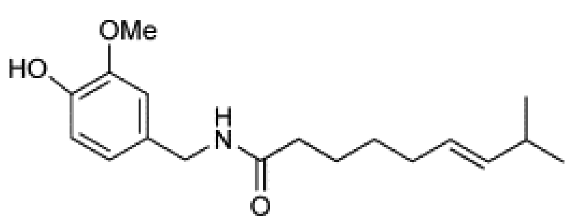
PBL Unit 1 - Shape of Things

Answers due by Exam 1 – Big Idea 1+2

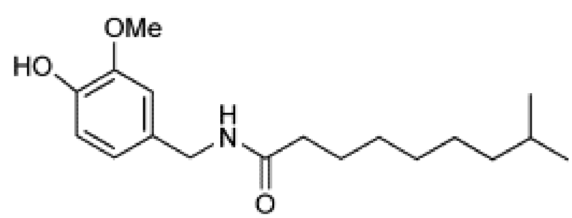
Capsaicin, the compound responsible for the heat in spicy foods, plays a fascinating role in how we experience flavor and sensation. When we consume spicy foods, capsaicin interacts with receptors in our mouths, specifically the TRPV1 receptors, which are also responsible for detecting temperature and physical abrasion. This interaction creates a burning sensation that can range from mildly irritating to intensely painful. Despite this discomfort, capsaicin can stimulate the release of endorphins, our body's natural painkillers, and can even contribute to various health benefits, such as boosting metabolism and reducing inflammation. The effects of capsaicin not only highlight the complex ways our bodies perceive and react to different stimuli but also underscore the intriguing relationship between flavor and pain.

Capsaicin is a complex molecule, with its chemical structure shown below. Its systematic name is 8-methyl-N-vanillyl-6-nonenamide, with many different parts of its structure creating the observations on reactivity. Capsaicin belongs to the capsaicinoid family – what we can call derivatives of capsaicin. A derivative has a similar structure and can exhibit similar functions with varying amounts of reactivity. Various derivatives of capsaicin, such as dihydrocapsaicin, capsiate, and capsaicinol, are shown below as well. These derivatives maintain the core functionality of capsaicin, though their varying side chains can influence their potency and interactions with receptors. Understanding the structural nuances of capsaicin and its derivatives helps elucidate how these compounds modulate sensory experiences and contribute to their diverse applications in both culinary and medicinal fields.

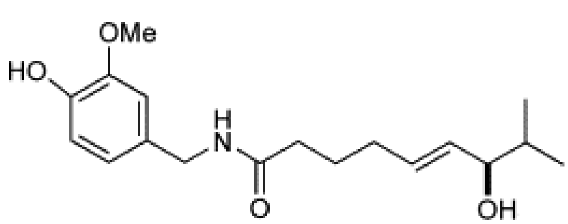
Capsaicinoids



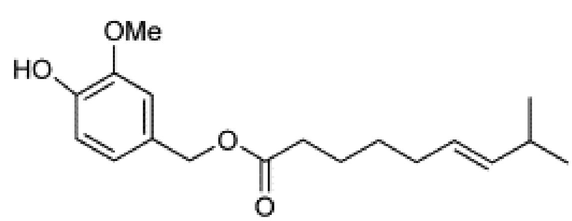
Capsaicin



Dihydrocapsaicin



Capsaicinol



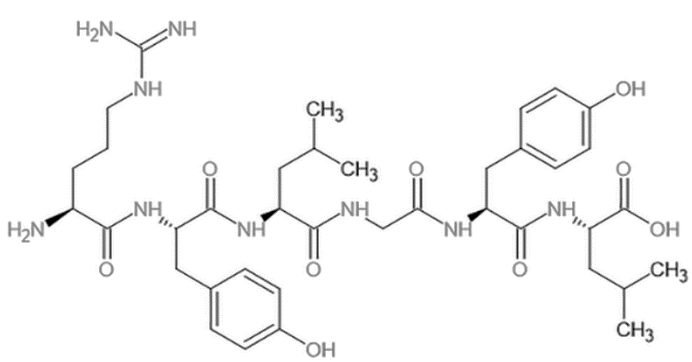
Capsiate

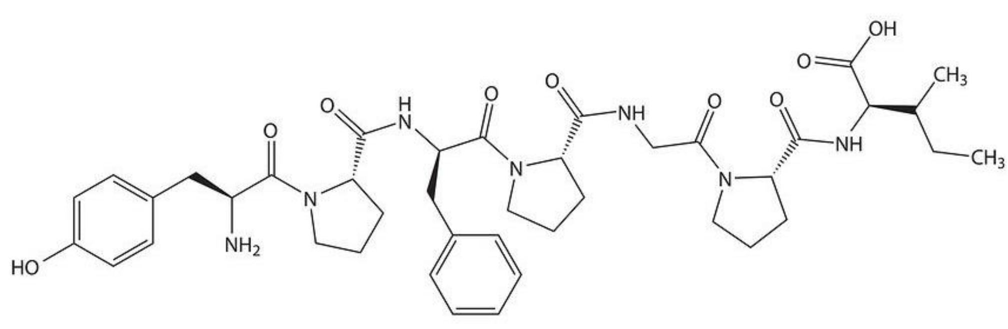
Milk is often used to counteract the spiciness of food due to its ability to neutralize capsaicin. Milk contains fat, particularly in the form of milk fat globules. Additionally, the protein casein has been shown to further aid in the neutralization of capsaicin. Dairy products such as milk, yogurt, and cheese are commonly recommended to alleviate the discomfort from overly spicy foods. The combination of fat and protein in milk provides an effective method for reducing the pungency and intensity of spiciness, offering relief and balancing the flavors of a dish.

Milk is a complex fluid composed of several key components, each with a distinct structure that contributes to its nutritional and functional properties. The primary components include water, proteins, fats, carbohydrates, vitamins, and minerals all shown below. Water constitutes the largest portion, making up about 87% of milk, and serves as a solvent for other components. Proteins, primarily casein and whey proteins, are vital for various bodily functions; casein forms micelles with a globular structure that stabilizes the milk, while whey proteins, such as lactalbumin and lactoglobulin, remain soluble in the liquid. Milk fat consists of triglycerides, which are esters of glycerol and three fatty acids, organized into globules suspended in the milk. Carbohydrates in milk are predominantly lactose, a disaccharide composed of glucose and galactose units linked by a β-1,4-glycosidic bond. Additionally, milk contains various vitamins such as A, D, and B12, and minerals like calcium and phosphorus, each existing in their specific ionic or molecular forms, contributing to the milk's overall health benefits and its role in human nutrition.

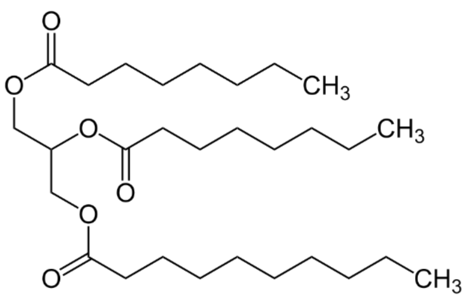
Common dairy components

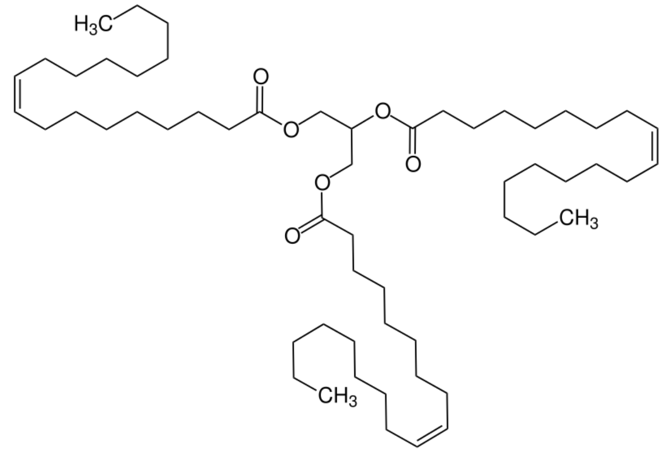
Proteins (mainly casein – these are chain segments as proteins are typically very long)



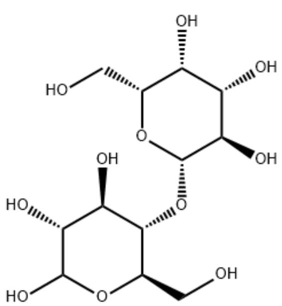


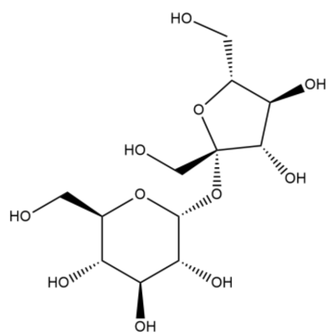
Fats (triglycerides)



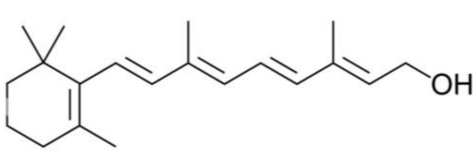


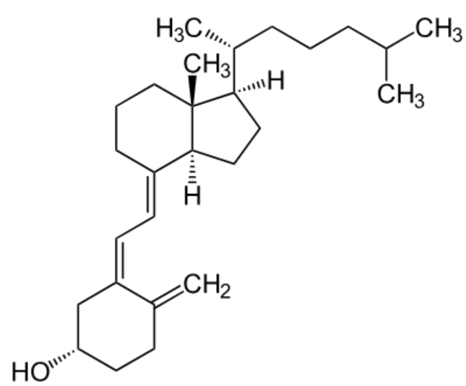
Carbohydrates (such as Lactose or sucrose)





Vitamins (A and D)





Questions:

1. What do you notice about the molecules in each component? List out some of the common structures within each component (E.g. What structural or atomic similarities do the capsaicinoids have? Make sure you list at least two similarities for each component)
2. For each similarity that you just listed, find the central atom or atoms and label each for hybridization, 3D shape, and electronegativity.
3. Are there some molecules below that are more polar than others? Which polar bonds do you see and what structures do they belong to? Highlight or list the polar bonds for each class of compounds including the dipole arrow (or delta charges) labels we did in class.

Water is done for you as an example below.

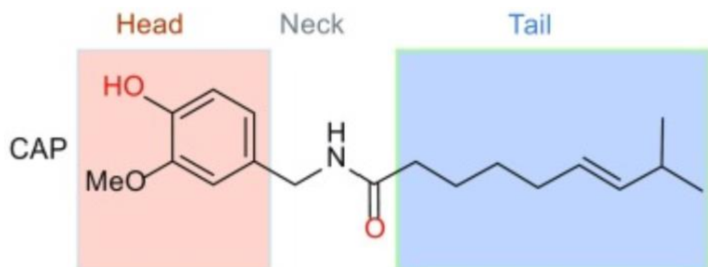
Component	**Similarities**	**Central Atom – Hybridization**	**Central Atom – 3D Shape**	**Central Atom - EN**	**Polarity**
Capsaicinoids					
Proteins					
Fats					
Carbohydrates					
Vitamins					
Water (H_2O)	OH groups	Oxygen would be sp^3 hybridized (two lone pairs and two covalent bonds)	Bent or Tetrahedral	Oxygen is more EN (3.5) than Hydrogen (2.1)	Yes, polar!

PBL Unit 2 - Shape of Things

Answers due by Exam 2 – Big Idea 3

Last unit, we discussed structure, hybridization, and polarity of many natural components in spicy food and dairy products. This time, we will start to identify some reactivity between these components and their more detailed shapes.

Many people over the world enjoy spiciness in foods. Indeed, spicy hot pot is a signature dish in southwest China and chili peppers are essential ingredients in Mexican cuisine. Many health benefits are believed to originate from chili pepper consumption. However, we humans are the only species that deliberately seeks spicy foods, while most animals are repelled by the irritating sensation. Plants of the genus *Capsicum,* such as chili peppers are the most common source of spiciness, as their fruits contain a group of pungent molecules named capsaicinoids. Among the capsaicinoids, capsaicin is the most abundant in quantity, though not much spicier than other capsaicinoids such as dihydrocapsaicin, homocapsaicin and homodihydrocapsaicin based on the Scoville scale. Similar to other capsaicinoids, capsaicin contains a vanillyl group (which we refer to as the Head), an amide group (the Neck) and a fatty acid chain (the Tail) (shown below).



Spiciness is a burning sensation caused by capsaicin in food. When we eat spicy food, capsaicin stimulates receptors in our mouth called TRPV1 receptors and triggers a reaction. The purpose of transient receptor potential vanilloid 1 (TRPV1) receptors is thermoreception—the detection of heat. This means they are supposed to deter us from consuming food that burns.

When TRPV1 receptors are activated by capsaicin, the sensation we experience is linked to the feeling of encountering something hot, near the boiling point of water. However, this pain is nothing more than an illusory side effect of our confused neural receptors—there is nothing actually "hot" about spicy food.

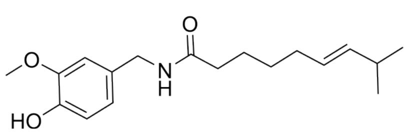
Since the discovery of its receptor, TRPV1 ion channel, how capsaicin activates this channel has been under extensive investigation using a variety of experimental techniques including mutagenesis, patch-clamp recording, crystallography, cryo-electron microscopy, computational docking and molecular dynamic simulation. A framework of how capsaicin binds and activates TRPV1 has started to merge:

1. Capsaicin binds to a pocket formed by the channel's transmembrane segments
2. It takes a "tail-up, head-down" configuration
3. Binding is facilitated by both hydrogen bonds and van der Waals interactions
4. Upon binding, capsaicin stabilizes the open state of TRPV1 by "pull-and-contact" with the S4-S5 linker

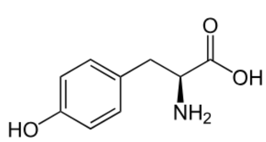
Questions

1. If you have heard the phrase “structure dictates function,” you may be aware that the chirality and stereochemistry of a molecule will determine if it is biologically active in the body. Unfortunately, the more stereocenters you have in a molecule, the more complex it’s reactivity could reveal. Are there any chiral carbons or alkenes present with stereochemistry in capsaicin? Determine what the stereochemistry is (R/S or E/Z) if so.

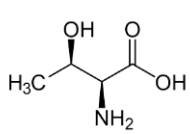
2. Research shows that hydrogen bonding and Van der Waals (LDF) interactions are imperative to the binding of capsaicin in TRPV1. It was found that residues Tyr511 and Thr550 in the third and fifth transmembrane domains are responsible for binding capsaicin to TRPV1.
    a. Using the molecules below, label the hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA) that are possible.
    b. Use the blank space draw one hydrogen bond interaction between capsaicin and one of the amino acids (using the dotted line notation we did in class).
    c. Both hydrogen bonding and Van der Waals interactions are important for capsaicin binding. Describe the Van der Waals interactions that would be occurring between these three molecules.



Capsaicin



Tyroseine (tyr)



Threonine (thr)

3. What happens when food is too hot to handle? The ability of several common beverages to put out the fire, or reduce the oral burn from capsaicin, has been tested. Using your information Unit 1 (from Big Idea 1+2 of PBL), determine whether the beverage or food component would solubilize capsaicin and successfully remove it from the binding site of TRPV1.

Component of Beverage	**What IMFs would be exhibited by the component? (Be descriptive here!)**	**Will capsaicin be soluble? (This may not be a simple yes or no answer)**
Water		
Ethanol (CH_3CH_2OH)		
Milk proteins		
Milk fats		
Milk carbohydrates		
Milk Vitamins		

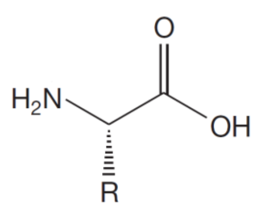
Which component above would be most effective to solubilize capsaicin and potentially unbind it from the TRPV1 site? Explain your thinking with at least 3-5 sentences and pictures where appropriate.

PBL Unit 3 - Shape of Things

Answers due by Exam 3 – Big Idea 4

We've been interacting with biological molecules and seeing how their physical properties may interact. Now we get a chance to see the reactivity of these and investigate the acidic nature of the molecules involved in the capsaicin binding. The questions are a little different for this PBL as they are embedded in the document so take a look and use the space to answer the questions as you read through the doc.

Looking at the structure of these molecules we have seen some common functional groups – amines, alcohols, phenols (alcohols attached to an aromatic ring), and carboxylic acids. In class we have investigated the quantitative (pKa) and qualitative (ARIO) aspects of acidity and bacisity. Let's take a closer look at the amino acid structure (the base unit of a protein!) to identify different acidic and basic sites. the general form of an α-amino acid contains both an amino group (NH_2) and a carboxyl group (CO_2H) bonded to the same C atom:



An α-amino acid

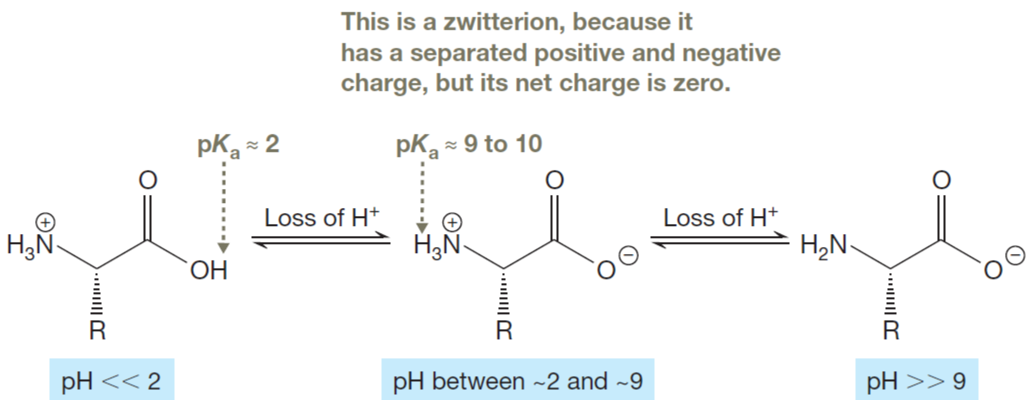
It turns out, however, that this is never the dominant form in aqueous solution because of the weakly acidic and basic nature of the functional groups present.

1. Remember, any functional group could be either an acid or a base or both! In the space below, brainstorm, what is a requirement for an acid? What is a requirement for a base?

2. Which functional group in the amino acid above is most basic, and which is most acidic? Why did you choose those designations? – give ARIO reasoning here, we will discuss pKa eventually.

What form, then, does an amino acid take in aqueous solution? The answer depends on the pH of the solution! When a solution is highly acidic (pH<2), the weakly basic functional group will be protonated. When the solution is highly basic (pH>9), the weakly acidic functional group will be deprotonated. At a pH between 2 and 9, a zwitterion forms – one that has both a positive and negative formal charge but a net charge of zero. The zwitterion forms due to the pH being in between the pkas of the functional groups (higher than the acidic site but lower than the less acidic, or more basic, site). The figure below explains the pH change.

*Notice the pKa is related the structural change during the transition of pH.



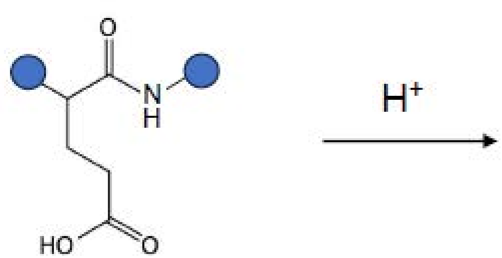
3. Using your knowledge of the general pKas listed above, ARIO, and the diagram, explain what the structure of the amino acid would look like at pH = 7 and the reasons for this appearance (use words or pictures as necessary).

Let's take a look back at the TRPV1 receptors and what pH can do to the capsaicin binding. It has been shown through research that the presence of protons increases the affinity of the receptor for capsaicin. This occurs when just one amino acid segment (out of ~800 total residues!) on TRPV1 becomes protonated and ultimately widens the binding site for a more effective IMF interaction with capsaicin (that we discussed last unit in our PBL). The segment that is reacting happens to be a Glutamic acid residue.

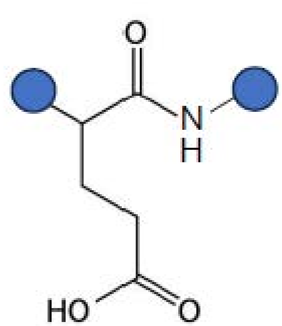
*Note: During peptide formation, the amino group (a terminus) reacts with the carboxyl group (c terminus) to form an amide functional group.

4. Using the molecule below, identify the most basic site, show the curved arrow mechanism of it's protonation, draw the product (protonated glutamic acid), and explain why you chose the site you did.

   * blue circles are meant to isolate our single glutamic acid residue and signify there are more amino acids in this chain that make up the TRPV1 receptor, but they are not important for the pH interaction here.



5. Resonance is important in the analysis of the most basic site above. Show all of the resonance interactions that exist in the molecule:

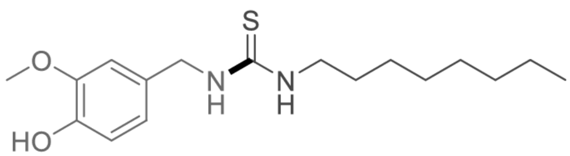


PBL Unit 4 - Shape of Things

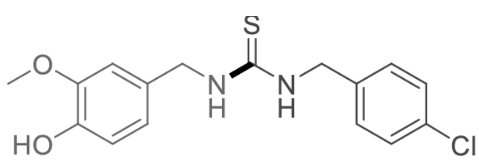
Answers due by the Final Exam – Big Idea 5

With the classification of capsaicin and other molecules you've been studying this year, we can use our knowledge to identify which compounds are soluble with each other and study their reactivity. Several problems appear below. Using the **entire sequence** of PBL from Big Idea 1-4, solve the problems!

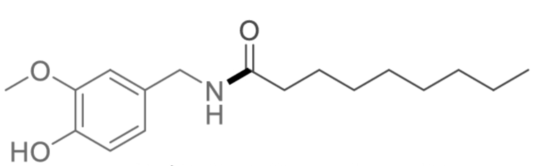
Problem 1: Below are capsaicin derivatives currently being studied for their analgesic potency. Derivatives are similar in structure and may have very similar functional groups but are different molecules. These molecules need to be studied in the lab. Choice of solvent will be the first thing an organic chemist must identify. Typical solvents are water, acetone (CH_3COCH_3), or hexane (C_6H_{14}).
Are the two molecules shown below soluble? Be sure to give evidence for your choice.

a. 

in water?

b. 

in acetone?

c. 

in hexane?

Capsaicin derivatives with thiourea structure (CDTS) is highly noteworthy owing to its higher analgesic potency in rodent models and higher agonism in vitro. Native Americans have used cayenne (Capsicum annuum, frutescens, or red pepper) as both food and medicine for at least 9,000 years. The hot and spicy taste of cayenne pepper is mostly due to a substance known as capsaicin, which helps reduce pain.

Problem 2: Specifically the CDTS is an interesting overall reaction of a amine with a thiocyanate. The thiocyanate is a complex structure.

(a) Draw the two major resonance contributors for the thiocyanate anion (SCN^-).

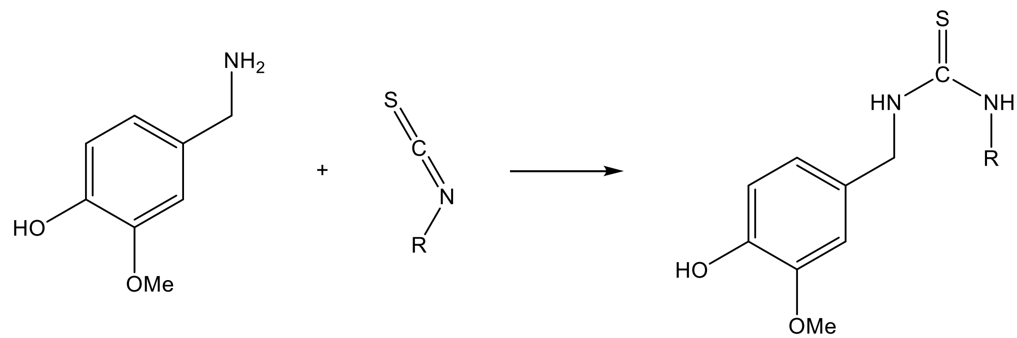
(b) Which site is more basic: the sulfur or nitrogen of SCN^-? Draw the conjugate acid of SCN^-.

(c) Which site is more nucleophilic: the sulfur or nitrogen of SCN^-? Draw the product formed when SCN^- reacts with CH_3I (1-iodomethane).

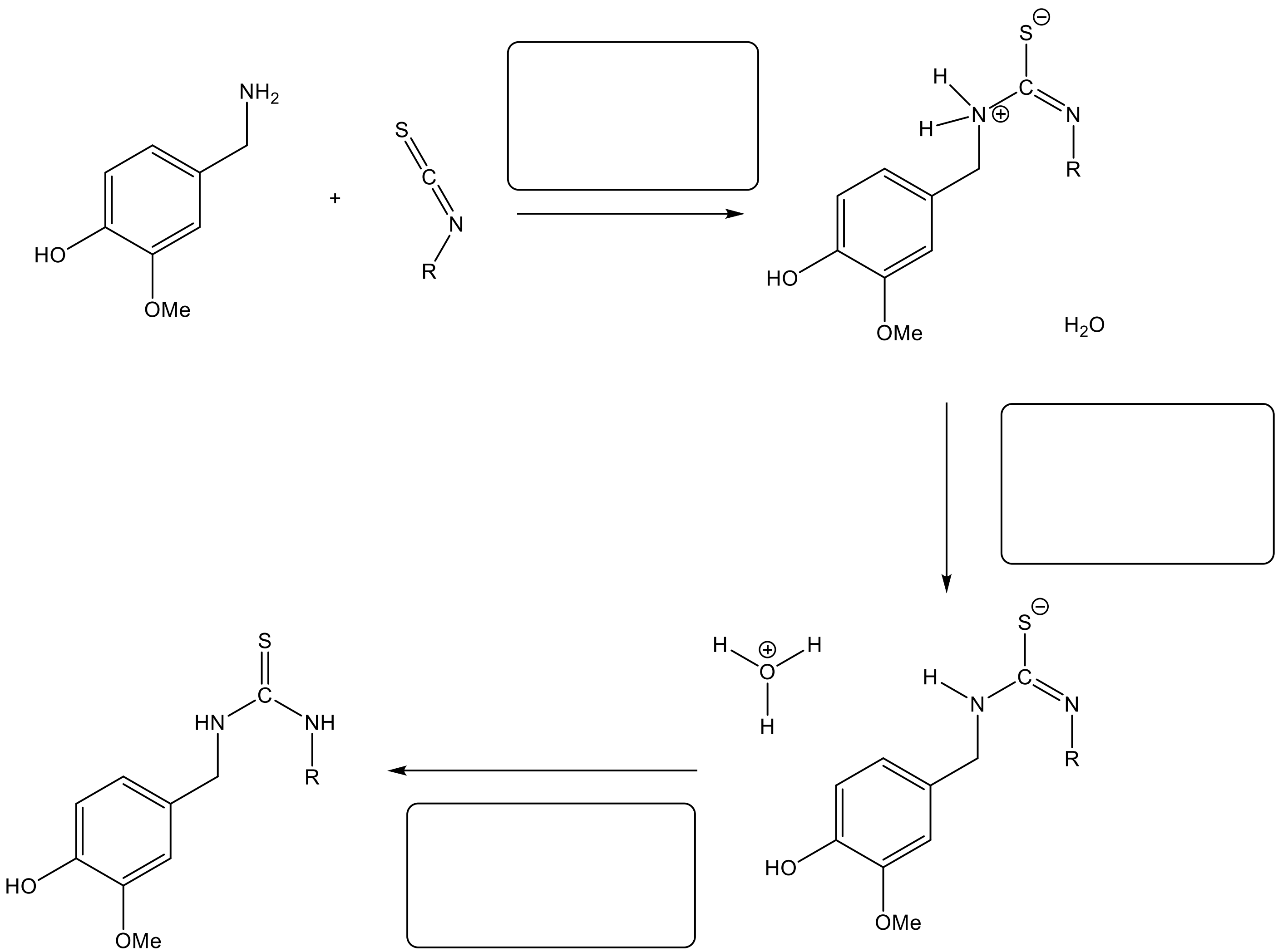
(d) Which site is the most electrophilic?

Problem 3: Synthesis of these derivatives can be done in the lab! Label the curved arrow mechanism on the reaction scheme below.

Overall reaction:



Add in the curved arrows and label the type of reaction step that is occurring:



PBL Unit 1 - Shape of Things

Big Idea #1: Organic molecules can be big and complicated, so chemists use a variety of techniques to communicate and simplify chemical structures.

Big Idea #2: Covalent bonds consist of electrons shared between atoms. This sharing means that electrons are “delocalized”, and chemists use various models to describe this electron delocalization.

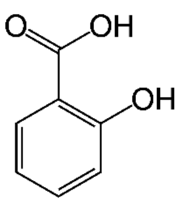
LT#3: Line angle formulas depict molecules with carbons (and the hydrogens bonded to them) omitted, but all heteroatoms (and the hydrogens bonded to them) included. It is the most common and quickest method for drawing organic molecules. **Chapter 1.12**	I can… • Draw a line angle formula from a given Lewis structure or condensed formula, and interconvert between the three. (**1.28, 1.30, 1.33**) Determine the molecular formula of a given line angle structure. (**1.29, 1.34**)
LT #4 Valence bond theory states that the overlap of atomic orbitals in space results in covalent bonds. The most common type of covalent bonds are σ bonding orbitals, which form when orbitals overlap along an internuclear axis. **Chapter 3.1**	I can… • Use VB theory to explain how the overlap of atomic orbitals results in new, shared orbitals. • Define and draw a simple example of a σ bonding orbital between two atoms.
LT #5 To account for molecular geometry and maximize orbital overlap, multiple atomic orbitals can combine to form hybrid atomic orbitals. These hybrid atomic orbitals then overlap with other atoms to form bonding orbitals. **Chapter 3.2-3.8**	I can… • Describe how hybridized orbitals are formed from atomic orbitals • Label the hybridization of an indicated atom in a molecule. (**3.8-3.11)** • Label the orbitals, in a depiction of a molecule, that were used to form an indicated bond. • Sketch the valence bond picture of a simple molecule containing σ orbitals, □ orbitals, and/or lone pairs. **3.1 – 3.3, 3.4, 3.7** • Explain the difference between a σ and π bond. • Determine the total number of σ and π bonds in a molecule. (**3.12, 3.14, 3.15**) Determine if two distinct configurations are possible for a given double bond. (**3.17, 3.19**)

Pain management can take on various forms for each individual. For organic chemists, drug design plays a critical role in their research. Gaining a deeper understanding of how these medications function is key to comprehending their applications and discovering ways to enhance their design. Below are several classes of pain management drugs. Please review each class carefully and answer the questions that follow.

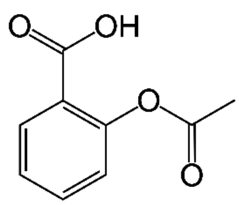
NSAIDs - Nonsteroidal anti-inflammatory drug

NSAIDs are a class of drugs that alleviate pain by reducing inflammation. They achieve this by inhibiting the activity of cyclooxygenase enzymes, which play a crucial role in the synthesis of biological mediators, such as prostaglandins involved in inflammation, and thromboxane involved in blood clotting. NSAIDs can be classified either by their chemical structure or by their mechanism of action. While older NSAIDs were categorized based on their chemical structure or origin, long before their mechanism of action was fully understood, newer NSAIDs are more commonly classified according to how they function.

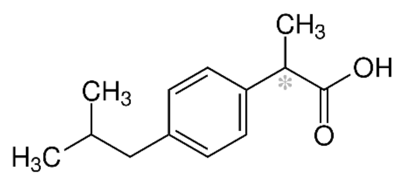
Common NSAIDs:



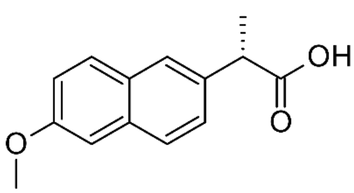
Salicylic Acid (Motrin)



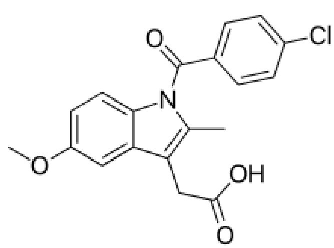
Acetylsalicylic acid (Aspirin)



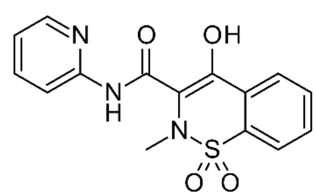
Ibuprofen



Naproxen (Aleve)



Indometacin (Tivorbex)

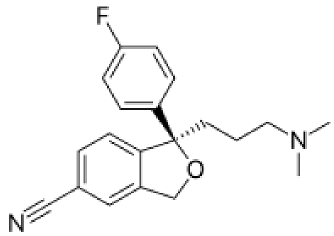


Piroxicam (Feldene)

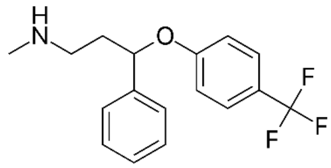
Antidepressants

Antidepressants can be highly effective for patients with chronic neuropathic pain, rheumatoid arthritis, and fibromyalgia, as they influence neurotransmitters like serotonin and norepinephrine, which in turn affect nerve activity. When pain is not caused by inflammation, NSAIDs may be ineffective, especially in cases where the pain’s origin is unclear. There are various types of antidepressants, each working in slightly different ways and carrying different side effects. Below are a few examples of antidepressants in the SSRI (selective serotonin reuptake inhibitors) subcategory.

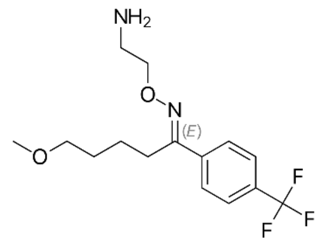
Common Antidepressants



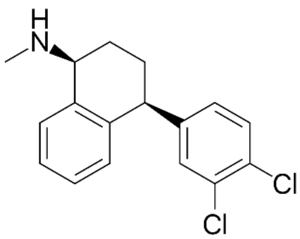
Citalopram (Celexa)



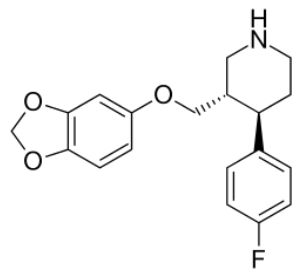
Fluoxetine (Prozac)



Fluvoxamine (Luvox)



Sertraline (Zoloft)

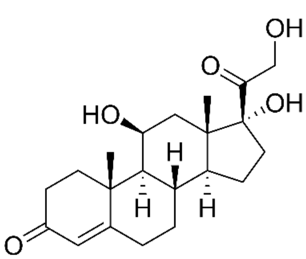


Paroxetine (Paxil)

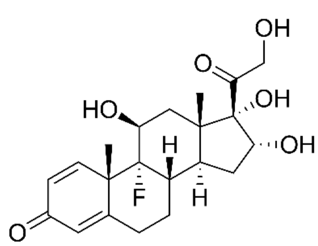
Steroids

Steroids mimic the effects of hormones naturally produced by the adrenal glands; small glands located above the kidneys. When injected into a joint or muscle, steroids help reduce redness and swelling (inflammation), which can alleviate pain and stiffness. When administered into the bloodstream, they can reduce inflammation throughout the body and suppress the activity of the immune system—the body's natural defense against illness and infection. This makes steroids effective in treating autoimmune conditions, such as multiple sclerosis (MS), where the immune system mistakenly attacks the body. It's important to note that steroid injections are distinct from anabolic steroids, which some individuals use to increase muscle mass.

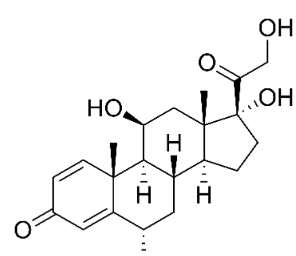
Common Steroids



Hydrocortisone



Triamcinolone



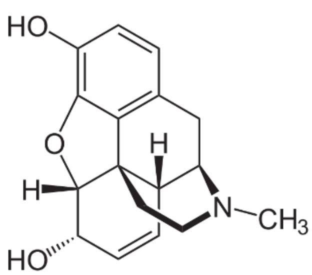
Methylprednisolone

Opioids

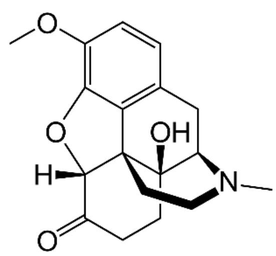
In the late 1990s, pharmaceutical companies assured the medical community that opioid pain relievers carried a low risk of addiction, leading healthcare providers to prescribe them more frequently. However, this increased prescribing contributed to widespread misuse of both prescription and non-prescription opioids, revealing that these medications could indeed be highly addictive.

Opioids are among the most potent painkillers available, but millions of Americans have struggled with misuse after becoming addicted to the calming and euphoric effects they produce. The active, biochemically effective form of an opioid is its positively charged structure, which has no effect on the body until it attains this charge. The positive charge on the nitrogen atom allows the drug to bind to its target site, where pain originates, providing relief. The typical acidity of the human body creates ideal conditions for opioids to become positively charged, ensuring that nearly all of the drug consumed becomes biochemically active throughout the body. Whether in the brain or at the site of injury, cells throughout the body will experience the drug's effects.

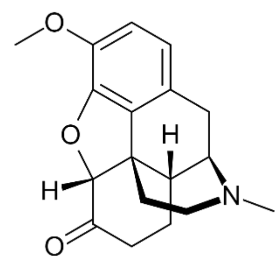
Common Opiods



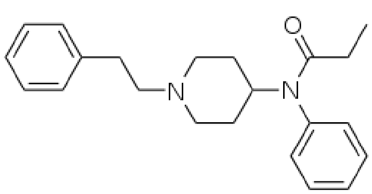
Morphine



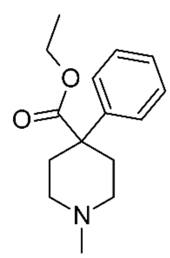
Oxycodone



Hydrocodone



Fentanyl



Pethidine

Questions:

1. What do you notice about the molecules in each class of medication? List out some of the common structures within each class (What structural similarities do the opioids have? What about the steroids? Make sure you list at least two similaries for each class)

2. For each similarity that you just listed, find the central atom or atoms and label each for hybridization, 3D shape, and electronegativity.

3. Which class of medication has polar bonds? Highlight or list the polar bonds for each class of compounds. Are there some molecules within the class that are more polar than others?

PBL Unit 2 - Shape of Things

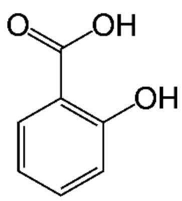
Answers due by Exam 2 – Big Idea 3

Still hovering around the topic of pain management, we have been discussing what the 3D shape means for molecules and their relationship to other stereoisomers. Some of these drugs have rings, chiral centers, and resonance! Look over each class again and answer the questions that follow.

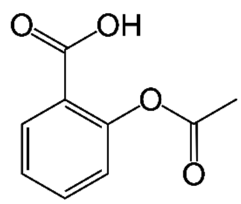
NSAIDs - Nonsteroidal anti-inflammatory drug

NSAIDs are a type of drug class that reduces pain through decreasing inflammation. NSAIDs work by inhibiting the activity of cyclooxygenase enzymes. In the cells, these enzymes are involved in the synthesis of key biological mediators (prostoglandins) which are involved in inflammation and thromboxanes which are involved in blood clotting. NSAIDs can be classified based on their chemical structure or mechanism of action. Older NSAIDs were known long before their mechanism of action was elucidated and were for this reason classified by chemical structure or origin. Newer substances are more often classified by mechanism of action.

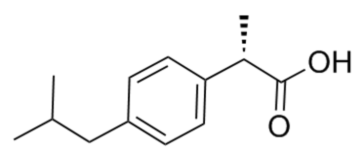
Common NSAIDs:



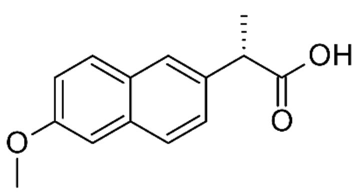
Salicylic Acid



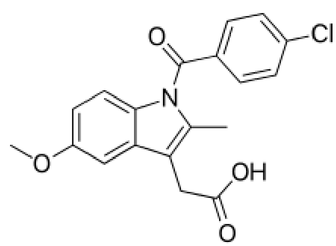
Acetylsalicylic acid (Aspirin)



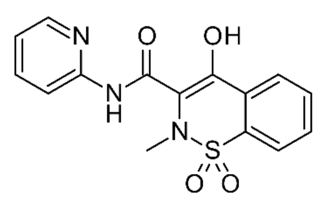
Ibuprofen (Motrin)



Naproxen (Aleve)



Indometacin (Tivorbex)

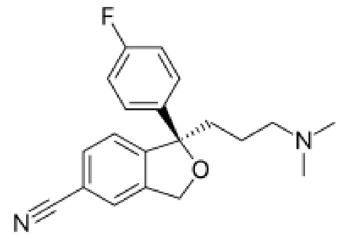


Piroxicam (Feldene)

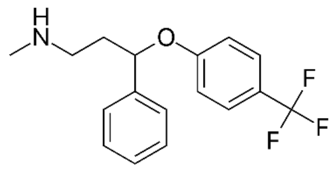
Antidepressants

Because antidepressants modulate neurotransmitters like serotonin and norepinephrine and therefore nerve activity they can be incredibly helpful to patients with chronic neuropathic pain, rheumatoid arthritis, and Fibromyalgia. Sometimes pain isn't caused by inflammations so NSAIDs don't work – pain with an unknown origin could be a problem. There are many types of antidepressants available that work in slightly different ways and have different side effects. Here are a few in the subcategory of SSRI (selective serotonin reuptake inhibitors) antidepressants.

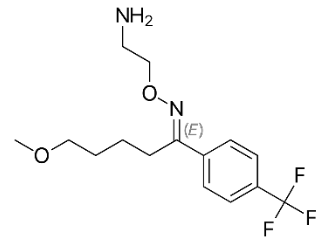
Common Antidepressants



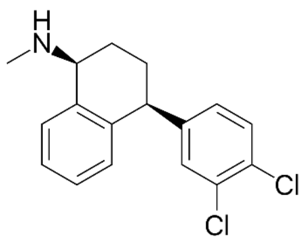
Citalopram (Celexa)



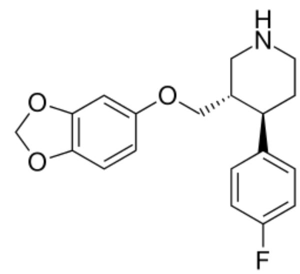
Fluoxetine (Prozac)



Fluvoxamine (Luvox)



Sertraline (Zoloft)

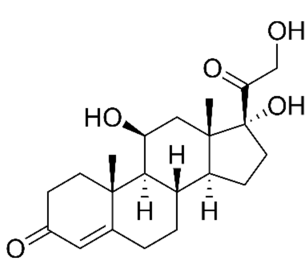


Paroxetine (Paxil)

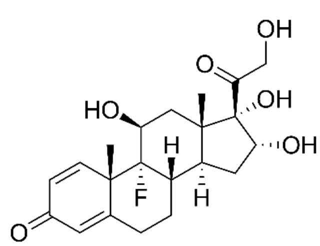
Steroids

Steroids closely copy the effects of hormones normally produced by the adrenal glands, 2 small glands found above the kidneys. When injected into a joint or muscle, steroids reduce redness and swelling (inflammation) in the nearby area. This can help relieve pain and stiffness. When injected into the blood, they can reduce inflammation throughout the body, as well as reduce the activity of the immune system, the body's natural defense against illness and infection. This can help treat autoimmune conditions, such as multiple sclerosis (MS), which are caused by the immune system mistakenly attacking the body. Steroid injections are different from the anabolic steroids used by some people to increase their muscle mass.

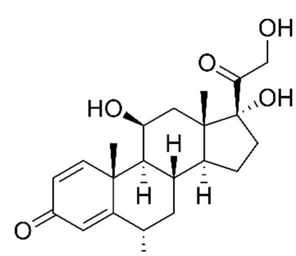
Common Steroids



Hydrocortisone



Triamcinolone



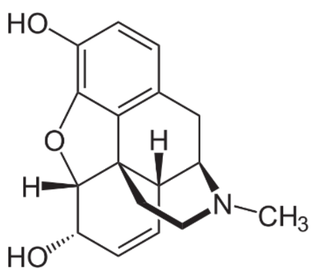
Methylprednisolone

Opioids

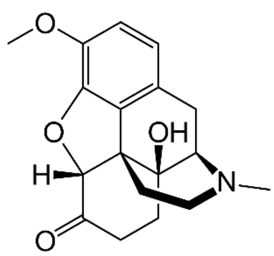
In the late 1990s, pharmaceutical companies reassured the medical community that patients would not become addicted to opioid pain relievers and healthcare providers began to prescribe them at greater rates. Increased prescription of opioid medications led to widespread misuse of both prescription and non-prescription opioids before it became clear that these medications could indeed be highly addictive.

Opioids are one of the most powerful pain medications available, but millions of Americans have struggled with prescription opioid misuse after getting hooked on the feelings of calm and euphoria they also induce. The positively charged form of the structure is the biochemically active form of the opioid—it won't have any effect on your body until it gains this positive charge. The positive charge on the nitrogen helps these drugs bind to the target site in your body where the pain is originating and provide relief. The typical acidity level of the average person's body provides ideal conditions for opioids to become positively charged. This means that nearly all of the drug that's consumed will be biochemically active throughout the body. Whether it's in the brain or at the site of injury, cells all over the body will feel the effects of the drug.

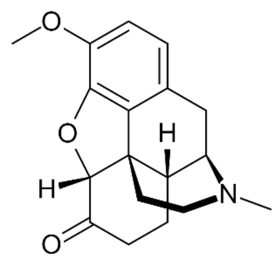
Common Opiods



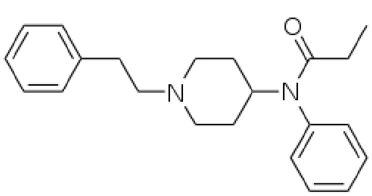
Morphine



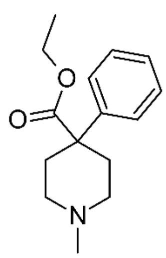
Oxycodone



Hydrocodone



Fentanyl



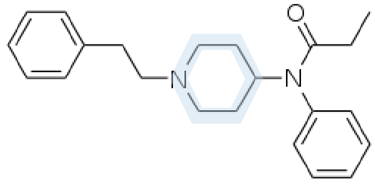
Pethidine

Questions:

1. **Identify the chiral carbons in the NSAIDs and Antidepressant categories**. For any molecule that has at least one chiral carbon, determine the R or S stereochemistry.

2. If you have heard the phrase "structure dictates function," you may be aware that the chirality of a molecule will determine if it is biologically active in the body. Unfortunately, the more chiral centers you have in a molecule, the more difficult it will be to isolate just one stereoisomer (and expensive too!). So pharmaceutical companies typically don't separate enantiomers – which is where side effects tend to come from! Looking at all the categories, **identify the molecules that have chiral carbons and for each calculate the maximum number of possible stereoisomers that would exist (2^n rule)**. You do not need to determine R or S stereochemistry NOR draw the stereoisomers – this is a quantification problem only.

3. We've been learning about chair cyclohexane in this Big Idea Section (#3). Fentanyl, an opioid, has a lovely disubstituted six membered ring (highlighted in blue). This adds even another layer of conformational analysis to the bioactive idea! **Draw the most stable ring form of fentanyl** (you can draw the substituents as condensed rather than bond line forms but pay attention to the axial and equatorial positions of those substituents.



PBL Unit 3 - Shape of Things

Answers due by Exam 3 – Big Idea 4

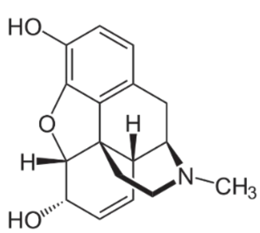
Opioids are one of the most powerful pain medications available, but millions of Americans have struggled with prescription opioid misuse after getting hooked on the feelings of calm and euphoria they also induce. But new research suggests there may be a way to chemically tailor opioids to reduce their addictive potential.

Opioids

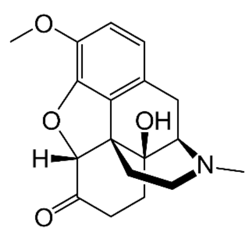
Opioids are one of the most powerful pain medications available, but millions of Americans have struggled with prescription opioid misuse after getting hooked on the feelings of calm and euphoria they also induce. The positively charged form of the structure is the biochemically active form of the opioid—it won't have any effect on your body until it gains this positive charge. The positive charge on the nitrogen helps these drugs bind to the target site in your body where the pain is originating and provide relief. The typical acidity level of the average person's body provides ideal conditions for opioids to become positively charged. This means that nearly all of the drug that's consumed will be biochemically active throughout the body. Whether it's in the brain or at the site of injury, cells all over the body will feel the effects of the drug.

Many of the addictive qualities of opioids are due to the feelings of calm and euphoria they induce in the brain. For conditions like arthritis and injury/wounds and postoperative pain, however, these drugs need to target only the diseased or injured areas of the body to provide pain relief. The question researchers face is whether it's possible to limit the effect of opioids to specific areas of the body without affecting the brain.

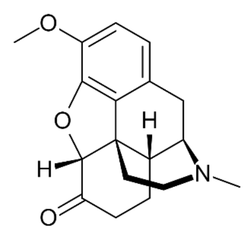
Common Opiods



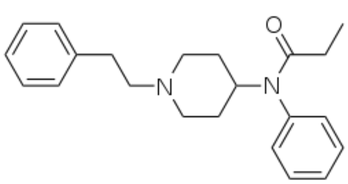
Morphine



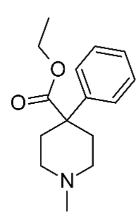
Oxycodone



Hydrocodone



Fentanyl



Pethidine

Questions:

1. Looking at the 5 opioids above, where is the most basic site? This basic site will be in all 5 of the molecules shown. What makes that site the most basic? (this can be a pKa/pKb type answer or a qualitative/ARIO based).

2. Draw the acid-base reaction, including arrows, that occurs when an opioid (pick one!) reacts with water (simulating the blood at pH 7.4) Hint: the opioid is the base and water is the acid.

3. One recently proposed solution to the addictive nature of opioids focuses on the acidity difference between injured and healthy tissue. Injured tissue is more acidic than healthy tissue due to a process known as acidosis, where lactic acid and other acidic byproducts produced by damaged tissue collect. This means that an opioid could potentially be altered to be positively charged and active only in injured tissue while staying neutral and inactive in normal tissue. The drug would be biochemically active only at a higher acidity level than found in healthy tissue. Therefore, doctors could prescribe lower doses of opioids so that patients were less likely to become addicted.

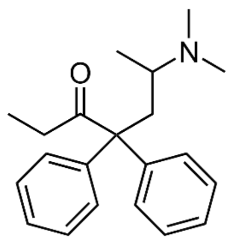
   If the acidity of injured tissue is greater, we could effectively decrease the basicity of the opioid in order to decrease its reactivity in the body (selectively protonate the opioid in injured tissue only). What could we do to adjust (specifically lower) the basicity of the opioids? Hint: bases are high areas of electron density, how do we make them weaker?

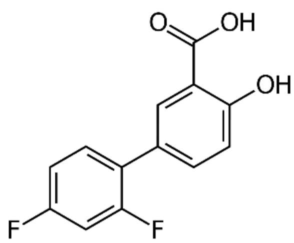
PBL Unit 4 - Shape of Things

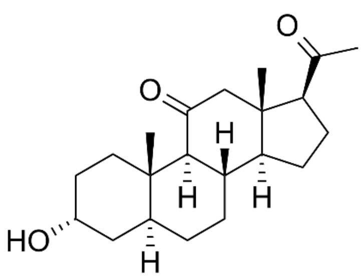
Answers due by the Final Exam – Big Idea 5

With the classification of pain killers you've been studying this year, we can use our knowledge to identify which class other compounds can go into and study their reactivity. Within a class of compounds, reactivity is typically the same. Several problems appear below. Using the entire sequence of PBL from Big Idea 1-4, solve the problems!

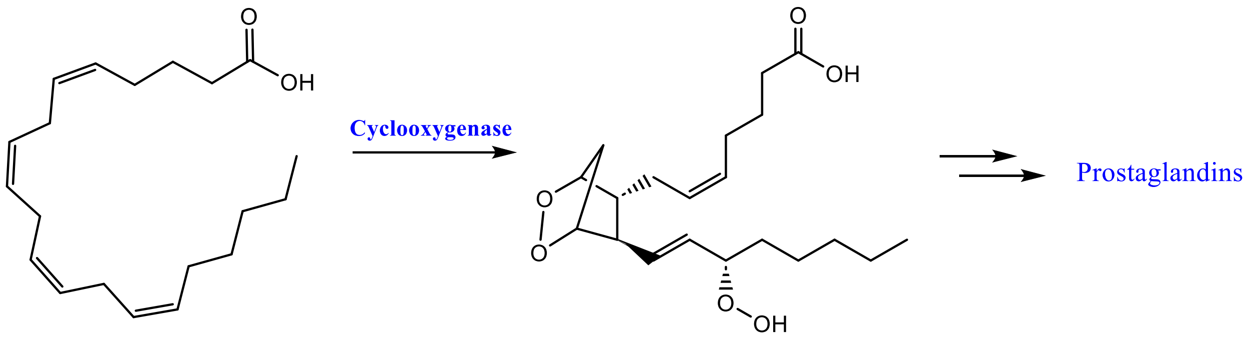
Problem 1: What class of compounds do the following unidentified molecules belong to?

1. 

2. 

3. 

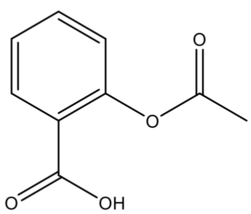
Problem 2: The reactivity of compounds within a given class can be similar. The NSAIDs react by inhibiting the activity of cyclooxygenase enzymes. In the cells, these enzymes are involved in the synthesis of key biological mediators (prostoglandins) which are involved in inflammation and thromboxanes which are involved in blood clotting. Prostaglandins have many important biological functions, including stimulating inflammation and inducing fever.



Arachidonic Acid

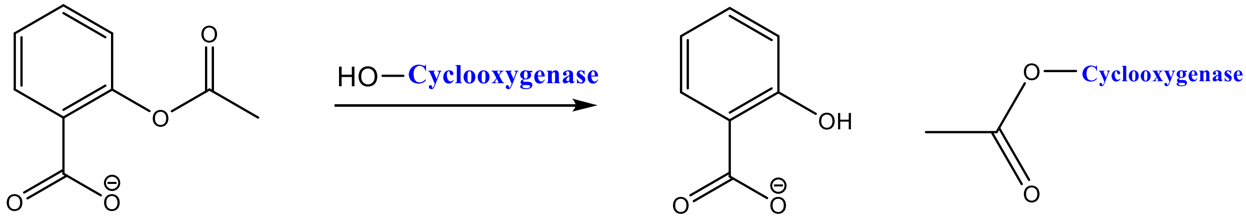
PGG2

1. At physiological pH (7.4), a common NSAID, aspirin is will be deprotonated. Give an explanation as to what proton is most acidic in aspirin and complete the curved arrow mechanism (use a generic **B:** for base).



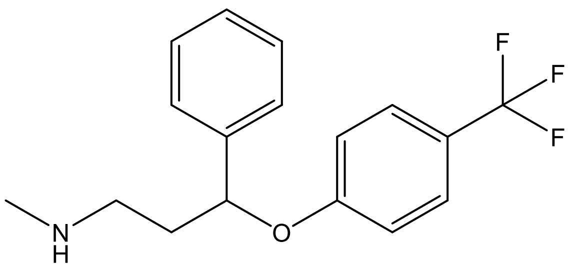
aspirin

2. An OH group of enzyme cyclooxygenase reacts with aspirin, resulting in the transfer of an acetyl (RCO) group from aspirin to cyclooxygenase. This process deactivates cyclooxygenase, thereby interfering with the synthesis of prostaglandins. What kind of reaction is occuring? (elimination, addition, or substitution?) Identify (highlight, circle, etc) the group(s) that are changing in the reaction shown above.



Problem 3: Another class of compounds we've investigated were the Selective serotonin reuptake inhibitors (SSRIs). SSRIs inhibit the serotonin transporter (SERT) at the presynaptic axon terminal. By inhibiting SERT, an increased amount of serotonin remains in the synaptic cleft to help with chronic neuropathic pain for an extended period of time.

1. Fluoxetine has one chiral center – circle it on the molecule below. The stereochemistry of this chiral carbon does not affect the mechanism of action in the body.



fluoxetine

2. It is hypothesized a substitution reaction may be taking place. Where is the easiest accessible electrophile on fluoxetine for an SN2 reaction to occur? Give an explanation as to why you chose that electrophile. Be sure to include a discussion of what makes a good electrophile.

Organic Chemistry Problem-Based Learning (PBL) Assignment:

PFAS and Their Environmental & Social Impacts

PBL Big Idea 1 + 2: Molecular Structure and Bonding of PFAS

Topic: Hybridization, Molecular Orbital Theory, and Polarity

Per- and polyfluoroalkyl substances (PFAS) are a class of synthetic organic compounds that have been used since the 1940s in a wide range of products, including non-stick cookware, water-repellent fabrics, firefighting foams, and food packaging. Their defining feature is a fully or partially fluorinated carbon chain that creates extremely stable carbon–fluorine bonds, the strongest in organic chemistry. These bonds contribute to the resistance of PFAS to heat, acids, bases, and microbial degradation, which is why they are often referred to as “forever chemicals.” Their strong polar head groups (e.g., carboxylic acids or sulfonic acids) and hydrophobic fluorinated tails create unique polarity patterns that make them both amphiphilic (having both polar and non-polar areas) and environmentally mobile. As a result, PFAS have been found globally in groundwater, rainwater, air, and even in human blood.

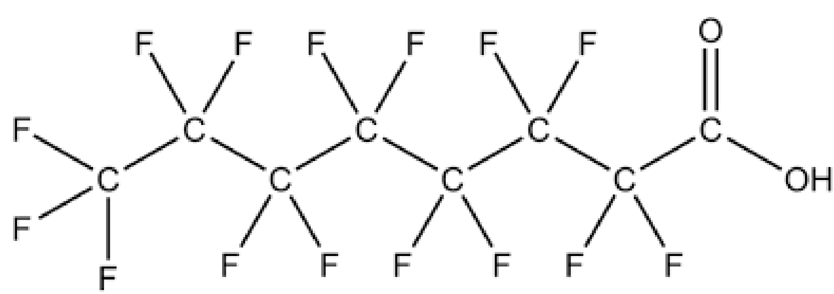
Understanding their molecular structure - including hybridization, molecular orbitals, and polarity - is essential to grasping why they persist so broadly in the environment and why they are difficult to remove using conventional remediation strategies.

Citations: - U.S. National Institute of Environmental Health Sciences (NIEHS), https://www.niehs.nih.gov/

health/topics/agents/pfc - Washington State Department of Ecology, https://ecology.wa.gov/waste-toxics/

Questions:

1. On the Lewis structure of perfluorooctanoic acid (PFOA) below, add in the lone pairs. Label the hybridization of each carbon atom in the structure.



2. Draw out the full Lewis structure **and** bond line structure of PFOS , perfluorooctanesulfonic acid, from the condensed: $CF_3CF_2CF_2CF_2CF_2CF_2CF_2CF_2SO_3H$

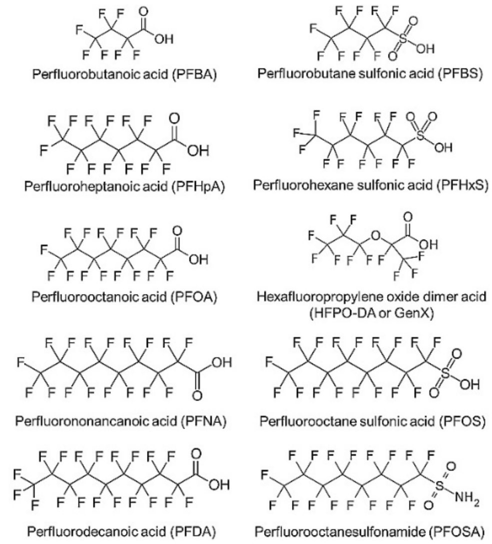
3. Describe the orbital overlap in the C–F bond. The C-F bond is strong, why do you think that is in comparison to other carbon-halogen bonds? Think about the characteristics of the orbitals overlapping.

4. Describe the geometry of a CR_2F_2 group using VSEPR theory (include shape name, bond angles, and drawn 3D shape). R here is the rest of the carbon chain that is important to consider for full geometry.

5. PFAS contamination has disproportionately affected Indigenous communities, low-income rural towns, and communities near military bases or chemical manufacturing sites. How does understanding molecular structure help us advocate for and protect these vulnerable populations? What responsibilities do chemists have in reducing harm from chemical design?

PBL Big Idea 3: PFAS Behavior in the Environment

Topic: Intermolecular Forces, Nomenclature, Conformational Analysis, Stereochemistry



PFAS are found in surface water, drinking water, soil, house dust, and even in common household items such as carpets, clothing, fast-food wrappers, and cosmetics. Their environmental mobility stems from their unique amphiphilic structure, which allows them to cross boundaries between air, water, and biological tissue. The strength and orientation of intermolecular forces, such as hydrogen bonding, dipole–dipole interactions, and London dispersion forces, play key roles in how PFAS behave in these diverse environments. Conformational flexibility of PFAS molecules, chain length, and molecular shape influence how they accumulate and persist.

Efforts to replace long-chain PFAS with shorter-chain alternatives (such as GenX) raise new questions about molecular structure, nomenclature, and stereochemistry in relation to toxicity and environmental fate. By exploring these compounds, we can connect organic chemistry concepts to real-world problems and chemical design decisions.

Citations: ACS PressPac (2025). “Ultrashort PFAS compounds detected in people and their homes.” https://www.acs.org/pressroom/presspacs/2023/october/ultrashort-pfas-compounds-detected-in-people-and-their-homes.html

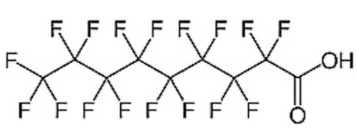
WA Ecology PFAS in food packaging: https://ecology.wa.gov/waste-toxics/reducing-toxic-chemicals/washingtons-toxics-in-products-laws/pfas-in-food-packaging

ACS C&EN: https://cen.acs.org/sections/pfas.html

Questions:

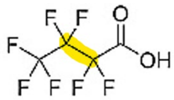
1. Looking at the PFAS above, what functional groups do you see?

2. PFAS are both hydrophilic and lipophilic. Hydro = water, Lipos = fat, phile = love or attraction to something. This combination allows PFAS to act as surfactants, meaning they can reduce the surface tension of liquids and help them mix with water. Use polarity and intermolecular forces of the PFAS structure below to explain this behavior.



Perfluorononancanoic acid (PFNA)

3. Draw two conformers of a short-chain PFAS – the lowest energy Newman and the highest energy Newman across the bond highlighted (yellow, C2-C3 bond) below. How does chain length affect flexibility and solubility?



Perfluorobutanoic acid (PFBA)

4. PFAS are often called "forever chemicals" because they don't easily break down in the environment and can accumulate in living organisms. The amphiphilic nature of PFAS you investigated in Question 2 influences their behavior in the environment. They tend to accumulate at air-water interfaces, with the hydrophobic tail facing the air and the hydrophilic head dissolving in the water. This can affect their transport in soil and water, as well as their ability to be adsorbed onto surfaces. Design a less persistent PFAS structure. What functional groups or chain features would you include and why? Would that make them more or less soluble in water or fat?

5. Some replacement PFAS (like GenX) were marketed as safer alternatives but are now being found in drinking water and human blood. How does chemistry education help the public question and evaluate claims of “green” or “safe” chemicals? What role should regulatory agencies and scientists play in preventing greenwashing?

PBL Big Idea 4: PFAS Reactivity and Persistence

Topic: Acidity, Basicity, Thermodynamics, Kinetics

PFAS are notoriously difficult to break down because the energy required to cleave a C–F bond is extremely high—over 100 kcal/mol. This thermodynamic and kinetic stability has led to widespread environmental persistence. PFAS have been detected in drinking water, wildlife, agricultural systems, and human blood. The U.S. Environmental Protection Agency and international scientists are urgently searching for chemical degradation techniques that can overcome the kinetic barriers to PFAS breakdown.

Recent research has focused on advanced oxidation processes, high-temperature incineration, photocatalysis, and microbial degradation. All of these processes hinge on chemical principles such as bond strength, reaction kinetics, acid/base behavior, and thermodynamic feasibility. Understanding these principles allows chemists to design more effective PFAS destruction technologies and evaluate the risks of their chemical byproducts.

Citations:

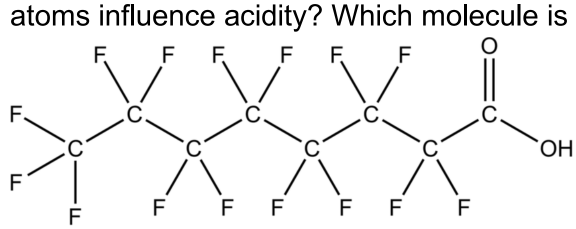
ACS Environmental Science & Technology, “Photodegradation pathways for short-chain PFAS,” https://pubs.acs.org/doi/10.1021/acs.est.4c11265

ACS PressPac (2025). “Research reveals potential alternatives to forever chemicals.” https://www.acs.org/pressroom/presspacs/2025/february/research-reveals-potential-alternatives-to-forever-chemicals.html

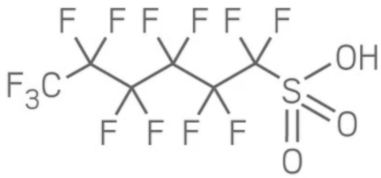
NIEHS: https://www.niehs.nih.gov/health/topics/agents/pfc

Questions:

1. Compare the pKa of PFOA (3.8) to acetic acid, CH_3COOH, (4.76). How do fluorine atoms influence acidity? Which molecule is more acidic?



2. In water, PFAS molecules with acidic functional groups (carboxylic acids or sulfonic acids) tend to ionize, meaning they lose a proton and become negatively charged ions. Show the ionization of the PFAS below with water: label acid, base, conjugate acid, and conjugate base. Be sure to show the curved arrow mechanism and products as well.



PFHxS

+ H_2O →

3. The C-F bond is a poor electrophile. Think about what an electrophile is and why are C–F bonds resistant to nucleophilic attack (and loss of leaving group)? Use kinetic (movement, shape) and thermodynamic (bond energy) reasoning to explain. Think about the 3D shape, the polarity, and the bond strength to enhance your explanation.

4. Many waste treatment facilities serving low-income or marginalized communities do not have access to advanced degradation technologies. What are the implications of this inequity? How can science policy address the distribution of remediation technologies?

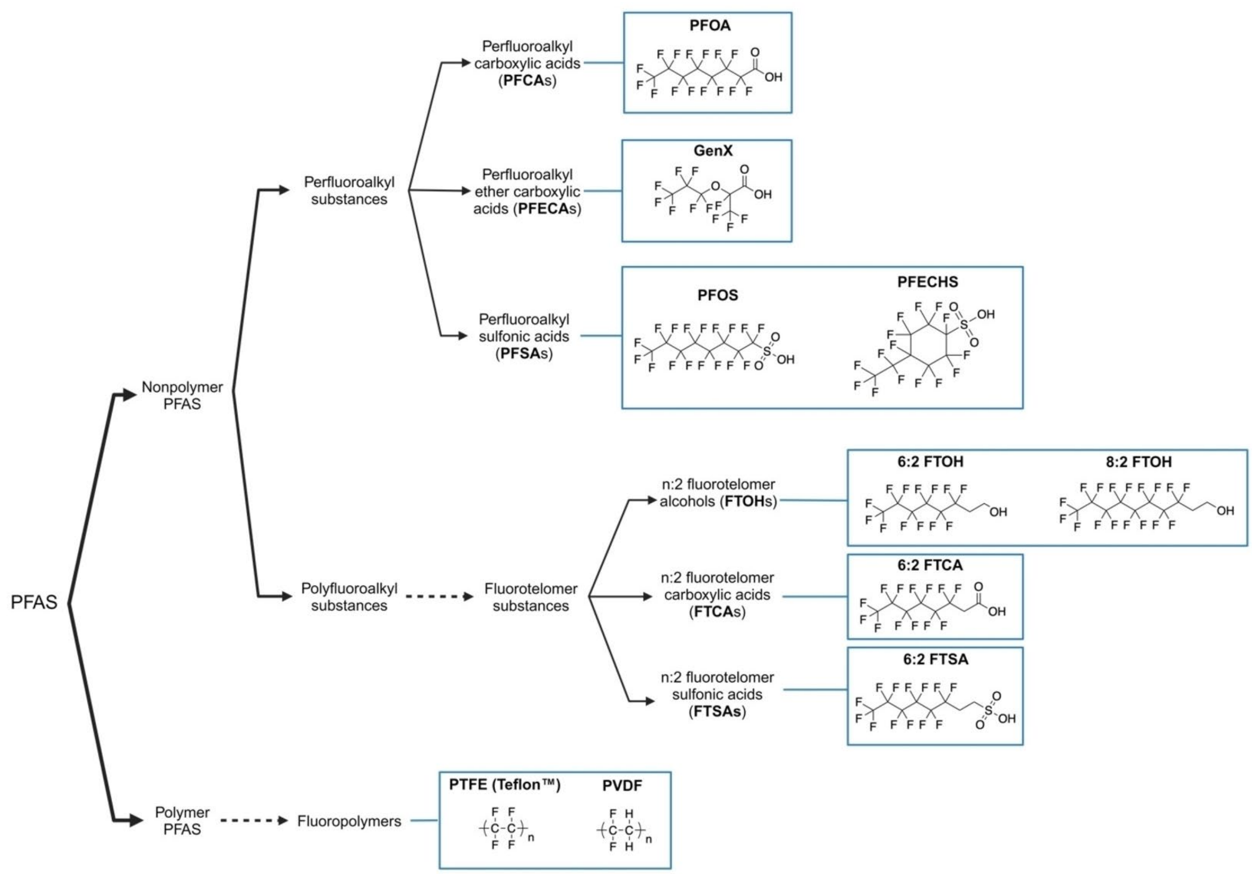
PBL Big Idea 5: Substitution and Elimination in PFAS Chemistry

Topic: SN1, SN2, E1, E2 Reactions with Alkyl Halides and Alcohols

The original industrial synthesis of PFAS compounds involved processes like telomerization and electrochemical fluorination. These processes created compounds like PFOA and PFOS, which are incredibly difficult to degrade. However, some researchers are now using classic organic reaction mechanisms—like nucleophilic substitution and β-elimination—to attempt degradation or chemical transformation of PFAS.

Unfortunately, the strong electron-withdrawing nature of fluorine makes SN1 and SN2 reactions difficult, as the leaving group (fluoride) is poor and sterics limit nucleophilic attack. Nevertheless, understanding these reaction mechanisms can help scientists and engineers propose feasible alternatives or predict side products during PFAS destruction. Additionally, designing fluorinated molecules with more labile functional groups could enable greener industrial production.

The PFAS family is broad, representing over 4,000 compounds. PFAS classification can be split into polymers and non-polymers. You have been discussing the non-polymer perfluoroalkyl substances this quarter. Review the functional group characteristics of the other PFAS categories below.



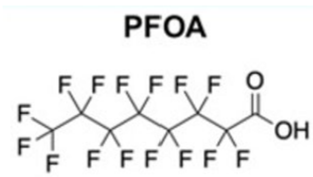
Citations:

ACS Environmental Science & Technology (2023). "Mechanisms for PFAS breakdown using strong nucleophiles," https://pubs.acs.org/doi/10.1021/acs.est.3c04855

ACS PressPac (2025). "Research reveals forever chemicals present in beer." https://www.acs.org/pressroom/presspacs/2025/may/research-reveals-forever-chemicals-present-in-beer.html

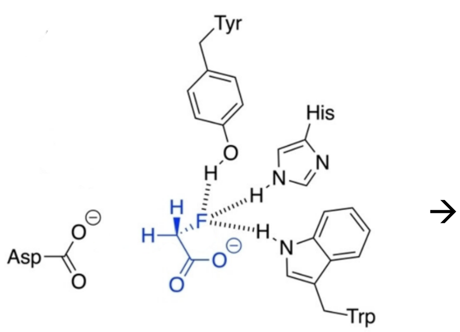
Questions:

1. Propose a substitution reaction with PFOA below and NaSH. Will this follow SN1 or SN2? Justify your answer by considering the electrophile requirements for the SN1 or SN2 reaction.



2. Would elimination (E2) be effective for degrading any of the PFAS categories? Discuss using E2 conditions and requirements as well as looking at the categories on page 1.

3. Fluoroacetate dehalogenase (FAcD) is a bacterial enzyme capable of breaking the C–F bond in the monofluorinated compound fluoroacetate. Fluoroacetate is a naturally occurring toxin produced by certain plants and gram-positive bacteria as a chemical defense mechanism against mammals. The defluorination reaction proceeds through an SN2 mechanism, where the carboxylate anion of the aspartate group acting as a nucleophile. Fluorine is recognized as a notoriously poor leaving group due to the strength of the C–F bond, however the 'halide pocket' triad of the enzyme containing tryptophan, tyrosine and histidine provides hydrogen bonding and electrostatic interactions to facilitate release of fluoride. Draw in the curved arrow mechanism and the products of the SN2 reaction below. The reactants are shown for you.



4. The production of PFAS often occurred in communities with limited regulatory oversight. How do corporate decisions about synthetic chemistry impact public health? How should chemists be trained to consider the societal impacts of their reaction design choices?