Sudha al. International Journal of Institutional & Industrial Research ISSN: 2456-1274, Vol. 3, Issue 1, Jan-April 2018, pp. 133-139

Studying Nucleophiles and Electrophiles

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Abstract: Organic chemistry students struggle with reaction mechanisms and the electron-pushing formalism (EPF) used by practicing organic chemists. Faculty have identified an understanding of nucleophiles and electrophiles as one conceptual prerequisite to mastery of the EPF, but little is known about organic chemistry students' knowledge of nucleophiles and electrophiles. This research explored the ideas held by second-semester organic chemistry students about nucleophiles and electrophiles, finding that these students prioritize structure over function, relying primarily on charges to define and identify such species, both in general and in the context of specific chemical reactions. Contrary to faculty who view knowledge of nucleophiles and electrophiles as prerequisite to learning mechanisms and EPF, students demonstrated that they needed to know the mechanism of a reaction before they were able to assess whether the reaction involved nucleophiles and electrophiles or not..

Keywords:

1. Introduction

A nucleophile is a "nucleus loving" species if we look at the word itself and translate its Greek roots. The nucleophiles are typically negatively charged or have at least one electron pair they can easily share to make a new chemical bond.

For instance, the CH_3O^- and CH_3NH_2 are a couple of examples of common nucleophiles. In the first case, we have a negative charge. Negatively charged species have an excess of electron density, which means they can easily share some of those excess electrons with electron-deficient species making a new bond. Important thing to remember her is that nucleophiles will always play a role of electron donors in chemical reaction.

What is an Electrophile?

So, what about the electrophiles? Well, they are the complete opposite. They are the "electron loving" species and they are typically either positively charged or have a partial positive charge ($\delta+$). In other words, electrophiles are electron-deficient species and are looking to get some more electrons from elsewhere. Electrophiles will often have electron-withdrawing groups (a group containing electronegative elements pulling the electron density towards themselves). Alternatively, electrophiles may also have polarizable π-bonds such as C=O or C=N.

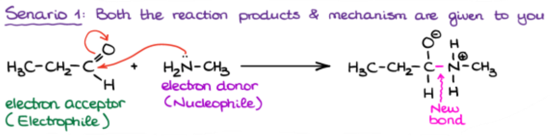
For example, in the picture at the beginning of this post we have a couple of electrophilic molecules. The first one has a very polar C=O bond which puts an extremely high partial positive charge ($\delta+$) on carbon. The second one is what we would call a carbocation—a species with 6 electrons around carbon. Since carbon does not have a complete octet around on the valence shell, it's rather unstable and electrophilic.

An important thing to remember about the electrophiles is that they are going to be the acceptors of the electrons in a reaction. By accepting some electrons from nucleophiles, electrophiles will "quench" their positive or partial positive charge making a more overall stable species.

How to Find Nucleophiles and Electrophiles in a Reaction

So, now when we know what the nucleophiles and electrophiles are, let's look at a few examples and try to find those in each reaction.

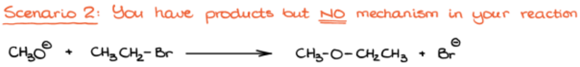
Example 1



In this first scenario we have a reaction with the products and the mechanism already given to us. This makes our task much easier. We simply need to follow the electron flow from one species to another. Thus, we can see that the molecule on the left (and aldehyde) is an overall electron acceptor, while the molecule on the right (an amine) is an electron donor. This way, we can classify the aldehyde in this reaction as an electrophile and the amine as a nucleophile. Notice, by the way, how nitrogen provided the electrons for the new bond in the product.

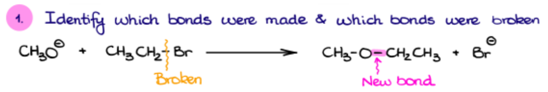
Example 2

Here's the second scenario.

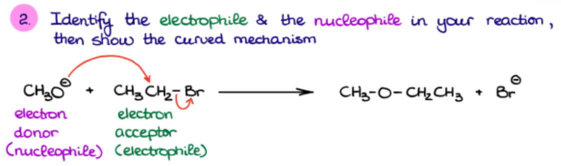


We have the reaction products, but we don't have the curved arrow mechanism to show us the electron flow from one species to another, so we'll have to figure that one for ourselves. So, the question is: how exactly are we going to do that?

Well, first, let's identify the bond made and bonds broken in this reaction. Based on the structure of our product here, we can see that we have made a new C-O bond. We also broke a C-Br bond since the Br⁻ is a free species on the product side.



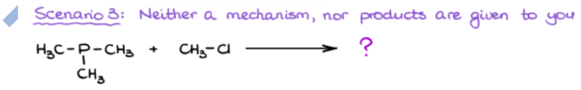
Next, we want to identify the electron flow in this reaction. In this case, it's reasonable to assume that the negatively charged species is going to be our nucleophile since it has an excess of electron density. Generally, if you have a reaction between a negatively charged species and a neutral one, the negative ion will be the nucleophile. Likewise, if you're dealing with a reaction between a neutral molecule and a positive ion (cation), then the neutral molecule will have a generally higher electron density and will act as a nucleophile. So, in this reaction, the negative oxygen is our nucleophilic piece, while the carbon attached to bromine is going to be an electrophile.



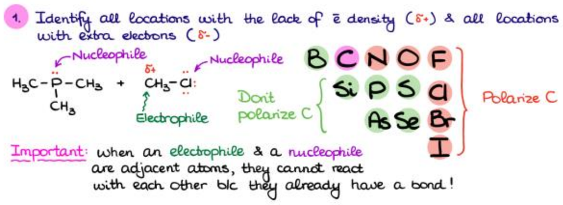
Remember, I knew that we are making the C-O bond, so since we've identified the O as a nucleophile, the corresponding C must be an electrophile. This is because you'll always move electrons from a nucleophile to an electrophile to make a chemical bond. I know I've already mentioned that before, but I just want to make sure that this fundamental principle sticks in.

Example 3

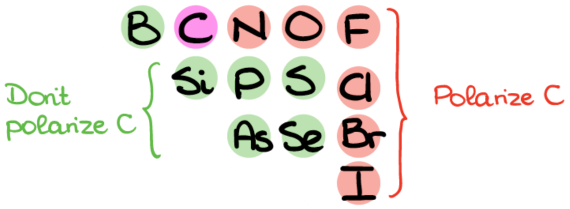
Alright, how about the third scenario now where we only have the reagents. We don't know the products or the mechanism, so we'll have to figure out everything for ourselves. This is, perhaps, the more common type of an exam question, so you're likely to see something like that on your exam or in your homework.



So, the first thing in figuring out what's going on in this reaction is to find all the places with high electron density (δ- or electron pairs) and places with low electron density (δ+ or + charges). Identifying the electron pairs is fairly easy: check the element's position in the periodic table, then see how many bonds it has, and add necessary electrons to complete the octet. Often, your instructor will already place all the electron pairs on the atoms in your molecules (especially early in the course).



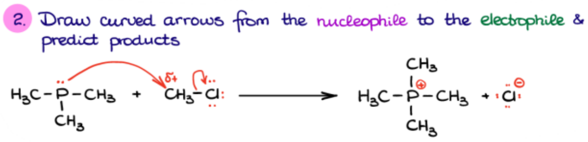
How are we going to deal with the partial charges though? Ideally, we'd need to look at the difference in electronegativity between carbon and other elements. Naturally, nobody expects you to remember the electronegativity values for all non-metals. There's however, a simple trick.



Here's the part of periodic table with the non-metals you may see in organic molecules. The ones that I highlighted in red will polarize carbon and add δ+ on carbon. The green elements, however, won't polarize carbon sufficiently, so those bonds won't really do much for the electron density on C in most cases. So, when C is bonded to N, O, F, Cl, Br, or I, we can go ahead and place a δ+ on that carbon. However, if your C is bonded to any other non-metal, leave it as is.

After you've identified the places in your molecules with electron surplus and places with electron deficiency, we can assign the potential electrophiles and nucleophiles. And here's something particularly important: when you have an adjacent nucleophile and an electrophile, you'll have to choose just one. Since our left molecule is only a nucleophile, the right molecule, thus, will be an electrophile.

And once we've identified our nucleophile and electrophile, we can propose an electron flow from one molecule to another using curved arrows.

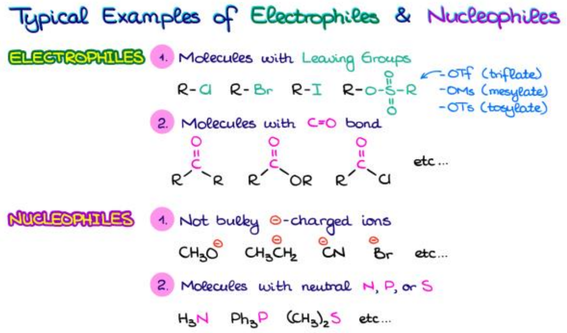


As nucleophile provides the electrons to the electrophile, we're going to show the arrow from phosphorus to the carbon. However, if the carbon atom accepts those electrons, it will have way too many electrons on the outer shell. So, to accept those electrons from the nucleophile it will have to break one of its bonds. As a rule of thumb, you always want to break a bond to what we call a better "leaving group." A leaving group is a species that is stable bearing a negative charge or becomes a neutral molecule upon dissociation. In this case we can either break a bond to Cl or to one of the H's. If we compare the H⁻ and Cl⁻ as the two potential leaving groups, the Cl⁻ is a much more stable ion. For the sake of time and staying on topic, we'll discuss the ion stability and why exactly the Cl⁻ is more stable than H⁻ in another post. So, to recap what I just said, to accept the electrons from P, we'll need to break the C-Cl bond.

Doing so, gives us the products in this reaction. And we're done! Remember, practice makes perfect. Make sure you go through enough practice problems identifying nucleophiles and electrophiles various examples using these steps. You want to be able to identify the nucleophiles and electrophiles automatically by just looking at your molecules. Normally, this will be the first step in most of the reaction mechanisms, so you'll be using this skill over and over again.

Typical Nucleophiles and Electrophiles

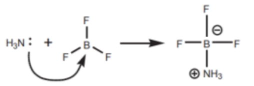
And while it is important to know the steps in identifying the nucleophiles and electrophiles in reactions, most of the time, you're going to see a lot of similarities from one molecule to the other. At the end of the day, organic chemistry is a science of patterns. And the whole ordeal with electrophiles and nucleophiles is not different.

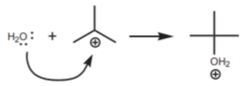


Here I have some examples of the typical electrophiles and nucleophiles you're going to see in your course. Your typical electrophiles will have good leaving groups like halides or sulfonate ester groups. They may also have polarizable C=O bonds like in aldehydes, ketones, or carboxylic acids derivatives. When it comes to nucleophiles, those are going to be either some smaller negatively charged species or molecules with N, P, or S atoms. While there are many examples of electrophiles and nucleophiles out there and it's just impossible to summarize them all in one table, these tend to pop up most often.

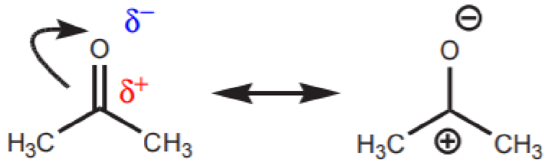
2. Reactions Between Nucleophiles and Electrophiles

As mentioned earlier, a good electrophile must be able to accommodate a new sigma bond between its electrophilic center and the nucleophile. When the electrophilic center is an atom with an incomplete octet, this is no problem.



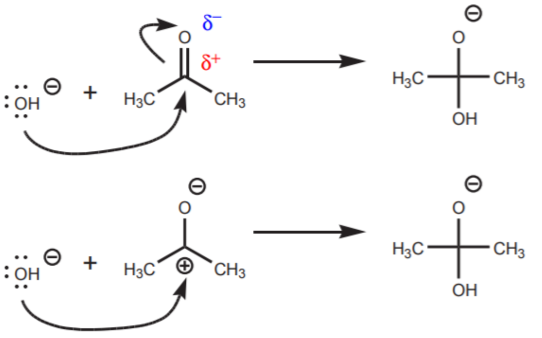


For electrophiles containing polarized pi bonds such as carbonyl groups, at least one resonance form shows an atom with an incomplete octet.



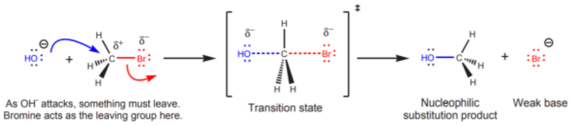
resonance forms of acetone

You can use either resonance structure to write the reaction between the nucleophile and the electrophile. The following are acceptable representations of a nucleophilic attack of hydroxide ion on acetone, but the second one makes it more apparent that the central carbon can take the extra bond.

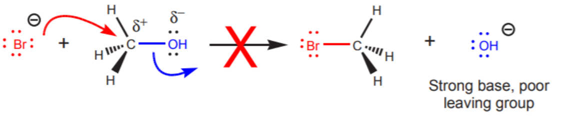


Two acceptable representations of the nucleophilic attack of hydroxide ion on acetone using different resonance structures.

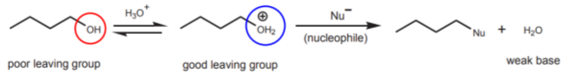
Sometimes the substrate has an electrophilic atom which is *sp3*-hybridized and already has a complete octet. In this case there are no pi electrons to displace as the new σ-bond forms. **The nucleophile must displace another group** as it bonds to the electrophile. The displaced group is called a **leaving group**. The leaving group can be displaced only if it leaves as a **weak base**, because weak bases are stable molecules that can take the electrons with them. In the following example, hydroxide ion is the attacking nucleophile. As it bonds to the *sp3* electrophilic carbon, it must displace another group. The leaving group in this case is the bromine atom. It is a **good leaving group** because it leaves as bromide ion, which is a weak base and can take the electrons with it.



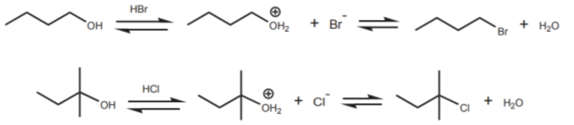
The reverse reaction, however, could not happen. Although bromide is a good nucleophile and methyl alcohol contains an electron deficient center (the carbon bonded to oxygen), the molecule does not contain a good leaving group. Hydroxide ion is a strong base, therefore it cannot be displaced by bromide.



Although the hydroxide ion is not a good leaving group, it is possible to do nucleophilic displacements on alcohols by protonating them with acid first. The protonated hydroxyl group is a potential water molecule, which is a weak base and therefore a good leaving group.



This approach has limitations. The most important is that the nucleophile must be a weak base, or it will prefer to react with the acidic protons. For all practical purposes, the only nucleophiles that can be used in this way are chloride and bromide ions. But this provides a good way to convert alcohols into primary, secondary, or tertiary chlorides and bromides.



Notice that in these case the reverse reaction **can** happen. Water is a good nucleophile and chloride and bromide are good leaving groups. One must isolate the product as it forms to keep it from reacting with water and go back to alcohol.

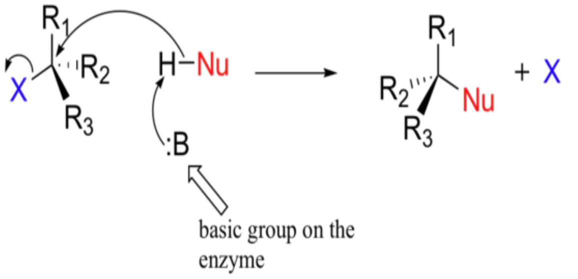
3. Nucleophile strength

Now, let's discuss some of the major factors that affect nucleophile strength or "nucleophilicity". First, you should realize that a strong nucleophile is a reactive or unstable nucleophile; one that is stable will be weak and unreactive. That means factors that stabilize a nucleophile will make it weaker.

Charge and nucleophilicity

The charge on a nucleophilic atom has a very large effect on its nucleophilicity. This is an idea that makes intuitive sense: a hydroxide ion is much more nucleophilic (and basic) than a water molecule, because the negatively charged oxygen on the hydroxide ion carries greater electron density than the oxygen atom of a neutral water molecule. In practical terms, this means that a hydroxide nucleophile will react in an S_N2 reaction with bromomethane much faster (about 10,000 times faster) than a water nucleophile.

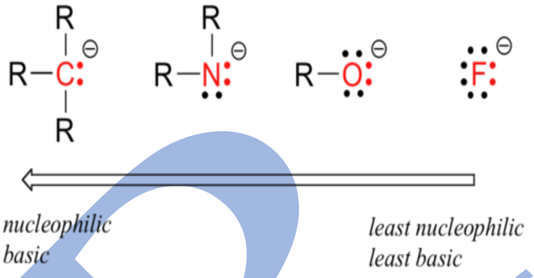
A neutral amine is nucleophilic, whereas a protonated ammonium cation is not. This is why enzymes which have evolved to catalyze nucleophilic reactions often have a basic amino acid side chain poised in position to accept a proton from the nucleophilic atom as the nucleophilic attack occurs.



Depending on the specific reaction being discussed, deprotonation of the nucleophile might occur before, during, or after the actual nucleophilic attack.

Periodic trends and solvent effects in nucleophilicity

There are predictable periodic trends in nucleophilicity. Moving horizontally across the second row of the table, the trend in nucleophilicity parallels the trend in basicity:

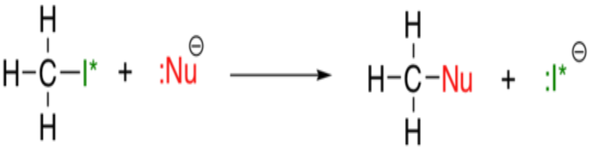


The reasoning behind the horizontal nucleophilicity trend is the same as the reasoning behind the basicity trend: more electronegative elements hold their electrons more tightly, and are less able to donate them to form a new bond.

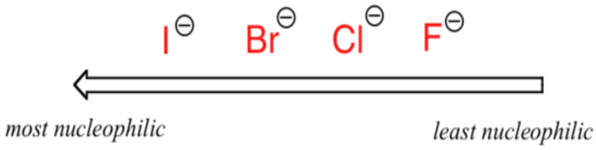
This horizontal trends also tells us that amines are more nucleophilic than alcohols, although both groups commonly act as nucleophiles in both laboratory and biochemical reactions.

Recall from **the previous section** that the basicity of atoms decreases as we move vertically down a column on the periodic table: $^-$SR (thiolate) ions are less basic than $^-$OR (alkoxide ions), for example, and bromide ion (Br^-) is less basic than chloride ion (Cl^-), which in turn is less basic than fluoride ion (F^-). Recall also that this trend can be explained by considering the increasing size of the 'electron cloud' around the larger ions: the electron density inherent in the negative charge is spread around a larger area, which tends to increase stability (and thus reduce basicity).

The vertical periodic trend for nucleophilicity is somewhat more complicated that that for basicity: depending on the solvent that the reaction is taking place in, the nucleophilicity trend can go in either direction. Let's take the simple example of the S_N2 reaction below:



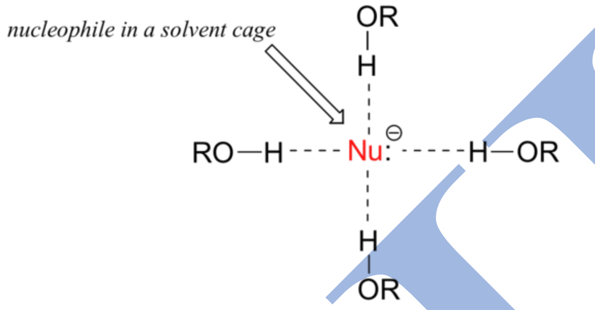
. . .where Nu^- is one of the halide ions: fluoride, chloride, bromide, or iodide, and the leaving group I* is a radioactive isotope of iodine (which allows us to distinguish the leaving group from the nucleophile in that case where both are iodide). If this reaction is occurring in a **protic solvent** (that is, a solvent that has a hydrogen bonded to an oxygen or nitrogen – water, methanol and ethanol are the most important examples), then the reaction will go fastest when iodide is the nucleophile, and slowest when fluoride is the nucleophile, reflecting the relative strength of the nucleophile.



Relative nucleophilicity in a protic solvent

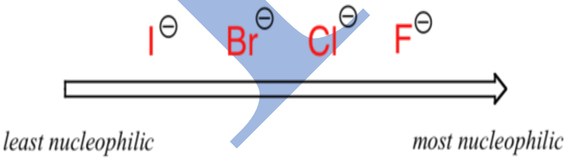
This of course, is opposite that of the vertical periodic trend for basicity, where iodide is the *least* basic (you may want to review the reasoning for this trend in **section 7.3A**). What is going on here? Shouldn't the stronger base, with its more reactive unbonded valence electrons, also be the stronger nucleophile?

As mentioned above, it all has to do with the solvent. Remember, we are talking now about the reaction running in a *protic* solvent like ethanol. Protic solvent molecules form very strong ion-dipole interactions with the negatively-charged nucleophile, essentially creating a 'solvent cage' around the nucleophile:



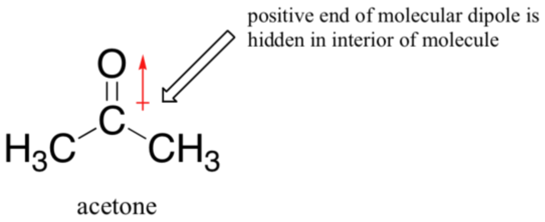
In order for the nucleophile to attack the electrophile, it must break free, at least in part, from its solvent cage. The lone pair electrons on the larger, less basic iodide ion interact less tightly with the protons on the protic solvent molecules – thus the iodide nucleophile is better able to break free from its solvent cage compared the smaller, more basic fluoride ion, whose lone pair electrons are bound more tightly to the protons of the cage.

The picture changes if we switch to a **polar aprotic solvent**, such as acetone, in which there is a molecular dipole but *no hydrogens bound to oxygen or nitrogen*. Now, fluoride is the best nucleophile, and iodide the weakest.



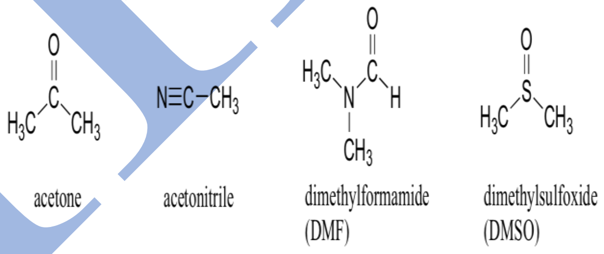
Relative nucleophilicity in a polar aprotic solvent

The reason for the reversal is that, with an aprotic solvent, the ion-dipole interactions between solvent and nucleophile are much weaker: the positive end of the solvent's dipole is hidden in the interior of the molecule, and thus it is shielded from the negative charge of the nucleophile.



A weaker solvent-nucleophile interaction means a weaker solvent cage for the nucleophile to break through, so the solvent effect is much less important, and the more basic fluoride ion is also the better nucleophile.

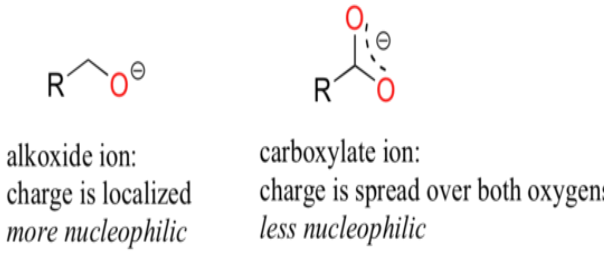
Why not use a completely nonpolar solvent, such as hexane, for this reaction, so that the solvent cage is eliminated completely? The answer to this is simple – the nucleophile needs to be in solution in order to react at an appreciable rate with the electrophile, and a solvent such as hexane will not solvate an a charged (or highly polar) nucleophile at all. That is why chemists use polar aprotic solvents for nucleophilic substitution reactions in the laboratory: they are polar enough to solvate the nucleophile, but not so polar as to lock it away in an impenetrable solvent cage. In addition to acetone, three other commonly used polar aprotic solvents are acetonitrile, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO).



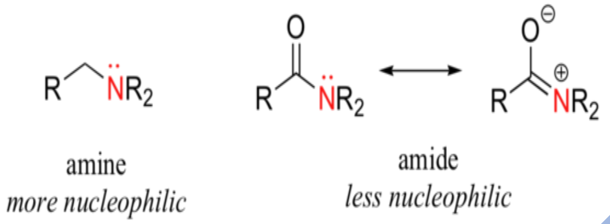
In biological chemistry, where the solvent is protic (water), the most important implication of the periodic trends in nucleophilicity is that thiols (RSH) are more powerful nucleophiles than alcohols (ROH). The thiol group in a **cysteine amino acid**, for example, is a powerful nucleophile and often acts as a nucleophile in enzymatic reactions, and of course negatively-charged thiolates (RS^-) are even more nucleophilic. This is not to say that the hydroxyl groups on serine, threonine, and tyrosine do not also act as nucleophiles – they do.

Resonance effects on nucleophilicity

Resonance also affects the strength of the nucleophile. The reasoning involved is the same as that which we used to understand resonance effects on basicity (see **section 6.4**). If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive – meaning less nucleophilic, and also less basic. An alkoxide ion, for example, is more nucleophilic and more basic than a carboxylate group (see figure), even though in both cases the nucleophilic atom is a negatively charged oxygen. In the alkoxide, the negative charge is localized on a single oxygen, while in the carboxylate the charge is delocalized over two oxygen atoms by resonance.

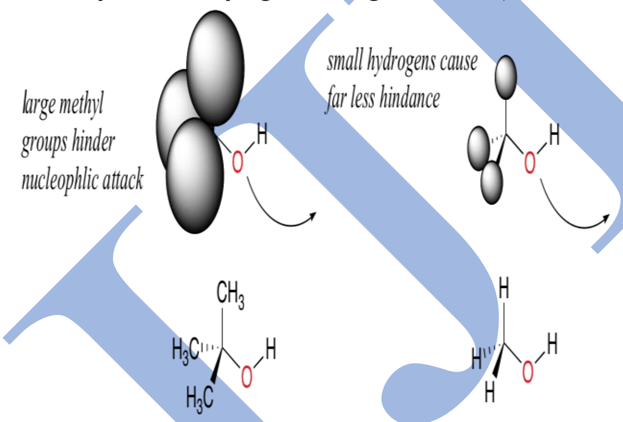


The nitrogen atom on an amide is less nucleophilic than the nitrogen of an amine, due to the resonance stabilization of the nitrogen lone pair provided by the amide carbonyl group.



Steric effects on nucleophile strength

Steric hindrance is an important consideration when evaluating nucleophilicity. For example, *tert*-butanol is less potent as a nucleophile than methanol. This is because the comparatively bulky methyl groups on the tertiary alcohol effectively block the route of attack by the nucleophilic oxygen, slowing the reaction down considerably (imagine trying to walk through a narrow doorway while carrying three large suitcases!).



It is not surprising that it is more common to observe serines acting as nucleophiles in enzymatic reactions compared to threonines – the former is a primary alcohol, while the latter is a secondary alcohol and therefore more hindered.

4. Conclusion

The reactions have been studied because the electrophile bears heteroatoms on the aromatic ring as substituent able to establish intramolecular HB that may be activated by solvation or by the nucleophile. On the other hand, the kinetic analyses shown that solvent effects are affected under a change of amine nature, showing that both nucleophiles in aqueous media are pH-dependent. However, aniline shows that the reaction rate coefficients are amplified when the acidity of the media is increased, while the inverse effect is observed with hydrazine. The kinetic study for aniline showed that is possible to postulate at first glance that prior to the nucleophilic attack, there is a protonation step that improve the reactivity of the substrate. On the other hand, the solvent effects open the possibility to establish an HB with the hydrazine moving the equilibria toward its zwitterionic form. This step would be complemented with an intramolecular HB formation that will operate as a perturbation that produces a dual response at the reaction centers by enhancing the electrophilicity of the substrate and the nucleophilicity of one of the nitrogen atom of the hydrazine molecule.

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