 is about alcohol dehydrogenase (ADH), the enzyme that both makes and breaks down alcohol. #2 is about the plant that is behind the traditional process for making tequila. #3 is about "terroir", the physical factors, such as soil and climate, that affect wine making.

- 1) A J Ragauskas et al, The path forward for biofuels and biomaterials. Review.
- 2) A E Farrell et al, Ethanol can contribute to energy and environmental goals. *Science* 311:484 & 506, 1/27/06.

Two major articles on biofuels, including ethanol. The 2nd paper is from UC Berkeley; a link to their web site is on my page of Internet resources, under Energy resources. There is an extensive exchange of correspondence on the broad topic of these articles, the economic viability of biofuels: *Science* 312:1743ff, 6/23/06. Taken together, these articles can serve to at least introduce the controversy about the economics of biofuels.

P J Hines, The invisible bouquet. *Science* 311:803, 2/10/06. Introduction to a feature section "Plant volatiles: from chemistry to communication." The first two articles are news stories on wine quality and on scents of flowers and fungi.

G Sunilkumar et al, Engineering cottonseed for use in human nutrition by tissue-specific reduction of toxic gossypol. *PNAS* 103:18054-9, 11/29/06. Gossypol is a toxic polyphenol terpenoid found in cotton plants. The high levels of this toxic compound in the seed limit the use of this abundant resource for human food. Previously, scientists were able to develop mutant cotton plants that lack gossypol; the problem was that they were highly susceptible to insects, thus showing the natural protective role of this chemical. Here, scientists report developing a cotton that lacks gossypol only in the seeds, but has normal levels elsewhere. The basic strategy for doing this makes use of two kinds of knowledge. First, they develop an RNAi (interfering RNA) that is specific for a key gene needed for making gossypol. Second, they target this RNAi to the seed, by using a seed-specific promoter. The results are encouraging, suggesting that the plant makes enough gossypol to protect itself, yet produces seeds that contain minimal levels of the toxic compound. For more, see my web page for BITN: Agricultural biotechnology (GM foods) and Gene therapy.

D B Rusterholz, Capsaicin, from hot to not; can new pain-relieving drugs be derived from this substance known to cause pain? *J Chem Educ* 83:1809, 12/06. Capsaicin is the "hot" of chili peppers. It is a specific chemical, now known to interact with specific receptors that are connected to your brain as "pain" receptors. It is possible that analogs of capsaicin might interact with the receptor without transmitting a pain signal - and some might be useful as anti-pain drugs. This article is a readable introduction to how capsaicin works and to this possible development of drugs based on it.

M J Caterina, Chemical biology: Sticky spices. Nature 445:491, 2/1/07. News. “The spiciness of foods such as horseradish is perceived through sensory neurons of the pain pathway. The lingering pungency of some such foods results from chemical modification of the channels that trigger these neurons.”

J D Todd et al, Structural and regulatory genes required to make the gas dimethyl sulfide in bacteria. Science 315:666, 2/2/07. DMS (dimethyl sulfide,  $\text{CH}_3\text{SCH}_3$ ) is an important atmospheric component, with implications for climate. It is made by a consortium of marine organisms. Here they identify part of the process carried out by bacteria. Also see Stensmyr et al (2002).

P Szuromi et al, Energy for the long haul. Science 315:781, 2/9/07. Introduction to special issue: Sustainability and Energy.

D Chandler, Physical chemistry: Oil on troubled waters. Nature 445:831, 2/22/07. News. “The nature of the boundary between water and oil is crucial to many nanometre-scale assembly processes, including protein folding. But until now, what the interface really looks like remained in dispute.”

S Mukherjee et al, Freshly crushed garlic is a superior cardioprotective agent than processed garlic. J Agric Food Chem 57:7137-7144, 8/12/09. Garlic and onion are famous for their sulfur compounds. The work here shows that fresh garlic may be better for you. They suggest that this is due to how the sulfur compounds are metabolized. Specifically, they suggest that fresh garlic can release  $\text{H}_2\text{S}$ , which may be cardioprotective. (An article on the S compounds of onion is listed on the web page of Old articles.)

**Computer resources** (See web page for details and links.)

Animations of elimination and substitution reactions. These reaction types are presented in some detail in Ch 7, which we skip. They come up in Ch 8, even though we do not go into their mechanisms.

From the Dept of Textiles and Apparel at Cornell, a practical guide to removing stains. Chemistry underlies much of this... what is soluble in what, largely determined by polarity.

MTBE, the ether used as a gasoline additive.

Thimerosal, a mercury-containing thiol that is used as a preservative in some vaccines.

Also see the web page section on Energy resources.

Reminder... See my web page on Primary etc for an overview of all of the meanings of these terms.

*Attached: three separate pages, each summarizing some aspects of the “oxygen” chapters.*

- *Oxygen functional groups*

- *Reactions*
- *Comparison of physical properties, vs functional group.*

*These pages summarize issues from Ch 8-12. Each of these is available at the website on the Handouts page for Org/Biochem, along with this Ch 8-9 handout.*