Anchoring Concepts: Linking chemistry concepts to toxicology topics within introductory chemistry courses

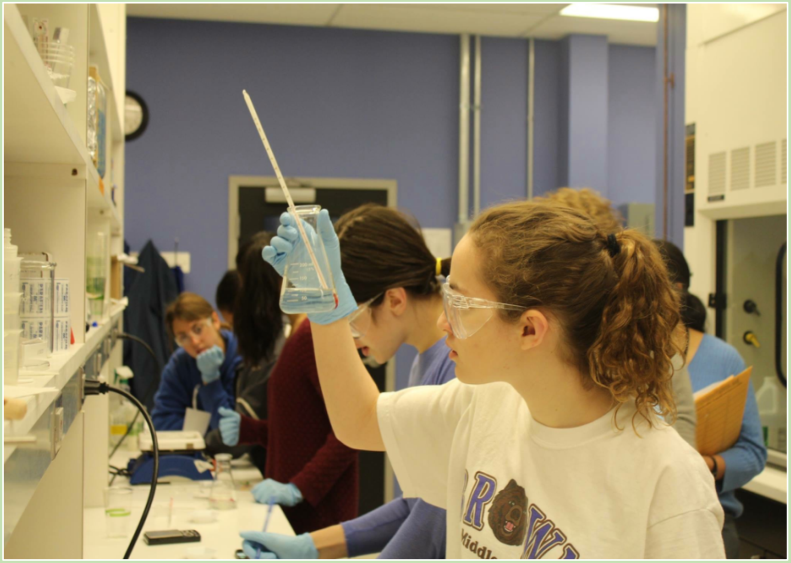
Amy S. Cannon, Ph.D.
Executive Director
Beyond Benign

2017 Green Chemistry & Engineering Conference
Toxicology for Chemists Workshop

Beyond Benign: Mission and Vision

Beyond Benign's **mission** is to equip educators, scientists, and citizens with the tools to teach and practice green chemistry to achieve a sustainable society.

We **envision** a world where scientists and citizens enter the workforce with the skills to design and choose greener, sustainable technologies that spur the innovation economy.



beyondbenign
green chemistry education

Beyond Benign: K–20 Programs

Professional Development for educators on green chemistry, toxicology and sustainable science

Green Chemistry Curriculum that replaces traditional hazardous chemicals in the lab and are based on real-world green technological innovations

Community Engagement through green chemistry and sustainable science hands-on activities

Lead Teacher Program that provides K-12 science educators with an opportunity to become green chemistry teacher leaders

A **College Student Fellows** Program to foster green chemistry and leadership skills for college students

The **Green Chemistry Commitment** for higher education institutions to integrate green chemistry across the sub-disciplines of chemistry

Toxicology for Chemists Curriculum that provides the next generation of scientists with the skills to create products that are safe for humans and the environment.

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green chemistry education

Green Chemistry Commitment

Green Chemistry Student Learning Objectives

Signing institutions agree that upon graduation, all chemistry majors should have proficiency in the following essential **green chemistry competencies**:

- **Theory:** Have a working knowledge of the twelve principles of Green Chemistry
- **Toxicology**: Have an understanding of the principles of toxicology, the molecular mechanisms of how chemicals affect human health and the environment, and the resources to identify and assess molecular hazards
- **Laboratory Skills**: Possess the ability to assess chemical products and processes and design greener alternatives when appropriate
- **Application**: Be prepared to serve society in their professional capacity as scientists and professionals through the articulation, evaluation and employment of methods and chemicals that are benign for human health and the environment

www.greenchemistrycommitment.org

The Twelve Principles of Green Chemistry

1. Prevention. It is better to prevent waste than to treat or clean up waste after it is formed.

2. Atom Economy. Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. Less Hazardous Chemical Synthesis. Whenever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

?

4. Designing Safer Chemicals. Chemical products should be designed to preserve efficacy of the function while reducing toxicity.

5. Safer Solvents and Auxiliaries. The use of auxiliary substances (solvents, separation agents, etc.) should be made unnecessary whenever possible and, when used, innocuous.

6. Design for Energy Efficiency. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

7. Use of Renewable Feedstocks. A raw material or feedstock should be renewable rather than depleting whenever technically and economically practical.

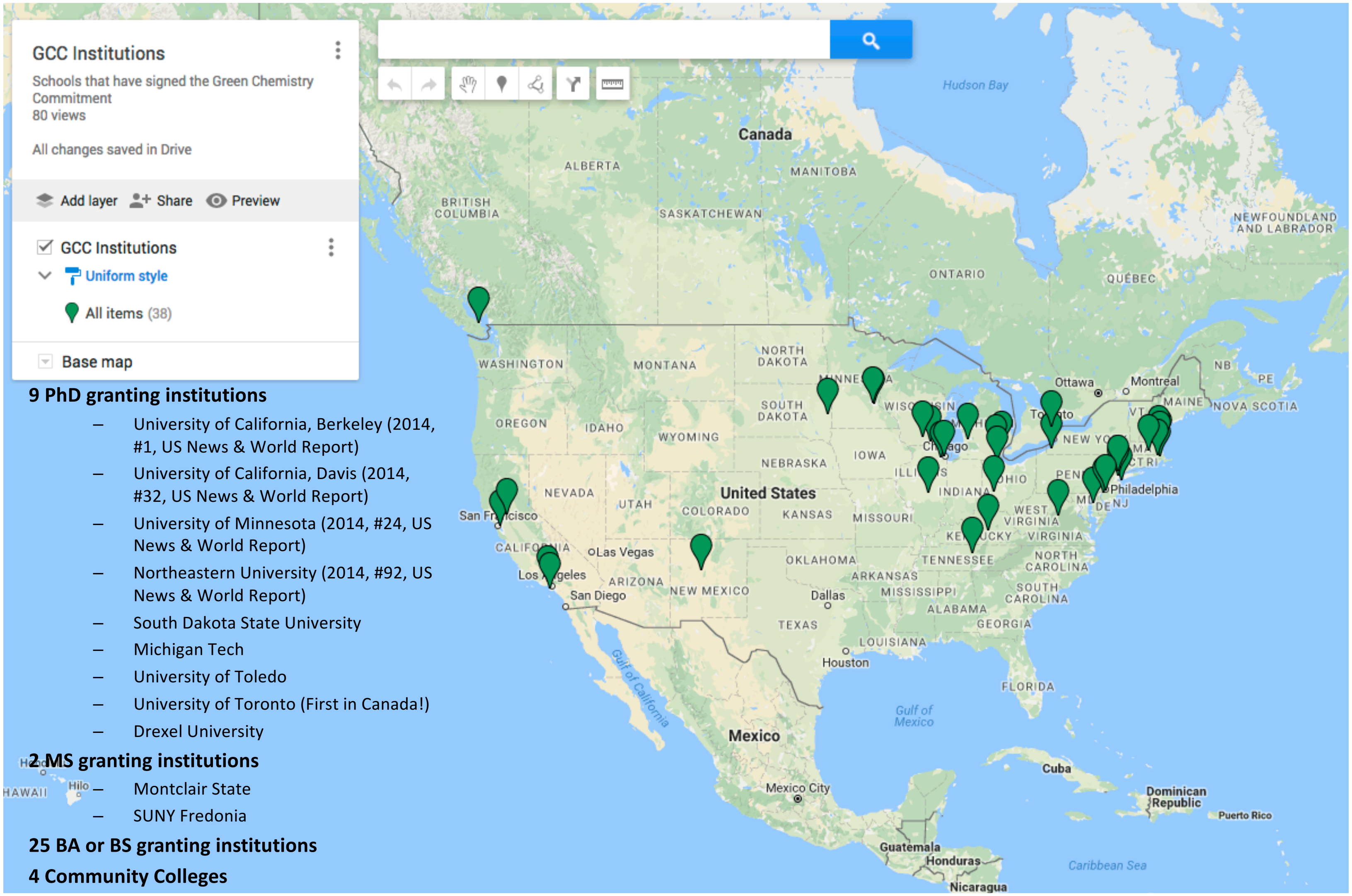
8. Reduce Derivatives. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible .

9. Catalysis. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Design for Degradation. Chemical products should be designed so that at the end of their function they do not persist in the environment and instead break down into innocuous degradation products.

11. Real-time Analysis for Pollution Prevention. Analytical methodologies need to be further developed to allow for real-time in-process monitoring and control prior to the formation of hazardous substances.

12. Inherently Safer Chemistry for Accident Prevention. Substance and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.



9 PhD granting institutions

- University of California, Berkeley (2014, #1, US News & World Report)
- University of California, Davis (2014, #32, US News & World Report)
- University of Minnesota (2014, #24, US News & World Report)
- Northeastern University (2014, #92, US News & World Report)
- South Dakota State University
- Michigan Tech
- University of Toledo
- University of Toronto (First in Canada!)
- Drexel University

2 MS granting institutions

- Montclair State
- SUNY Fredonia

25 BA or BS granting institutions

4 Community Colleges

4 Methods of Implementing Toxicology

- **Independent Course**
- **Student-Led Course**
- **Seminar Series**
- **Integrating into Existing Chemistry Course**

Toxicology Working Group

- Addressing the knowledge gap of toxicology and understanding molecular hazards in the chemistry curriculum
- Comprised of Green Chemistry Commitment signers & outside stakeholders
- Collaborate with industry experts
- Organize Symposia and Workshops
  - Green Chemistry & Engineering Conference, June 13-15, 2017
  - Society of Toxicology Conference, 2018
  - BCCE, 2018

The Green Chemistry Commitment
TRANSFORMING CHEMISTRY EDUCATION

Toxicology Working Group

Undergraduate → **Graduate**

- **General Chemistry**
- **Organic Chemistry**
- **Biochemistry**
- **Physical Chemistry**
- **Inorganic Chemistry**
- **Analytical Chemistry**
- **Research**

Example Learning Objectives/Questions

What is hazard? What is toxicology?
Understanding how structure impacts toxicity
Toxicokinetics and Toxicodynamics (ADME)
How does thermodynamics impact toxicity?
Inorganic chemicals and redox reactions in the body
Using tools to identify biomarkers for toxicity
How can I predict the toxicity of my product?
How can I minimize the toxicity of my chemical process on human health and the environment?

Awareness → **Predictions**

Today's discussion

1. Review Anchoring Concept Map: Organic Chemistry
2. Introduce case studies
   - **Relationship Between pKa and Skin Irritation**
   - **Design for Biodegradability**
     - Electrophilic Aromatic Substitution
     - Alkanes: nomenclature and isomers
   - **Bond strength and persistence**
   - **Chirality**
   - **Electrophilic-Nucleophilic Reactions**

American Chemical Society Anchoring Concept Maps

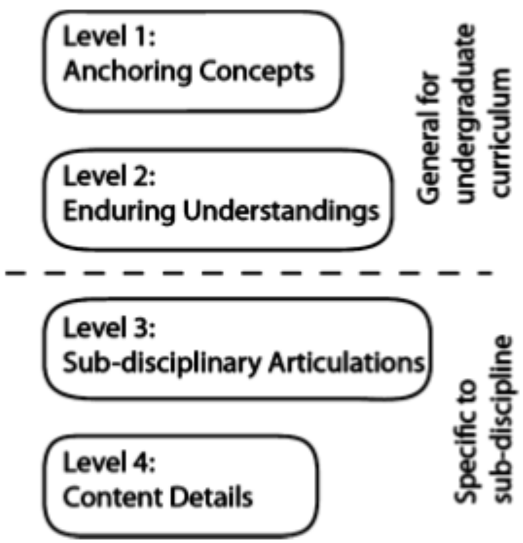


Figure 1. Levels of the ACCM depicting the consistency of the top two levels and the specialization of levels 3 and 4.

I. Atoms: Matter consists of atoms that have internal structures that dictate their chemical and physical behavior.
   A. Atoms have unique chemical identities based on the number of protons in the nucleus
      1. The atomic number and mass number are used to determine average atomic weight and identify isotopes, which play a part in understanding techniques such as MS, or NMR, or IR and rates of reactions via kinetic isotope effects.
         a. Stabilization of anions helps to explain pKa values and relative acidities of protons.

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Relationship Between pKa and Skin Irritation

pKa values can assist in predicting compound toxicokinetic behavior for:

- Skin Irritation
- Gastrointestinal absorption
- Membrane permeability
- Protein binding
- Metabolic transformations

pKa as an indicator of skin irritation:
pKa > 8 and pKa $\leq$ 4

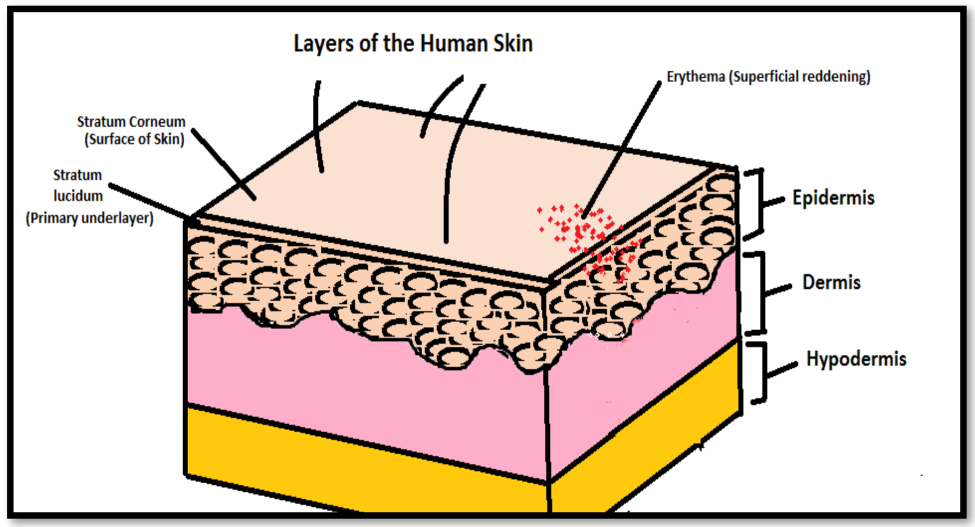
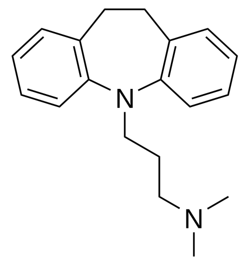
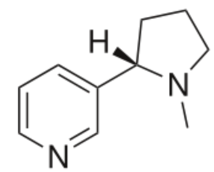


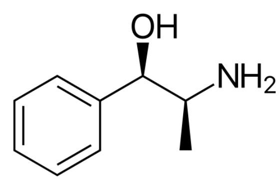
Figure 1: Layers of the human skin with Erythema skin irritation location.

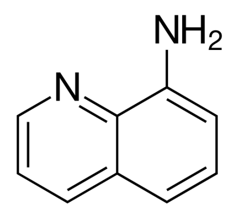
Relationship Between pKa and Skin Irritation

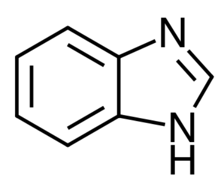
1. Research the following structures:
    - Imipramine
    - Nicotine
    - Norephedrine
    - 8-Aminoquinoline
    - Benzimidazole
2. Identify their pKa value (literature)
3. Identify the most acidic H
4. Predict whether or not they will be skin irritants
5. Look at the SDS to see if there is any reported evidence of skin irritation











Relationship Between pKa and Skin Irritation

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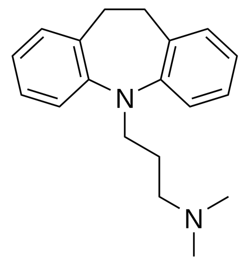

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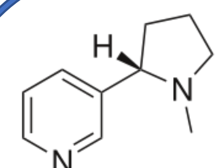
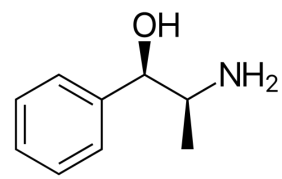
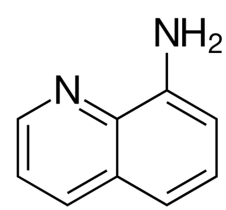


7.84

9.0





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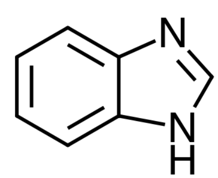

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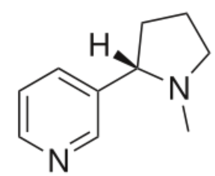
Relationship Between pKa and Skin Irritation

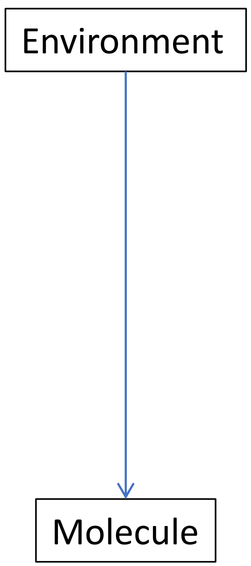
Context: Nicotine patch; dermal drug delivery



Nicotine case study:

- LD50 (70 mg/kg (rat, oral))
- Nicotine toxicity
- Understanding dose and exposure mechanisms
- Toxicokinetics and Toxicodynamics

Design for Biodegradability

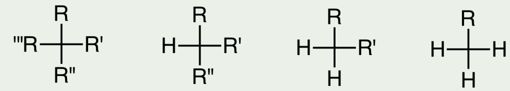
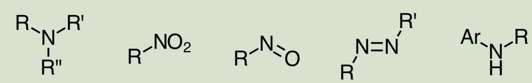
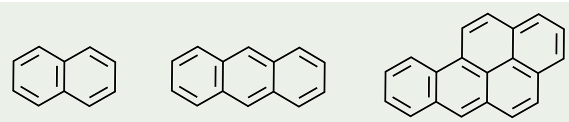
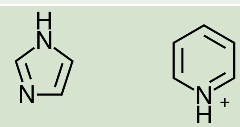
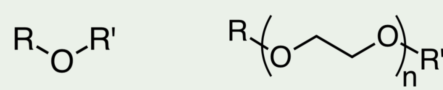


- Appropriate microorganisms do not exist or are not present in the environment
- There are inadequate nutrients for the microbial population
- The temperature, pH or pO_2 is too low or too high; ionic conditions are unsuitable
- Concentration of substrate is too high (toxic) or too low
- The substrate is adsorbed or covalently attached to clays, humus, etc., or is physically inaccessible
- The substrate is not accessible to attack because it is too large and/or insoluble
- The substrate:
  - Is not transported into the cell
  - Is not a substrate for the available enzymes
  - Is not an inducer for appropriate enzymes or transport systems
  - Does not give rise to products that can integrate into normal metabolism
  - Is converted into products that are toxic or interfere with normal metabolism

Chem. Reviews, 2007, Vol. 107, No. 6, 2207-2227

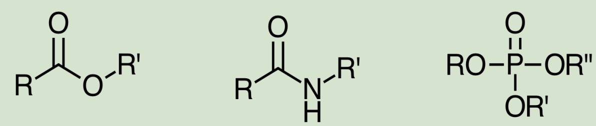
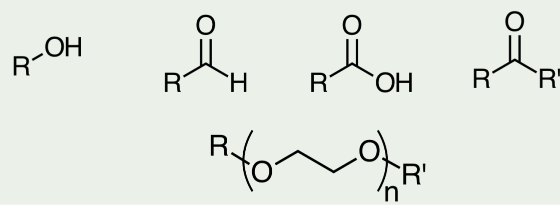
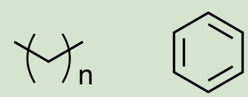
Design for Biodegradability

Features that increase resistance to aerobic biodegradation:

Feature	Structure
Halogens: Especially chlorine and fluorine and if more than 3 in a molecule	R−X
Chain branching if extensive: Quaternary C's are problematic	
Tertiary amine, nitro, nitroso, azo, and arylamino groups	
Polycyclic aromatic residues	
Heterocyclic residues	
Aliphatic ether bonds (except in ethoxylates)	

Design for Biodegradability

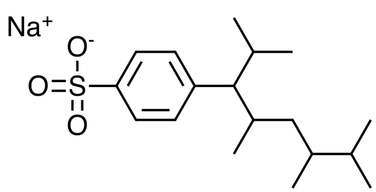
Molecular features that generally increase aerobic biodegradability:

Feature	Structure
Groups susceptible to enzymatic hydrolysis (esters, including phosphate esters) and amides	
Oxygen atoms in the form of hydroxyl, aldehyde, or carboxylic acid groups, ketones (not ether, with the exception of ethoxylate groups)	
Unsubstituted linear alkyl chains (especially ≥ 4 carbons) and phenyl rings	

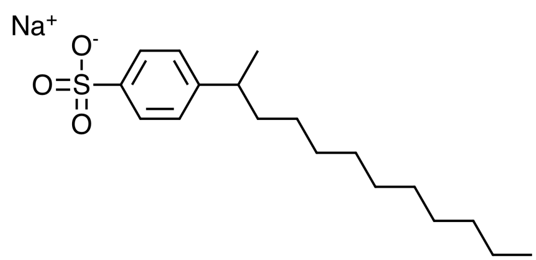
Design for Biodegradability

Alkylbenzene Sulfonates:

- Became the standard for household laundry products in the 1940's
- Tetrapropylene alkylbenzene sulfonate (TPBS) was derived from a petroleum fraction and easy & economical to make
- TPBS degraded only ~50% in sewage plants, resulting in excessive foaming (also in rivers)
- Conc. of TPBS in river waters was high (2 mg/L) and water would foam when coming out of the tap
- Linear alkylbenzene sulfonate (LAS) replaced TPBS by the early 1960's
- LAS is almost completely biodegradable in sewage treatment (more than 98%)
- Public pressure/policy: TPBS was cheaper to make, but public pressure changed the economics



TPBS



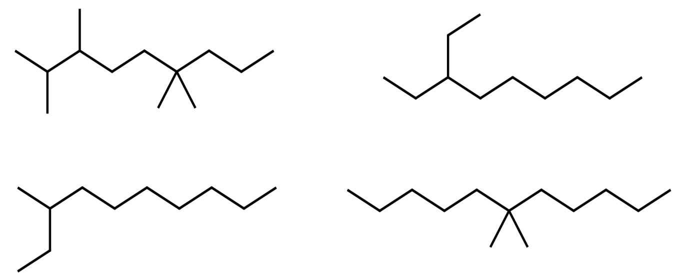
LAS

Cheer: https://www.youtube.com/watch?v=lMxlAIeI8QI
Dash: https://www.youtube.com/watch?v=F1YTHr4mTQA

Design for Biodegradability

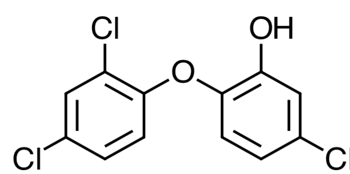
Organic Chemistry Concepts:

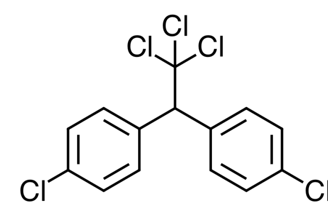
- Naming of alkyl chains
- Understanding and identifying isomers
- Condensed and bond-line formula
- Identifying functional groups



Toxicology Concepts:

- Persistence/Biodegradability
- Half-life





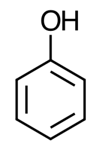
Design for Biodegradability

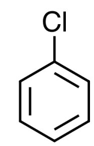
Organic Chemistry Concepts:

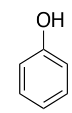
- Electrophilic aromatic substitution (electrophilic addition where oxygen is added to a phenyl ring)
- Substituent effects

Toxicology Concepts:

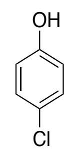
- Persistence/Biodegradability
- Half-life



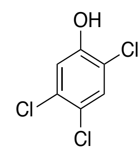




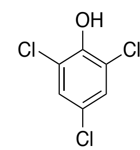
phenol



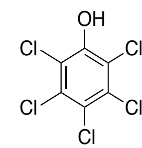
synthetic intermediate in the preparation of dyes and drugs



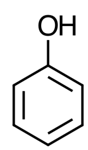
"Dowicide 2" pesticide

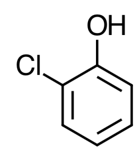


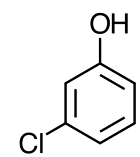
"Dowicide 2S" fungicide antiseptic

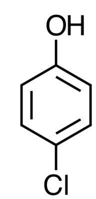


pesticide disinfectant





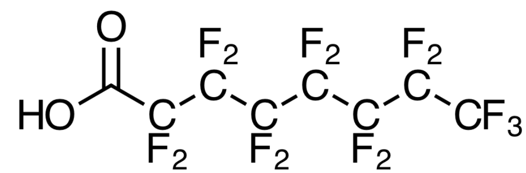




Bond Strength

Organic Chemistry Concepts:

- Bond strength
- Bond length



Toxicology Concepts:

- Persistence
- Structure and function

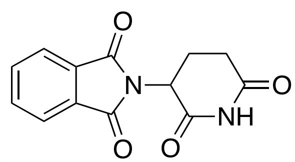
	Carbon-Fluorine	Carbon-Chlorine	Carbon-Bromine	Carbon-Iodine
Structure				
C-X Bond Length				
C-X Bond Strength (kJ mol-1)				

Study: some highly fluorinated chemicals are harder to filter from water, http://michiganradio.org/post/study-some-highly-fluorinated-chemicals-are-harder-filter-water

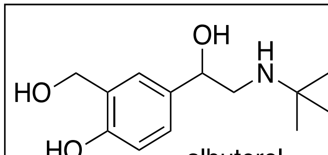
Chirality

Organic Chemistry Concepts:

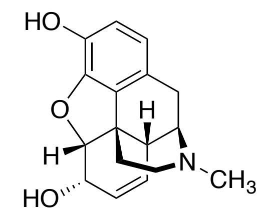
- Chirality
  - Identify chiral center
  - How many stereoisomers?



thalidomide



albuterol



morphine

Toxicology Concepts:

- Structure and function

Toxicity: a dash or a wedge? Read section 4.2.1.1,page 5851 about the toxicokinetics and toxicodynamics of Thalidomide R and S enantiomers. List the differences between the two enantiomers in their toxicity and efficacy.

Voutchkova, Adelina M.; Osimitz, Thomas G.; Anastas, Paul T. "Toward a Comprehensive Molecular Design Framework for Reduced Hazard" *Chem. Rev.* **2010**, *110*, 5845-5882.

Chirality

Questions:

1) Other opiate derivatives that are close structural relatives to morphine are listed below. Use your favorite search engine to find the structures of each of these compounds and draw them in the corresponding boxes. Label each stereocenter with the correct *R* or *S* designation.

2) Interestingly, diamorphine can be prescribed in the UK to alleviate pain. When injected into a vein, diamorphine is 2-3 times as potent as morphine, meaning smaller amounts are required to generate the desired effect in patients. Based on their structures, which compound is more water soluble?

diamorphine (a.k.a. heroin)

etorphine

pethidine (a.k.a. demerol)

Electrophilic-Nucleophilic Reactions

Organic Chemistry Concepts:

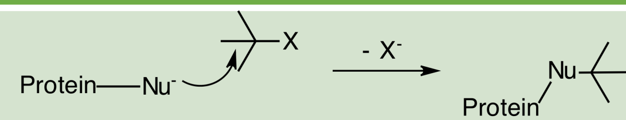
- Electrophiles and Nucleophiles
- Reactions (S_N1, S_N2, Acylation, Michael Addition, Schiff Base Formation, S_NAr)

Toxicology Concepts:

- DNA and protein binding
- Toxicological reaction mechanisms

Measurement and Estimation of Electrophilic Reactivity for Predictive Toxicity, Cronin, M.T.D., et. al., Chem. Reviews, 2011, 111, 2562-2596.

Electrophilic-Nucleophilic Reactions

<table>
<tr><th>Mechanism</th><th>Protein Binding Reaction</th></tr>
<tr><td>S_N2</td><td>
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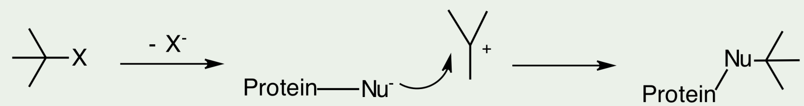
<tr><td>S_N1</td><td>
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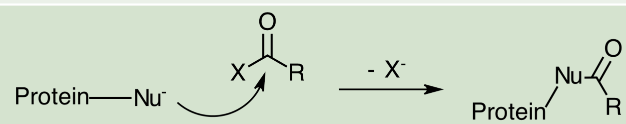
<tr><td>Acylation</td><td>
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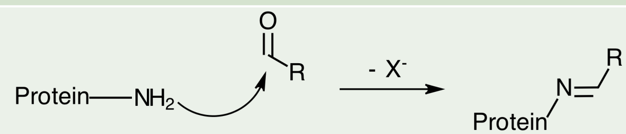
<tr><td>Schiff Base Formation</td><td>
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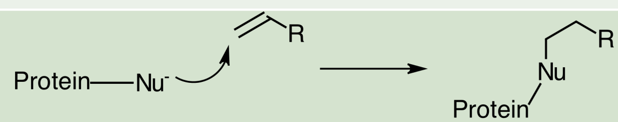
<tr><td>Michael Addition</td><td>
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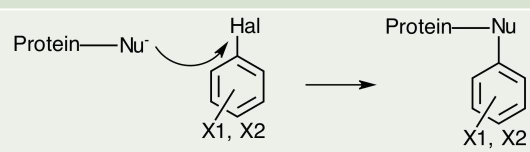
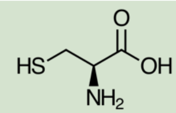
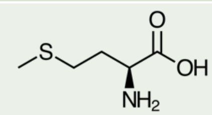
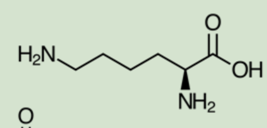
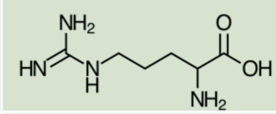
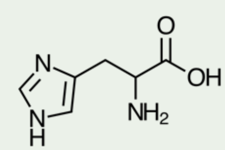
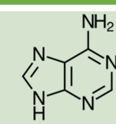
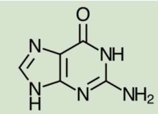
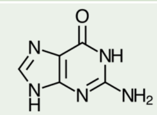
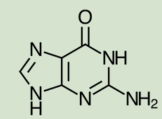
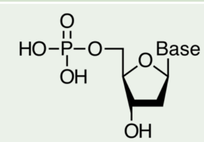
<tr><td>S_NAr</td><td>

X = electron withdrawing groups (NO2, CN, etc.)</td></tr>
</table>

Electrophilic-Nucleophilic Reactions

Hardness (1-4 least to most)	Amino acid sites	Structure
1	Thiol-group of cysteine	
2	S-atoms of methionine	
3	Primary amino-groups (e.g., lysine, arginine)	
4	Secondary amino-group of histidine	

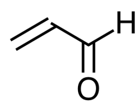
Electrophilic-Nucleophilic Reactions

Hardness (1-4 least to most)	Nucleic acid sites	Structure
1	Primary amine groups of purine bases (e.g., arginine, guanine)	 
2	In-ring N-atoms of purine and pyrimidine bases (e.g., N7 of guanine)	
3	O-atoms of purine and pyrimidine bases (e.g., O6 of guanine)	
4	Phosphate O-atom (P=O)	

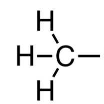
Electrophilic-Nucleophilic Reactions

Discussion Questions:

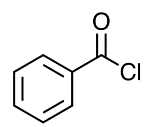
- Given the following xenobiotic molecules, propose which of the 6 reaction mechanisms each electrophile will undergo with a corresponding biological nucleophile
- Propose a mechanism with a biological nucleophile



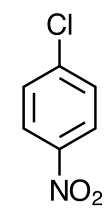
Acrolein



Methyl iodide



Benzoyl chloride



4-nitrochlorobenzene

Electrophilic-Nucleophilic Reactions

Toxicity	Reaction site	Main reaction mechanism
Skin sensitization	Chemically modified skin proteins (e.g., Cys, Lys, or Ser residues) leading to T-cell mediated allergic response	Protein haptenation via S_N2, S_NAr, MA, SB, Ac
Respiratory sensitization	Chemically modified proteins in the lung (e.g., Lys residues)	SB, protein cross-linking, S_N1, S_N2, Ac
Skin irritation	Skin proteins and lipids in the stratum corneum	SB, S_N2, MA, Ac, A_N
Elevated acute toxicity and cytotoxicity (aquatic or terrestrial)	Cellular GSH; interaction with nucleophiles (-OH, $-NH_2$, -SH groups) in biological macromolecules (e.g., inhibition of acetylcholine esterase)	Electrophilic reactivity via S_N1, S_N2, acylation, MA, SB (in contrast to polar and unpolar narcosis)
Mutagenicity and carcinogenicity	DNA or RNA gene mutation via adduct formation, base pair substitutions, and frameshifts; interaction with regulatory molecules	S_N1, S_N2, acylation, MA, SB
Chromosomal aberration	Alteration of DNA and sequence of genetic material (number of structure of chromosomes), which often alters embryonic development; inhibition of topoisomerases and interaction with nuclear proteins associated with DNA (e.g., histone proteins)	DNA and protein binding mechanisms
Hepatotoxicity	Attack of hepatocytes, the bile duct, or sinusoidal endothelium, Kupffer, or Ito cells by: 1) direct cell stress, direct mitochondrial impairment, and specific immune reactions; 2) direct and death receptor-mediated pathways leading to mitochondrial permeability transition; 3) apoptosis and necrosis	Protein binding and receptor-mediated mechanisms (e.g., interaction with P-450 enzyme family, leading to damaged mitochondrial functions and possible idiosyncratic effects)

Next Steps

- Provide feedback
  - How do you see using these materials?
  - What format is best for your use?
- Adopt in your course (and tell us about it!)
- Join our Working Group
- Sign up for notifications on new drafts

Amy_Cannon@beyondbenign.org