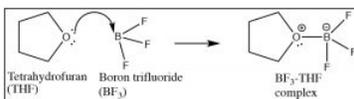
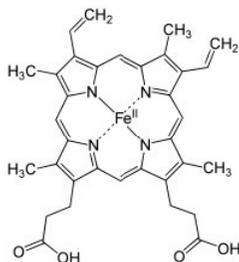


1.4: Lewis Acids and Bases, Electrophiles and Nucleophiles

As we have seen, any reaction in which a proton (H^+) is transferred from one molecule to another can be considered as a Lewis acid–base reaction, but now it is time to broaden the scope of Lewis acid–base reactions. The structural requirement for a Lewis base is essentially the same as those we discussed for a Brønsted base. That is, a Lewis base must have an accessible lone pair of electrons that can be donated into a bond with a Lewis acid. For example, many (but not all) nitrogen and oxygen containing molecules have such available lone electron pairs and so can be considered as Lewis bases.^[12] It is the Lewis acid that can take a number of different forms (and so, can be harder to recognize). A Lewis acid must be able to accept a pair of electrons. In practice this means a variety of substances (besides H^+) can act as Lewis acids: for example, any species with empty orbitals that are energetically accessible can be a Lewis acid. Common examples of this situation are compounds of Group III elements (specifically B and Al); these have only three valence electrons. Examples include BF_3 (↑) and AlCl_3 ,^[13] both of which have a partial positive charge on the central atom and an empty orbital that can accept electrons.

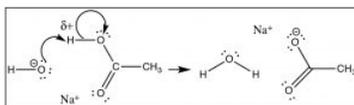


Other examples of Lewis acids are metal ions such as Fe^{2+} , Fe^{3+} , Cu^{2+} , and Mg^{2+} ; these, by definition, have empty orbitals. The same situation holds true for many transition metal salts, for example TiCl_4 and NiCl_2 .^[14] In biological systems, examples of Lewis acid–base complexes include the active site of the oxygen transport complex in hemoglobin (and myoglobin), which consists of an iron ion complexed with 4 nitrogens, which are part of a porphyrin ring. A similar iron-porphyrin complex is found associated with the cytochrome proteins that participate in the ATP synthesis reaction associated with in the electron transport chain of the mitochondria (\rightarrow). Chlorophyll, the green pigment that is part of the light capture system in algae and plants has a similar structure, except that the Lewis acid at the center of the complex is Mg^{2+} rather than Fe^{2+} . This has the interesting effect of making chlorophyll species appear to be green, rather than the red observed in blood. This is caused by the difference energy gaps between the molecular orbitals in an Fe complex as compared to a Mg complex with a porphyrin ring. We will discuss this effect in more detail later. As we will also see later, Lewis acids are important class of reagents in organic chemistry because they can interact with a wide range of bases.

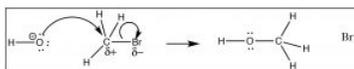


Electrophiles and Nucleophiles

The next logical step in expanding our ideas about Lewis acids and bases is to consider reactions that involve carbon. We will first consider reactions in which carbon acts like the Lewis acid, that is, it accepts a pair of electrons to form a new bond with a Lewis base. So, what situations would we make a carbon act in this way? We can rule out (for now) carbon compounds with an empty orbital (akin to boron). Why? Because all stable carbon compounds form 4 bonds and there are no low-lying empty orbitals that can be used to accept electrons.



But let us first look at the proton (H^+) transfer reaction as a model (\rightarrow). In this case the bond with the Lewis base (OH^-) is formed at the same time as the bond to the conjugate base (of the acid) is broken. We see that the δ^+ on the H means that the bond to the H is partially ionized. The H is “on the way” to becoming H^+ —a species that does have an empty and accessible orbital. The δ^+ on the H attracts the negative (or δ^-) charge on the base, and the reaction is initiated, forming a new bond between the O and the H, and at the same time breaking the old O – H bond.



We can imagine that a carbon compound with a δ^+ on the C might behave in a very similar way. In this molecule (H_3CBr) the C – Br bond is polarized so that there is a small positive charge on the C, which attracts the negatively charged hydroxide (\rightarrow). Formation of the O – C bond occurs with the simultaneous breaking of the C – Br bond.

Consider the analogies between these two reactions – the mechanisms of how and why the electrons move are similar. The only real difference between the two reactions is that in the first an H^+ is transferred from an C (on the carboxylic acid) to the OH^- , while in the second, a methyl group is transferred to the OH^- . Now for a change in nomenclature: when such a reaction involves a C atom (a carbon center) rather than call the electron deficient carbon a Lewis acid, we call it an *electrophile* (electron or negative charge loving). Similarly, the hydroxide ion (which acts as a Lewis base) is now called a *nucleophile* (positive charge loving). This change in terminology is not just to confuse students! In fact, there are subtle differences between Lewis acids and bases and electrophiles and nucleophiles that make the distinction between the two useful. In particular, while all Lewis bases are nucleophiles, as we will see, not all nucleophiles are bases.

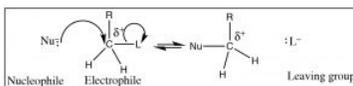
So now we have to ask ourselves, what factors make a particular C within a molecule an electrophile? How can we recognize a nucleophile? What criteria do we use to estimate the strength of a particular electrophile or an nucleophile? Can we ever get carbon to act as a nucleophile? If we can answer these questions, we can predict the outcome of a wide array of reactions.

What makes a particular carbon an electrophile?

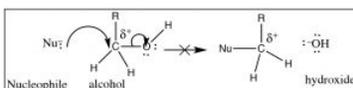
The simplest of organic compounds are hydrocarbons, and the simplest of hydrocarbons are known as alkanes. Alkanes typically have the formula $\text{C}_n\text{H}_{2n+2}$ (or if C_nH_{2n} if there is one ring of carbons, subtract 2H for every extra ring). All of the bonds within an alkane are sigma (single) bonds; they do not contain pi (double) bonds.^[15] In an alkane, each carbon is fully saturated, it makes four single bonds and (as noted above) there are no double or triple bonds. C – C bonds are of course, completely non-polar since the electrons are equally distributed between two identical atoms, however C – H bonds are also relatively non-polar since the electronegativities of C and H are quite similar. In practice this means that alkanes are limited in their reactivity. The most common reactions that an alkane can take part in are reactions with oxygen to produce CO_2 and H_2O . This reaction is highly exothermic, although there is a significant activation energy, so it requires an initial input of energy (typically a spark, a burning match) to start the reaction, but then the energy from the formation of the strong C = O and O – H bonds (which is why the reaction is exothermic) can be used to initiate more reaction. The actual reaction mechanism is complex; it proceeds via a series of highly reactive (unstable) free radicals (species with unpaired electrons)^[16]. While this reaction is obviously highly important—this is still how we generate much of the energy to run our cars and electrical power stations, from an organic chemistry perspective it is not very interesting in large part because it is more or less uncontrollable. That is, if you have enough oxygen once started the reaction generates CO_2 and H_2O , regardless of which hydrocarbon you begin with.^[17]

All this is to say that alkanes are not good candidates for the kinds of reactions we are considering, they have neither nucleophilic nor electrophilic carbons. So, let us turn our attention to carbon compounds with elements other than C and H and both sigma and pi bonds (this is, of course, the rest of organic chemistry). Here we find a very different situation: the range of reactions and the types of products can seem almost unlimited. While it is impossible (and certainly undesirable) to memorize every reaction and every potential product, it is possible to organize your understanding of chemical systems so that you can make plausible predictions as to which reactions may occur. By knowing reaction mechanisms, and when they are relevant, you can also predict which reactions will occur and therefore what products will form. As you might recognize, this is the same strategy we have used to consider acid–base reactions, which can be understood much more broadly than simple proton (H^+) transfer reactions. Thinking in an electrophile–nucleophile context provides an entrée into much of organic chemistry.

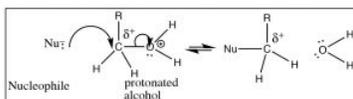
For reactions (other than reactions involving free radicals, like combustion) to occur, there is generally a “handle” within the substrate: a place where the electron density is not evenly distributed, a site at which reactants of opposite charge interact (and react). In the example we used previously, the electrophilic carbon has a δ^+ on it; this partial charge arose because the C was bonded to a more electronegative element. Such a partially positively charged C is attractive to any species with a negative (or partial negative) charge. Note that, for now, we are going to restrict the type of carbon atom that we are considering to either a **primary** (that is a carbon with only one alkyl group (denoted by R) and 2 hydrogens, CH_2R) or a **methyl** carbon (CH_3). As we will see things become more complicated when we start to add more alkyl groups around the site of attack—so we will come back to that later.



To identify such a partially positively charged C one would look for C's bonded to groups (atoms) that are more electronegative, that is, that will act to withdraw electrons from the carbon (denoted by L below). But since carbon cannot form more than four bonds as the nucleophile comes in and forms a bond, another bond must break. The electronegative atom (L) (or group of atoms), is known as the “leaving group” (oh, how dull) needs to be stable when it leaves with the extra pair of electrons. We can, in fact, predict the characteristics of a good leaving group. For example, the bond to the leaving group should be polarized, and since the leaving group takes the electron pair with it, the group should be stable with this extra pair of electrons on it (L^-). Another way of saying this is that the leaving group should be electronegative and breaking the $C-L$ bond should produce a weak base. Halide ions are examples of good leaving groups, and their order of reactivity is $I^- > Br^- > Cl^- > F^-$. This ranking mirrors their acid strength rankings—that is, HI is the strongest acid and HF is the weakest—which means F^- is the strongest base (and therefore least likely to leave)



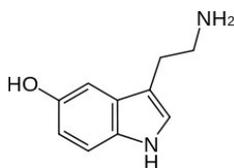
So, what about oxygen, in the form of an alcohol $O-H$ group, as a leaving group? (\rightarrow) It certainly fulfills the requirement that the $C-O$ bond be polarized, but if you follow the reaction through it would mean that the leaving group would be a hydroxide ion ($-OH$), a very strong base. Therefore, alcohols (ROH) are not likely to be attacked by a nucleophile.



There are ways, however, ways to make an alcohol reactive. For example, if we can carry out the reaction in an acidic solution, the alcohol will be protonated (at least some of the time), and therefore the leaving group will be a water molecule, a stable entity (\rightarrow).

What makes a good nucleophile?

As we have noted, a Lewis base is also a nucleophile, so the trends you have learned about the strengths of Lewis bases also hold for nucleophiles. So, for example, nucleophilicity decreases across a row in the periodic table so $NH_3 > H_2O > HF$ in the same way as base strength does (recall this is because the lone pair is more available on the N than on F). But since this is organic chemistry, we should have some organic groups dangling off the nucleophiles. So for example, instead of a hydroxide nucleophile, we could use an alkoxide nucleophile (for example, $CH_3CH_2O^- Na^+$ sodium ethoxide), or we could use amine nucleophiles like serotonin (the nitrogen in the NH_2 group here is more nucleophilic than the OH group, and the N in the ring). In addition, if we compare nucleophiles with the same nucleophilic atom, a negatively charged species is more nucleophilic than the uncharged form, so $OH^- > H_2O$, and $NH_2^- > NH_3$ (and by analogy any organic derivatives behave the same way).

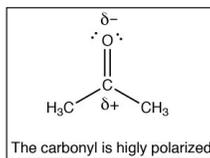


Besides the nucleophiles that are easily recognizable because they are bases, there is another class of nucleophiles that are somewhat different; they have a lone pair of electrons, but they are not particularly basic. The most common examples are the halide ions, which are weak bases and good leaving groups. So, the question arises: why are halide ions such good nucleophiles? The reason for this has to do with their polarizability (that is, the extent to which an electron cloud can get distorted) of the nucleophile. A very large anion-like iodide has a very polarizable electron cloud because the electrons extend much further out from the nucleus than, for example, the electron cloud in fluoride. This means that the electron cloud for iodide can begin partial bond formation to the carbon much earlier than the one for fluoride, and therefore iodide reacts much faster than fluoride.^[18] This logic allows us to explain why the nucleophilicity of halide ions increases as you go down a group: $I^- > Br^- > Cl^- > F^-$.

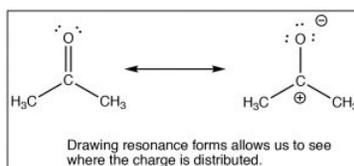
Although we will return to this reaction in greater detail later, let us take a look at the range of possible reactions that this generic scheme enables us to predict – with the caveat that we are considering simple carbon substrates. Reactions like this are called

nucleophilic substitutions, because the species that attacks the carbon is a nucleophile, and the overall effect of the reaction is that we have substituted the nucleophile for the leaving group. This particular example is called an S_N2 reaction which stands for Substitution, Nucleophilic, 2nd Order, and we will come back to discuss the reaction in much more detail later.

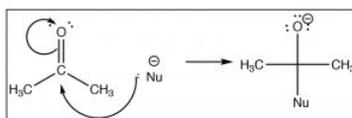
Another type of carbon nucleophile



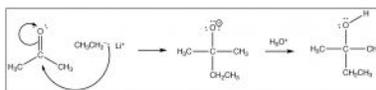
The S_N2 reaction is a mainstay of organic chemistry, by varying the substrate (carbon electrophile) the leaving group, and the nucleophile we can construct a huge array of different compounds. Another very important type of compound that has an electrophilic carbon (i.e. a carbon that is subject to nucleophilic attack) is one which contains a carbonyl group ($C=O$). The carbonyl group is highly polarized, with a large δ^+ on the carbon. This can be rationalized by the idea that there are two bonds to the electronegative oxygen and therefore the oxygen has even more tendency to pull electrons away from the carbon than a single bonded oxygen would. One way to visualize this is to draw resonance structures for the carbonyl group as shown, where the electrons from the double bond are now located on the O. We will come back to how to draw resonance forms in much more detail later.



Once we understand how compounds with carbonyl groups are polarized, we can predict (at least for the first step) how these compounds will react. For example, if we have a reasonably good nucleophile (here shown as Nu^-) we might predict that it would attack at the carbonyl carbon. The difference in this reaction and an S_N2 reaction is that there is no leaving group. Instead the electrons from one of the $C-O$ bonds move onto the oxygen as shown.



There are a number of ways that this reaction can continue, the most obvious of which is that if the reaction is in contact with a solvent that has acidic protons (e.g. water or an alcohol), the O^- can simply protonate in an acid base reaction. As we will see later, the course of the reaction also depends on what the nucleophile is. Here we will give the simplest example which is the reaction of a ketone (acetone) with a carbon nucleophile (CH_3CH_2Li , ethyl lithium). For now, we will not worry about how to make ethyl lithium, but rest assured it is possible! When the negatively charged carbon electrophile adds to the carbonyl we make a new carbon-carbon bond. This is followed by addition of water to protonate the oxygen, to produce an alcohol. The overall reaction is a **nucleophilic addition**.



Questions to Answer

Try your hand at predicting the outcomes for these reactions by drawing arrow pushing mechanisms.

- $CH_3CH_2I + NaOH \rightarrow$
- $CH_3Br + NaN_3 \rightarrow$
- $CH_3CH_2Cl + NH_2CH_3 \rightarrow$
- $CH_3OH + H^+ \rightarrow$

What nucleophile and electrophile would you react together to form these products?

- $\text{CH}_3\text{OH} + \text{Br}^-$
- $\text{CH}_3\text{CH}_2\text{NH}_3^+ + \text{Cl}^-$
- Construct a generalizable model for the $\text{S}_{\text{N}}2$ reaction and explain the role of the substrate (the carbon electrophile), the leaving group, and the nucleophile.

Construct a generalizable model for the nucleophilic addition reaction and explain the role of the substrate (the carbon electrophile), and the nucleophile. What functional groups would undergo a nucleophilic addition?

- What would make a carbon in a compound a nucleophile? How could you go about making a particular carbon nucleophilic?

This page titled [1.4: Lewis Acids and Bases, Electrophiles and Nucleophiles](#) is shared under a [CC BY-NC-SA 4.0](#) license and was authored, remixed, and/or curated by [Melanie M. Cooper & Michael W. Klymkowsky](#).