The Golden Rules of Organic Chemistry

Your goal should be to understand, not memorize organic chemistry. The following 7 Golden Rules should be learned at the beginning of this semester. These simple ideas explain a very large number of things about the way organic molecules interact. Thus, understanding the 7 Golden Rules will allow you to develop an intuitive feel for organic chemistry, and things will make sense! (Warning: this means you will start thinking like a chemist, but, of course, no one needs to know if you don't want them to know.)

1. Atoms prefer filled valence shells. This rule explains why atoms make bonds, and the type of bonds created. A corollary is that centers of electron density (bonds and lone pairs of electrons) repel each other so they stay as far apart as possible. This latter rule, the basis for the so-called VSEPR model, explains 3-dimensional molecular structure.

2. The most important question in chemistry is "Where are the electrons?" The answer is that electrons are generally in higher amounts around the more electronegative atoms (e.g. F, Cl, O, N). The electronegative atoms pull electron density away from the less electronegative atoms (e.g. C, H) to which they are bonded. Thus, understanding electronegativities provides a simple method of deciding which portions of a molecule have a relatively high electron density, and which portions have a relatively low electron density.

3. Nature hates unpaired electrons. If a molecule must have an unpaired electron (a.k.a. radical), it is better to have the unpaired electron distributed over as many atoms as possible through resonance, inductive effects, and hyperconjugation.

4. Nature hates localized charges. If a molecule must have a charge, it is better to have the charge distributed over as many atoms as possible through resonance, inductive effects, and hyperconjugation. In addition, when given the choice, it is better to have more negative charge on a more electronegative atom (e.g. O), and more positive charge on a less electronegative atom (e.g. C).

5. Most reactions involve nucleophiles (molecules with a location of particularly high electron density) attacking electrophiles (molecules with a location of particularly low electron density). When in doubt, transfer a proton! Thus, simply understanding where electrons are provides you with the best way of analyzing new molecules so that you will be able to PREDICT how they will react.

6. Steric interactions (atoms bumping into each other) can prevent reactions by keeping the reactive atoms away from each other.

7. Pi electrons prefer to be delocalized over as many adjacent sp^2 hybridized atoms (or sp hybridized atoms in some cases) as possible, and aromaticity is the most stable form of pi electron delocalization. Pi electrons cannot delocalize onto or through sp^3 hybridized atoms since an sp^3 atom has no 2p orbital available.

There are two Golden Subrules:

1. In mechanisms, proton transfers are generally the fastest possible reaction, so this usually happens before other possible processes such as nucleophilic attack. The exception is deprotonation of non-acidic carbon atoms such as in alkanes, these can be slow.

2. If a five or six-membered ring can be formed, intramolecular reaction will predominate if a molecule has two functional groups that can react with each other. Other rings can sometimes be formed, but when five or six-membered rings are not possible, intermolecular reactions become important competing reactions.

How to Think About Reactions

A good way to think about chemical reactions is that they are like crimes. Both crimes and chemical reactions need motive and opportunity to take place.

Motive

For reactions, the motive refers to the thermodynamic driving force. In other words, a reaction can be thought of as having a motive (thermodynamic driving force) if the products are more stable than the reactants. If the reaction does have a motive (thermodynamic driving force), it is said to be thermodynamically favorable and it will occur if given the opportunity. Reactions will have a favorable motive (thermodynamic driving force) if ΔG for the process is negative ($\Delta G = \Delta H - T\Delta S$). The $\Delta G = \Delta H - T\Delta S$ equation can be hard to apply to new situations, but the following rules of thumb can be helpful.

1. Reactions will usually have a motive (thermodynamic driving force) if stronger bonds are made than are broken in going from starting materials to products. This is primarily a DH effect.

2. In reactions involving proton transfers, the reaction will generally have a motive (thermodynamic driving force) if the products represent the weaker acid and/or weaker base. Recall that equilibrium favors formation of the weaker acid/weaker base in an acid-base reaction. This is primarily a ΔH effect.

3. Reactions will usually have a motive (thermodynamic driving force) if a greater number of smaller molecules are created from fewer larger molecules, especially if a small gaseous molecule such as CO_2, N_2 or HCl is produced as a product. This is primarily a ΔS effect.

Of course, the above rules of thumb also predict when reactions are not likely to have a favorable motive (thermodynamic driving force) as well. For example, reactions will usually not have a favorable motive (thermodynamic driving force) if weaker bonds are made than are broken in going from starting materials to products. This is primarily a ΔH effect.

Opportunity

Even if reactions have a motive (thermodynamic driving force), they can only occur if given the opportunity for the atoms and electrons to rearrange into the product. This rearrangement of atoms and electrons is what we refer to as the mechanism of the reaction. For a reaction to have an opportunity to react, the reaction cannot have an energy barrier that is too large. In other words, the mechanism cannot have any species (i.e. transition state) in it that is too high in energy (too unstable) to be formed at a given temperature. The Golden Rules of Chemistry are used to help predict the relative stabilities of proposed transition states. An obvious corollary to all of this is that reactions find the lowest energy opportunity (mechanism) to react out of all the possibilities, that is why reactions can usually be thought of as having a single mechanism. Thus, predicting mechanisms comes down to predicting the relative stabilities of potential transition states using the Golden Rules of Chemistry as a guide.* Great rule of thumb for most mechanisms: Each step involves a nucleophile attacking an electrophile, and when in doubt as to what to do, transfer a proton!

*The emphasis in this class is on qualitative thinking. Even though modern computers can usually calculate exact motives (thermodynamic driving forces) and exact transition state energies with a high degree of quantitative accuracy, that will not help you unless you have a suitable computer handy. The Golden Rules of Chemistry presented here are intended to give you the qualitative tools you need to think about chemistry without the aid of a computer calculation.