

SUPPLEMENTARY MATERIAL

1. VSEPR Theory

Author ACD asks her students to think about how they position themselves when they get on a non-crowded elevator. The most common response students give is that they spread out and don't stand right next to the others. She then explains that this is what electron pairs do as well. Because they repel each other, they want as much space as possible in between one another other.

2. Charge is a High Energy State

In Organic systems with nonpolar solvents, charged species are typically higher in energy and more reactive than neutral species. Think of this as similar to an agitated or high energy person who gets on a subway versus a calm or low energy person. Who do you think is more likely to create a problem or start a fight? Just like the higher energy person is more reactive so is a charged species higher in energy and more reactive (when in a nonpolar solution).

3. Nucleophile Strength

Students have trouble remembering which nucleophiles are stronger (and tend to result in S_N2 and E2 mechanisms) and which are weaker (and tend to result in S_N1 and E1 mechanisms).

Author GH tells students to think of these nucleophiles as molecules that can attack *you*. If they are strong enough to burn your skin (like lye or its organic correlate - alkoxide), they will be strong enough to attack in S_N2 and E2 mechanisms. On the other hand, if you can safely pour them on your skin or even drink them (like water and ethanol), then they are not very strong and will favor S_N1 and E1 mechanisms. It is of course important to emphasize that there are significant exceptions: for example, halide ions are good nucleophiles, yet weak Bronsted bases

and safe to touch and eat; while cyanide ion, although a weak Bronsted base and good nucleophile, is not safe to eat!

4. Backside Attack in S_N2 Reactions

Why does the nucleophile approach and attack carbon from behind? Well, imagine if you need to move a heavy object in your small apartment - like your refrigerator - for example. Isn't it much easier if you can get directly behind the fridge and push from behind in the direction in which you want to go? If space is too tight and you must push from the side (from an angle), it is much harder because you don't have as much force. Well, the same is true for the nucleophile. It can push much harder if it can push in a straight line, rather than from an angle.

5. Steric Hindrance

Author ACD compares steric hindrance to crowding on the subway. When one tries to enter a packed subway car, steric hindrance prevents you from entering. It takes a lot of energy to force yourself onto a packed subway car. The same is true when a nucleophile tries to attack a sterically crowded carbon. The nucleophile has difficulty getting in and it takes extra activation energy for it to attack.

6. Why $S_N1/E1$ Reaction Mechanisms Require *Protic* Polar Solvents

Imagine that there is a fire in an apartment building and that people are standing at their apartment windows desperate to escape. But the only way for them to escape is to jump. And they must jump into the nets of fire fighters who are waiting down below to catch them. This is kind of the situation of a leaving group trying to leave an electrophilic carbon. In a substitution or elimination reaction, the leaving group can only leave if there is a receptive (usually polar) solvent available to catch it and solvate it.

But in an S_N1 or $E1$ reaction, it is not easy for the leaving group to leave. The leaving group really needs the waiting arms of the solvent to “catch it”. An S_N1 or $E1$ reaction is as if all of a sudden that there is a disabled person or small child that needs to jump. This person needs special attention. The same is true with the leaving group of an S_N1 or $E1$ reaction. Only if a protic solvent is waiting (equipped with a strongly positive dipole to “catch” the leaving group) can the leaving group leave.

7. Carbocation Rearrangements

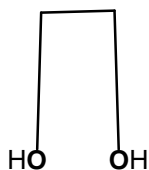
Think of a rearrangement as similar to what happens when you attend a concert or sports event. If you see empty, unclaimed seats with a better view, don't you rush to grab them? Well, the molecule does the same thing. If a molecule sees the chance to become more stable (e.g. by rearranging from a second to a tertiary cation), it jumps at the chance.

8. When Teaching Synthesis

Author GH plays the song “The First Cut is the Deepest” (Sheryl Crow version) when she teaches the topic of synthesis. She does this because she finds that students often jump in very quickly when solving synthesis problems and they often don't stop to think first about their strategy. GH plays this song to make the point to them that they need to first stop and think about their first disconnection, that this disconnection is crucial, and that they should decide about it before they move forward to tackle any synthesis problem.

9. Ethylene Diol as a Protecting Group of Carbonyl Compounds

A student once pointed out to author GH that the ethylene diol molecule (if drawn in a certain way) looks like a pair of headphones. Accordingly, author GH sometimes refers to this molecule as the headphones molecule to help students recognize and remember it.



The Headphones Molecule

10. Acid Catalysis (in Acetal Formation or Acyl Substitution)

Think of an acid catalyst like Spray 'n Wash ®. If you have a stain on your clothes, you can just throw them in the wash and hope for the best. Or you can pretreat with a spray to loosen the stain first which will then help it be removed more effectively during the wash cycle. An acid catalyst is like Spray 'n Wash ®. It helps weaken the connection between the carbonyl carbon and oxygen to make it easier to kick out the leaving group (bond to O), aka the stain.

11. Acyl Substitution

In acyl substitution, a variety of different nucleophiles can attack and a variety of different leaving groups can leave. It is sometimes hard to keep straight what seem like so many different reactions. But what varies from one reaction to the next is really just nucleophile strength and the ease with which the leaving group is able to leave.

- a. Sometimes if the nucleophile is very strong (like LiAlH_4 or an alkyl lithium) and if the leaving group is a good leaving group, the nucleophile will attack twice. I think of this as a mugger who is very strong who easily grabs your wallet and maybe gets your cell phone too.
- b. But in other cases, the nucleophile is not strong enough to do anything (e.g. NaBH_4 attacking an ester) or is only strong enough to attack once (e.g. a Gilman reagent on an acyl halide). This is kind of like a weaker mugger who you might be able to fend off.

- c. Sometimes the leaving group is a poor leaving group, a strong base that is held on tightly, like if you hold onto your belongings very tightly. Then the nucleophile/mugger will have a very hard time displacing the leaving group/your wallet and the nucleophile/mugger will have to be much stronger to do so. (For example, less reactive acyl compounds like amides and carboxylic acids require stronger nucleophiles like LiAlH_4 in order to react).

12. Acyl Substitution: The Tetrahedral Intermediate

In acyl substitution, the nucleophile doesn't directly displace the leaving group. Instead, it knocks out one bond of the carbonyl creating a tetrahedral intermediate. It is then the carbonyl oxygen that forces the removal of the leaving group. Author GH tells students to think of this as if the nucleophile has hired a hitman (the carbonyl oxygen) to do its dirty work of "knocking off" the leaving group.

13. Foreign Languages and the Vocabulary of Organic Chemistry

Often terminology used in Organic Chemistry comes from Romance or Germanic languages. One example is the usage of the terms, *vicinal* and *geminal*, which students often confuse. Author ACD reminds them that vicinal in Spanish and French (*vecino*, *voisin*) means neighbor and that geminal (*gemelo*, *jumeau*) means twin. This not only helps students keep the two terms straight, but it brings smiles to the faces of non-native English speakers.

14. Chemical Shift

How can you remember how chemical shift works in NMR? Just remember: "To the left, to the left, electronegative groups shift the signal to the left" (sung to the lyrics and tune of the Beyoncé song "Irreplaceable").