

Nucleophilicity versus Basicity:

An important concept that, sadly, most students never really understand in commanding fashion

Don't be
that
student!



I see it every year, every semester: students begin studying substitution and elimination reactions (S_N1 , S_N2 , E1, and E2) and are introduced to the world of determining whether a compound behaves as a base or a nucleophile. We need to evaluate whether a compound is considered a strong base, a weak base, or not a base at all; at the same time, we also consider whether that same compound is an excellent nucleophile, a fair nucleophile, or a lousy nucleophile. This dual assessment is important in our prediction of final product outcomes for reactions presented to us and is also important for answering concepts & reasoning problems.

However, most students never learn how to do this in a way that showcases actual understanding.

Sad Trombone



So instead of developing a repetitive, predictable way of understanding how to apply a repeating principle, the student is now trying to memorize charts and slides that say what things are characterized as, but the student doesn't know WHY anything is categorized as it is.

And in usual organic chemistry fashion, the student trying to approach things in this manner eventually gets burned on an exam the moment they see something they haven't seen the exact version of before because they lack the tools to diagnose and think critically.

It's like a young student memorizing all the answers on a multiplication table going up to 12x12, yet not actually understanding what multiplication is; you ask that student "now what is 13x10?" and they cannot answer.

Bases and nucleophiles both donate electrons, so they are both considered Lewis bases

At the most fundamental level, students are taught that bases and nucleophiles are both electron donors, so they are both classified as Lewis bases. This is a true statement. We are taught that bases bond to a hydrogen while nucleophiles bond to a carbon or any other atom that isn't hydrogen. *For purposes of simplicity within this document, we will assume all discussions of being a nucleophile refer to bonding to carbon since carbon is the atom most often acting as an electrophile in our course.*

So on the surface level, it seems like bases and nucleophiles are only differentiated by what they actually attack. However, this overlooks a MAJOR difference between these categories.

Basicity measures a thermodynamic quality while nucleophilicity measures a kinetic quality

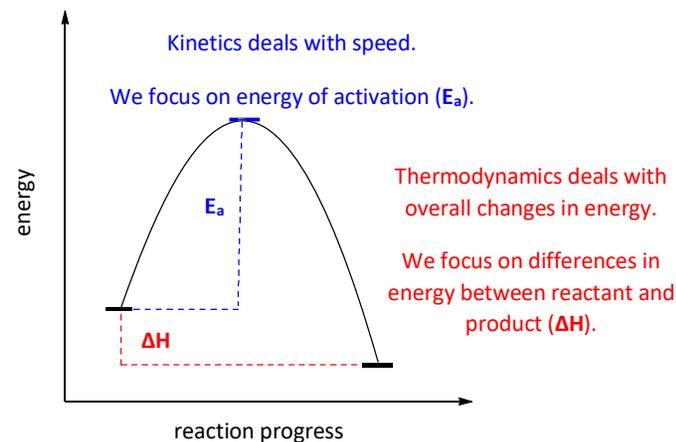
The MAJOR distinction behind how bases differ from nucleophiles is something that too many students are either never taught, or the importance of this is not emphasized. It is the following:



Basicity measures a thermodynamic quality while nucleophilicity measures a kinetic quality.

Of course, the statement above only has value if we understand what it means. Thermodynamics is always looking at differences in energies between starting compounds and final compounds (the ΔH); kinetics is looking at rates of reactivity, which means how quickly and easily something can happen (the E_a).

In other words, kinetics is looking at the top humps of energy diagrams while thermodynamics is looking at the lower platforms of energy diagrams.



What is basicity?

When saying basicity measures a thermodynamic quality, we're saying basicity is looking at the overall reactivity (or, we can say it is measuring the overall stability) of a lone pair because we are evaluating end-result reactivity. Thermodynamics measures end-result stability levels of reactants and products, it does not measure how easy or hard (how fast or slow) it is to get from reactant to product.

Basicity is (for the most part) a synonym for reactivity, and the metrics we use for assessing the reactivity are the same metrics used for assessing acidity. The job of a Bronsted-Lowry base is to provide a reactive lone pair that will get the job done of tearing off a hydrogen; the job of a Bronsted-Lowry acid is to leave behind a stable lone pair after a hydrogen is torn away.

Most organic chemistry students never develop a strong command of basicity because it is typically taught as "the opposite of acidity". Too often, basicity is treated as an afterthought to acidity, and students end up with a slipshod understanding that fails them when they are pressed for answers.



Organic chemistry tends to be “acidity-centric” – we focus on Bronsted-Lowry acid-base from the vantage point of acidity, and then basicity is often treated like an afterthought where we hear generic stuff like “the strongest base comes from the weakest acid”.

I’m not saying, “the strongest base comes from the weakest acid” (and vice-versa) is untrue, but history has shown me that students relying exclusively on that flimsy catchphrase usually struggle with questions about basicity. They lack a sensible approach for making wise decisions about where a compound will protonate because they don’t actually understand HOW to assess basicity and how to make reasonable decisions. And for sure, these students usually lack the understanding of how to define a compound as a strong base, as a weak base, or as non-basic.

Two Concepts: One for Simplifying How to Identify a Possible Base, and One for Categorizing Basicity

A more comprehensive analysis on basicity where the trends and metrics are discussed in depth can be found in my documents about acid-base principles; presented here are two simple concepts for helping us know if a compound can even act as a base and also for categorizing base strength.



1. **There are only 4 atoms we typically use as bases in this course: hydrogen anions (hydrides), carbons, nitrogens, and oxygens.** Note that all four of these are from rows 1 and 2 on the periodic table. This is a backdoor way of saying larger atoms (those in rows 3, 4, and 5) can be nucleophiles but are unlikely to be acting as bases.
2. **If you understand and know pK_a values and you know how to figure out the pK_{aH} value of a compound, you have a powerful tool for ranking the strength of basicity.** That term pK_{aH} is another way of saying “the pK_a of the conjugate acid”. In other words, it means we add an imaginary hydrogen to whatever it is we are evaluating for basicity, and then we determine the pK_a value now that the imaginary hydrogen has been added.

For example, if we are evaluating the basicity of water (H_2O) and wanted to get the pK_{aH} value, we would add an imaginary hydrogen to it and now have H_3O^+ (the hydronium ion). Since the pK_a of H_3O^+ is -1.7 (which is often rounded to -2 for simplicity), we say the pK_{aH} of water is -1.7 (or -2). Using the information below, we could now classify water as a weak base.

Basicity is on a spectrum, and knowing the pK_{aH} value allows us to categorize basicity by using these guidelines (*note the designations of values lower than 0 and higher than 14; I point this out to correlate it to the pH scale of 0-14 we all learned in general chemistry*):

Weak bases have pK_{aH} values less than 0.

A base typically has a pK_{aH} values greater than 7

Strong bases have pK_{aH} values greater than 14.

What is nucleophilicity?

Nucleophilicity is NOT a measurement of lone pair reactivity. That's basicity. While lone pair reactivity is a factor, nucleophilicity measures how quickly and readily (by readily, I mean able) a lone pair of electrons can get to a carbon. Nucleophilicity is measuring a rate of reaction, so it is about kinetics.

Allow me to paint the picture of concepts we can call "arm length" and "fist strength"

One way to imagine nucleophilicity is to think of it as the idea of punching someone in the face where we measure how easily (how fast) the fist gets there, not how hard the fist smashes the face. In this analogy, your fist is the electrons being "donated", and the face being punched is the electrophilic carbon being attacked.

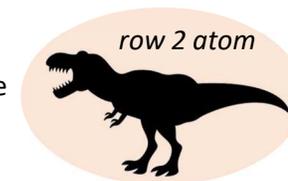


Because your hand is at the end of your arm, you have a physical limitation that in order to connect to the face, the face cannot be further away from you than the length of your arm. This is where "arm length" is going to matter.

NOTE: This idea of arm length has a direct correlation to the organic chemistry term/concept of "polarizability".

How hard the fist smashes the face – let's call this "fist strength" – can be thought of as how reactive the electrons are. This IS where basicity comes into play because the measurement of reactivity IS the measurement of the basicity. **Fist strength = basicity.**

In this analogy, the length of your arm ("arm length") is defined by which atomic shell of electrons is doing the donating. Row two atoms like carbon, nitrogen, oxygen, and fluorine have their outermost shell of electrons very close to their nucleus; these atoms have very short arms (think Tyrannosaurus Rex). If we go to the extreme for an arm length of a nucleophilic atom we will be working with, we can say row five iodine has the longest arm because iodine's outermost shell is the fifth shell.



Arm length matters a lot, because regardless of how strong and powerful your "fists of fury" are, it doesn't mean anything if your fist can't reach the face it is trying to punch. With nucleophilicity, we are not measuring strength of punch; we are measuring the speed of the fist reaching the face. We're going to see that the power of the punch delivered by the iodine anion (iodine anion's fist strength) is a lot wimpier and softer than, say, the power of the oxygen anion's punch (oxygen anion's fist strength); however, the iodine often has a huge "competitive advantage" for reaching the face just because of differences in arm length. Once you thoroughly understand this stuff and how these two metrics of arm length and fist strength factor into a reaction, it will then make sense as to how something can be classified as a sensational nucleophile while being a lousy base (and also the corollary, how something can be a horrible nucleophile while being a strong base).

Key metrics to consider for nucleophilicity

Similar to how we have metrics for evaluating acidity and basicity, we also have metrics for evaluating nucleophilicity. And just as we do with acids and bases, we have to understand how to do a multi-variable evaluation in order to rank nucleophiles as excellent, moderate, and poor. We might use other words for categorizing nucleophiles (for example, good/fair/poor), but I would encourage students to NOT use terms like strong and weak for categorizing nucleophiles since those terms make more sense for describing basicity.

The fact that we will see that iodine is usually classified as one of our best nucleophiles while it is simultaneously one of the weakest bases should make it clear why a little part of me dies each time I hear someone call iodine a “strong nucleophile”. Iodine can be called an excellent nucleophile because of how capable it is of using its long arm to get its electron fist to the carbon, but it’s not like that iodine wimpy fist is breaking any jaws when it connects. Hence, the reason I shudder when I hear iodine called a “strong nucleophile”.



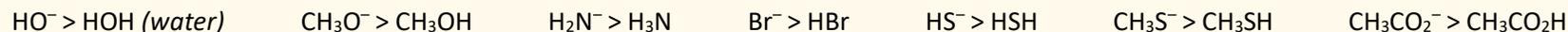
The key metrics we use when evaluating nucleophilicity are:

- Lone Pair Reactivity (the power of the punch)
- Sterics (obstacles that make it harder to reach the target)
- Arm Length
- Solvent Effects

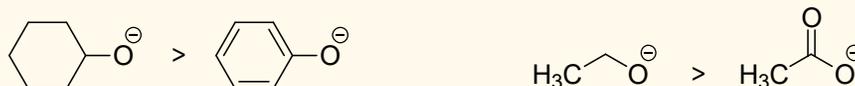
Lone Pair Reactivity (the power of the punch)

The metric of lone pair reactivity is perhaps the easiest to describe because it is the exact same metric as how we measure basicity. That discussion can be found elsewhere (as mentioned earlier in this document, you could look over my documents on basicity), so I’d like to quickly outline two points that affect lone pair reactivity with regards to thinking about nucleophilicity.

1. For nucleophiles with the same attacking atom, the anionic form is more nucleophilic than the neutral form.



2. If we’re evaluating two oxygen anions, a resonance-delocalized version of the oxygen anion will be less nucleophilic than a non-delocalized oxygen anion. *Note: we can use this apples-to-apples comparison for any two of the same atoms as long as both are anions or both are neutral.*

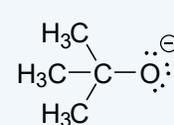


Sterics (obstacles that make it harder to reach the target)

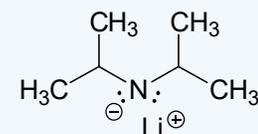
Steric obstructions will make things more difficult for any nucleophile to land its electrons onto a carbon electrophile. It is important to understand that sterics refers to actual substituents that are attached directly to the nucleophilic atom or attached to the atom adjacent to the nucleophilic site.

Do not confuse sterics with size of atom! For example, we do NOT want to say a row 5 atom like iodine is relatively gigantic when compared to a row 2 atom like oxygen, so that means iodine is sterically bulky. No. Iodine is big because of electron shells – that is NOT the same as being big and sterically encumbered because you have three alkyl groups attached next door to your attack site.

Organic chemistry's two most famous strong bulky bases: *tert*-butoxide and LDA. Sterics make these unlikely to act as nucleophiles.



tert-butoxide
 $pK_{aH} \approx 18$



LDA
(lithium diisopropyl amide)
 $pK_{aH} \approx 38-40$

If we take a break from the analogy of the first punching the face, we can also consider the nucleophilic site to be like a snarling dog's vicious teeth!! Let's go with the idea that the dog wants to chomp down on its target; as shown below, the exact same biting dog becomes unable to bite its target if a lot of obstruction is surrounding its bark-hole.

no steric issues

This dog has no problem clamping its teeth onto the desired target because the mouth is not obstructed. We could picture this as an example of no steric issues around the reactive site.



steric obstruction shutting down (or at least, greatly diminishing) nucleophilicity

Now let's say we put one of these cones around the dog's head (and let's pretend the dog in this picture is the exact same dog to the left). Now there is all kinds of obstruction and barriers around the mouth making it impossible – or, at best, extremely difficult – for the dog to sic its teeth onto the target. **This is how sterics hurts nucleophilicity.**



Organic chemistry's two most famous "bulk-masters" (The Incredible Bulks!) when it comes to obstruction around the reactive site of the electron pair are *tert*-butoxide and LDA (shown at the top of the page). Because of the size of the substituents surrounding the row 2 atoms (and remember, row 2 atoms have short arms like a Tyrannosaurus Rex), the substituents make it super difficult for the oxygen or nitrogen to successfully get close enough to the carbon to punch it in the face. For this reason, we classify these as poor nucleophiles even though they are both strong bases*.

*Recall that pK_{aH} values over 14 tell us we have a strong base, and the pK_{aH} of *tert*-butoxide is about 18 while the pK_{aH} of LDA is somewhere between 38-40.

Arm Length

We've already laid the groundwork for this concept, now let's apply it. Since a big part of organic chemistry is analyzing and understanding trends (*as they say, "the trend is your friend"*), let's apply the understanding of arm length by comparing the fluorine anion as a nucleophile versus the iodine anion since these are two atoms from the same column of the periodic table.

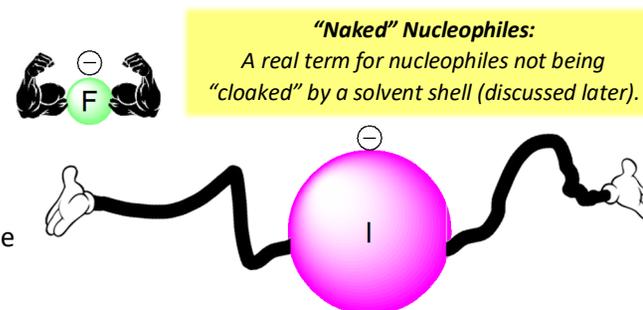
If we use our metrics of basicity to examine the reactivity of these two, we see that fluorine is technically more reactive than iodine because fluorine's pK_{aH} (which is HF) is 3.2 while iodine's pK_{aH} (which is HI) is about -10. Remember: a higher pK_{aH} means more reactive. This tells us that iodine is a very weak base because the pK_{aH} is (a lot) less than 0 while fluorine is still in the spectrum of not all that basic (because the pK_{aH} is less than 7 but greater than 0), but also not considered a weak base (because the pK_{aH} is greater than 0).

Because of these reactivity properties, think of fluorine as being able to "throw a stronger punch" if it were using its electron hands as fists. In other words, the metric we use for measuring basicity strength can be used to think of how powerful the punch would feel when it is delivered. Being more basic means being more reactive, and this translates to throwing the more powerful punch; being punched in the face by fluorine would hurt more than being punched in the face by iodine.

In order for fluorine, with its short but powerful arms, to punch you in the face, the fluorine would need to get up real close to you to deliver the blow. Contrast this to iodine: iodine's punch would be much wimpier because it is actually a lot weaker than fluorine (by weaker, I'm referring to our basicity metric that we discussed), but because of the unbelievably long arm the iodine has, the iodine can very easily reach your face from afar.

The longer arm is often a key factor in being able to reach the face even when it isn't delivering the most powerful punch. However, arm length primarily matters when we have factors making it more difficult for the short-armed nucleophiles to get up real close to the face. If there is nothing preventing the nucleophiles of any arm length from approaching the carbon face and punching it, then long arm length is no longer a key advantage for reaching the face. In this situation of having no limitations for getting up close to the face and getting there without resistance, we would say base strength (lone pair reactivity) is – most likely – the primary factor for determining the rate of the attack.

We already discussed sterics as a limiting factor for getting close to the face, but there is one more important factor to consider. It is the fourth metric, the metric usually LEAST understood by students – solvent effect.



Solvent Effects

“Shouldn’t the most reactive lone pair also make for the fastest acting nucleophile?” I think this is a totally reasonable question to ask, and the answer would be YES if we didn’t have steric issues (already discussed) and solvent effect issues.

Most schools put little emphasis on this concept of solvent effect. However, if it has ever been discussed in your class, you will need to have a working understanding of how solvent can impact reaction rates and nucleophilicity. Also, questions about this concept are fair game on tests like the MCAT. I will keep my entire discussion focused on how the nucleophile is impacted; I will skip the concomitant discussion of solvent effects on leaving groups.

Sooooo . . . IF the solvent is NOT having an effect on the nucleophile, then we ARE pretty much following the rules of basicity where we say a stronger base makes for a better nucleophile (but still, we factor in steric considerations). However, if the solvent is having an effect, we have a twist.

The solvent typically has an effect when it is a hydrogen bond donor (H-bond donor)

Envision the solvent as the “swimming pool” that everything exists in. It is everywhere in the mix! In fact, it makes sense to assume that there are more molecules of the solvent than there are of anything else in the mix. **Hydrogen bond donors (H-bond donors) are any compounds containing a hydrogen bonded directly to oxygen, nitrogen, or fluorine;** the most common examples we work with as solvents are water, alcohols, and carboxylic acids. Be aware that we do many reactions where the solvent also plays the role of the nucleophile.

Think of nucleophiles as electron donors on a quest to pacify their hunger for something positively (or partially positively) charged. We expect the nucleophile to be hunting for an electrophilic carbon. However, if the omnipresent solvent is an H-bond donor, multiple molecules of the solvent will have an H-bond interaction with our nucleophilic site causing a reduction in the nucleophile’s overall hunger. The attraction of the partial positive charge of the H-bond donating hydrogens to the negatively (or partially negatively) charged nucleophilic atom will be like a swarm of killer bees descending upon a victim. The result of this interaction is to reduce the overall charge magnitude of negative charge character on the nucleophilic site, so nucleophilicity is diminished.



Killer bees are like polar protic solvent molecules swarming a nucleophile with their H-bond donating hydrogens.

This H-bonding effect results in an across-the-board decrease in overall nucleophilicity of all nucleophiles, but it is not a linear, proportional decrease. Atoms forming stronger hydrogen bonds with the solvent are affected more severely. However, the major impact that the solvent makes on the overall ordering/ranking of nucleophilicity is discussed on the next page, and this feature (solvation of nucleophile) is what too many students cannot explain.

Solvation of the Nucleophile

We used the image of the killer bees swarming the unlucky target and reducing the nucleophilicity because of hydrogen bonding, but this is not the only consequence of the swarming. Think of the bees as creating an added “shell” around the body of whatever is being surrounded, and the severity of this shell mirrors how strongly the hydrogen bonds adhere. We call this “solvation”; solvation is the making of a solvent shell through H-bonding.

If we go back to the imagery of short arms and long arms, we recall that the short arm nucleophiles – those in row two – need to be able to get very close to the face in order to punch it. Adding the barrier of a solvent shell around one of these short arm nucleophiles is going to make it more difficult for the arms to reach the target. On top of this, the row two atoms like oxygen, nitrogen, and fluorine are among our most electronegative atoms, so these will form the strongest H-bonds with a polar protic solvent. Think of that like attracting more killer bees!

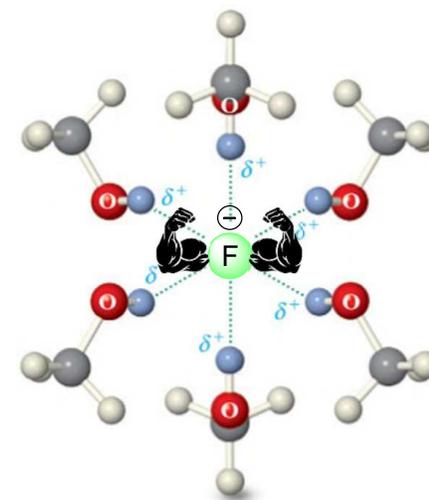
If the solvent is an H-bond donor, it will likely hurt the nucleophilicity of a small atom (the atoms with short arms) way more than it hurts the nucleophilicity of a larger atom (the atoms with longer arms). **In other words, the smallest nucleophilic atoms tend to be hurt the most by H-bonding with the solvent.**

Because the smallest atom is hampered the most, we observe a trend that for atoms from the same vertical column, nucleophilicity decreases severely as we go up the vertical column and get smaller because the solvent is having more and more of a damaging effect on the smallest, most electronegative atoms.

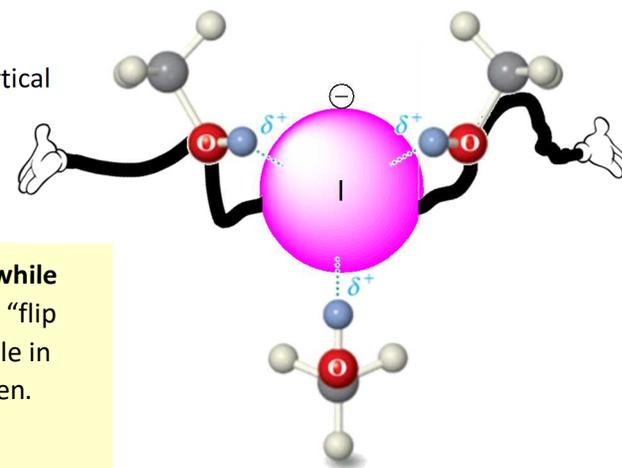
This means in polar protic solvents, the smallest atom in the column becomes the worst nucleophile while the largest atom in the column becomes the best nucleophile. A polar protic solvent causes fluorine to “flip the script” and become the worst nucleophile in the column while iodine behaves as the best nucleophile in the column. The concept holds true for column 6 also: sulfur becomes the better nucleophile over oxygen.

ATTENTION!

In most situations where you are asked about the nucleophilicity trend for atoms in a vertical column on the periodic table, you should assume the solvent is a polar protic solvent *UNLESS the problem specifically tells you otherwise.* Teachers (and the MCAT) will ask questions about this trend, so you definitely want to understand this.



Hey fluorine, not such a TOUGH GUY anymore now that you're surrounded by a solvent shell of methanols! Am I right? Think of it as if the methanols are “holding down” the fluorine.



Iodine is not very obstructed by the solvent shell. Weaker H-bonds with iodine means the shell is weaker (and composed of fewer molecules of methanol) than the one around fluorine, and the long arms of iodine makes it possible for iodine to still punch carbon.