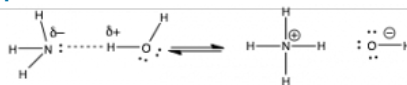
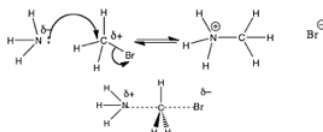


7.4: Nucleophiles and Electrophiles



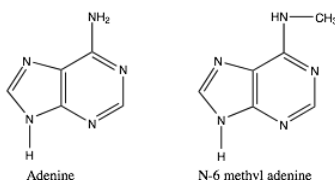
The Lewis acid–base model is more inclusive than the Brønsted–Lowry model, but we often use the Brønsted–Lowry model because it is easier to follow the proton transfer from one molecule (the acid) to another (the base). In aqueous solutions, the Brønsted–Lowry theory also allows us to use the concept of pH to quantify acidity (as we will see shortly). Both the Lewis and Brønsted–Lowry models capture the overarching principle that most chemical reactions are initiated by an electrostatic interaction between a positively-charged portion of a molecule to a negatively-charged portion of the same, or another, molecule.^[10] As we will see in the next chapter, molecules must collide with one another in order for reactions to occur between them—they do not react at a distance. When the reacting particles collide, there has to be some continuous pathway through which bonds rearrange and produce products. The first step in this pathway often involves Coulombic (electrostatic) interactions between specific regions of the molecules involved. Of course, whether or not such Coulombic interactions are stable depends upon the kinetic energies of the colliding molecules and exactly how they collide with one another. Catalysts often speed reactions by controlling how molecules collide with or interact with one another. This figure (\rightarrow) shows the reaction of H_2O and NH_3 , in which the positive end of one molecule interacts with the negative end of the other. If we consider this as a Lewis acid–base reaction, the same principle holds true. It turns out that we can profitably consider a wide range of reactions using the principle of Coulombic attraction. For example, ammonia (and other nitrogen compounds) can react with carbon-containing molecules if the appropriate conditions are met.



In the figure (\rightarrow) the nitrogen is behaving as a Lewis base, donating its lone pair of electrons to the carbon. However, it is a little more difficult to see the analogy with a Lewis acid at the carbon site. What we can see is that there is an electronegative, polarizing group (in this case a bromine atom) bonded to the carbon. The presence of a bromine atom polarizes the $\text{C}-\text{Br}$ bond, giving the carbon a slight positive charge. This makes the carbon susceptible to attack by the lone pair of the nitrogen. Since carbon does not have an empty orbital to accept the lone pair into, and carbon can never form more than four bonds, something has to give. What gives is the $\text{C}-\text{Br}$ bond, which breaks, and the bromine carries away the electrons from the bond with it, producing a bromide ion, Br^- .

This type of reaction, while is essentially a Lewis acid-base reactions, is usually described using yet another set of terms, probably because these reactions usually belong in the realm of organic chemistry, which was once considered a distinct chemical discipline. For organic chemists, the species with the lone pair (in this case the NH_3) is called the nucleophile (literally, “nucleus-loving”) and is attracted to a positive center of charge. The species that accepts the lone pair of electrons, in this case the CH_3Br molecule, is called the electrophile (literally, “electron-loving”). The species that is released from its bond with the carbon is called the leaving group. Leaving groups must be relatively electronegative (as in the case of Br) or stable when associated with an extra pair of electrons. So, good leaving groups are weak bases. Conjugate bases of strong acids are excellent leaving groups because they are stable.

If we analyze the reaction in the figure further, we see the nitrogen nucleophile approaching the carbon electrophile: as the bond forms between the C and N , the bond breaks between the C and the Br . The bond-breaking and bond-making occur simultaneously. Given what we know about water and aqueous solutions, we might even be so brave as to predict that the product ($^+\text{NH}_3\text{CH}_3 \text{Br}^-$) will rapidly lose a proton in aqueous solution to produce CH_3-NH_2 and H_3O^+ . This kind of reaction is often referred to as a methylation (a $-\text{CH}_3$ group is a methyl group). The product is an N-methylated derivative of ammonia.



As we have already seen, nitrogen compounds are common in biological systems. We now see how these compounds can also act as nucleophiles, and how methylation of nitrogen is a fairly common occurrence with a range of effects. For example, methylation and demethylation of the nitrogenous bases in DNA adenine and cytosine is used to influence gene expression and mark newly synthesized DNA strands from older, preexisting DNA strands. At the same time, various methylated sequences (such as CpG) are much less stable than the unmethylated form, and so more likely to mutate.^[11] Methylation reactions are quite common in other biological reactions as well. For example, epinephrine (also known as adrenaline, the fight-or-flight hormone) is synthesized in the body by methylation of the related molecule norepinephrine.

Considering Acid–Base Reactions: pH

It is almost certain that you have heard the term pH, it is another of those scientific terms that have made it into everyday life, yet its scientific meaning is not entirely obvious. For example: why does an increase in pH correspond to a decrease in “acidity” and why does pH change with temperature?^[12] How do we make sense of pH and use that information to better understand chemical systems?



The key idea underlying pH is that water undergoes an acid–base reaction with itself. Recall that this reaction involves the transfer of a proton from one water molecule to another. The proton is never free or “alone”; it is always bonded to an oxygen within another water molecule. Another important point about pH is that the reaction is readily reversible. Under normal conditions (room temperature), the reaction proceeds in both directions. If we look at the reaction, it makes intuitive sense that the reactants on the right (H_3O^+ and ^-OH) can react together to give two H_2O molecules simply because of the interaction of the positive and negative charges, and we have already seen that the forward reaction does occur. This is one of the first examples we have seen of a reaction that goes both forward and backward in the same system. As we will see, all reactions are reversible at the nanoscale (we will consider the implications of this fact in detail in the next chapter). In any sample of pure water, there are three different molecular species: water molecules (H_2O), hydronium ions (H_3O^+), and hydroxide ions (^-OH), as shown in the figure (\rightarrow). These three species are constantly interacting with each other through the formation of relatively weak H-bonding interactions, which are constantly forming and breaking. Remember, in liquid water, the water molecules are constantly in motion and colliding with one another. Some of these collisions have enough energy to break the covalent H—O bond in water or in the hydronium ion. The result is the transfer of H^+ and the formation of a new bond with either another water molecule (to form hydronium ion) or with a hydroxide ion (to form a water molecule). To get a feeling for how dynamic this process is, it is estimated that the average lifetime of an individual hydronium ion is on the order of 1 to 2 picoseconds (1×10^{-12} ps), an unimaginably short period of time. In pure water, at 25°C , the average concentration of hydronium ions is 1×10^{-7} mol/L. We use square brackets to indicate concentration, so we write this as:

$$[\text{H}_3\text{O}^+] = 1 \times 10^{-7} \text{ M} \quad (7.4.1)$$

Note that this is a very, very, very small fraction of the total water molecules, given that the concentration of water molecules $[\text{H}_2\text{O}]$ in pure water is $\sim 55.4 \text{ M}$.

In pure water, every time a hydronium ion is produced, a hydroxide ion must also be formed. Therefore, in pure water at 25°C , the following equation must be true:

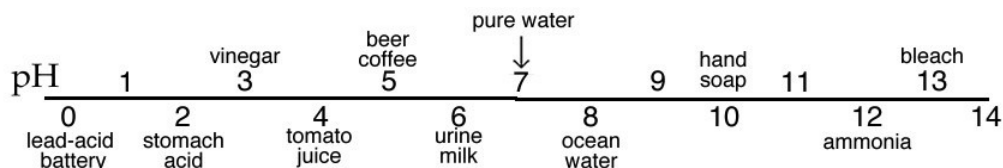
$$[\text{H}_3\text{O}^+] = [^-\text{OH}] = 1 \times 10^{-7} \text{ M} \quad (7.4.2)$$

It must also be true that the product of the hydronium and hydroxide ion concentrations, $[\text{H}_3\text{O}^+][^-\text{OH}]$, is a constant at a particular temperature. This constant is a property of water. At 25°C , this constant is 1×10^{-14} and given the symbol K_w , 25°C . So why do we care? Because when we add an acid or a base to a solution of water at 25°C , the product of $[\text{H}_3\text{O}^+][^-\text{OH}]$ remains the same: 1×10^{-14} . We can use this fact to better understand the behavior of acids, bases, and aqueous solutions.

For many people, dealing with negative exponents does not come naturally. Their implications and manipulations can be difficult. Believe it or not, the pH scale^[13] was designed to make dealing with exponents easier, but it does require that you understand how to work with logarithms (perhaps an equally difficult task). pH is defined as: $\text{pH} = -\log[\text{H}_3\text{O}^+]$.^[14]

In pure water (at 25°C), where the $[\text{H}_3\text{O}^+] = 1 \times 10^{-7} \text{ M}$, $\text{pH} = 7$ (pH has no units). A solution with a higher concentration of hydronium ions than pure water is acidic, and a solution with a higher concentration of hydroxyl ions is basic. This leads to the

counter-intuitive fact that as acidity $[\text{H}_3\text{O}^+]$ goes up, pH goes down. See for yourself: calculate the pH of a solution with a $[\text{H}_3\text{O}^+]$ of 1×10^{-2} M (pH = 2), and of 1×10^{-9} M (pH = 9). Moreover, because it is logarithmic, a one unit change in pH corresponds to a change in $[\text{H}_3\text{O}^+]$ of a factor of 10.



The pH scale is commonly thought of as spanning units 1–14, but in fact many of the strongest acid solutions have $\text{pH} < 1$. Representations of the pH scale often use colors to indicate the change in pH. This convention is used because there are many compounds that change color depending on the $[\text{H}_3\text{O}^+]$ of the solution in which they are dissolved. For example, litmus^[15] is red when dissolved in an acidic ($\text{pH} < 7$) solution, and blue when dissolved in a basic ($\text{pH} > 7$) solution. Perhaps you have noticed that when you add lemon juice (acidic) to tea, the color changes. Do not get confused: solutions of acids and bases do not intrinsically differ in terms of color. The color change depends on the nature of molecules dissolved in the solution. Think about how changes in pH might affect molecular structure and, by extension, the interactions between molecules and light (a topic that is more extensively treated in the spectroscopy supplement).

It is important to note that at 37°C the value of K_w is different: $[\text{H}_3\text{O}^+][\text{OH}^-] = 2.5 \times 10^{-14}$ and therefore the $\text{pH} = 6.8$. Weirdly, this does not mean that the solution is acidic, since $[\text{H}_3\text{O}^+] = [\text{OH}^-]$. The effect is small, but it is significant; it means that a pH of 7 does not always mean that a solution is neutral (it depends on the temperature). This is particularly important when the concept of pH is applied to physiological systems, since the body is usually not at room temperature.

Now let us consider what happens when we add a Brønsted–Lowry acid to water.



For example, if we prepare a solution of 0.10 M HCl (where we dissolve 0.10 mol HCl(g) in enough water to make 1 liter of solution), the reaction that results (see figure) contains more hydronium ion (H_3O^+). Now if we measure^[16] the pH of the solution of 0.10 M HCl, we find that it is 1.0 pH units. If we convert back to concentration units from pH (if $\text{pH} = -\log[\text{H}_3\text{O}^+]$, then $[\text{H}_3\text{O}^+] = 10^{-\text{pH}}$), we find that the concentration of H_3O^+ in 0.10 M HCl is 0.10 M. This makes sense, in light of our previous discussion about how HCl completely dissociates into Cl^- and H^+ (associated with water molecules).

	$[\text{HCl}]$ M	$[\text{H}_2\text{O}]$ M	$[\text{H}_3\text{O}^+]$ M	$[\text{OH}^-]$ M	$[\text{Cl}^-]$ M
Before reaction	0.10	~ 55.5	1.0×10^{-7}	1.0×10^{-7}	0
After Reaction	~ 0	~ 55.4	$\sim 1.0 \times 10^{-1}$	1.0×10^{-13}	1.0×10^{-1}

This table gives the concentrations of all the species present both before and after the reaction. There are several things to notice about this table. Because the measured $\text{pH} = 1$ and we added 0.1 M (or 10^{-1} M) HCl, it is reasonable to assume that all the HCl dissociated and that the vast majority of the H_3O^+ came from the HCl. We can ignore the H_3O^+ present initially in the water. Why? Because it was six orders of magnitude ($0.0000001(10^{-7})$) smaller than the H^+ derived from the HCl (10^{-1}). It is rare to see pH measurements with more than three significant figures, so the H_3O^+ originally present in the water does not have a significant effect on the measured pH value. Although we are not generally concerned about the amount of hydroxide, it is worth noting that $[\text{H}_3\text{O}^+][\text{OH}^-]$ remains a constant (K_w), and therefore when $[\text{H}_3\text{O}^+]$ increases the $[\text{OH}^-]$ decreases.

Although a number of substances dissolve in water, not all ionize, and not all substances that ionize alter the pH. For example, NaCl ionizes completely when dissolved in water, yet the pH of this solution is still 7. The Na^+ and Cl^- ions do not affect the pH at all. However, if we make a 1 M solution of ammonium chloride (NH_4Cl), we find that its pH is around 5. Although it might not be completely obvious why the pH of this solution is 5 and the pH of a 1 M NaCl solution is 7, once you know that it is (and given what you know about pH), you can determine the concentrations of H_3O^+ , NH_4^+ , NH_3 , OH^- and Cl^- present (see Chapter 8). The question is: Why are NH_4Cl and HCl so different? (We consider this point in Chapter 9.)

Making Sense of Vinegar and Other Acids

Now let us consider another common acid: acetic acid. If wine is left open to the air, it will often begin to taste sour because the ethanol in wine reacts with oxygen in the air and forms acetic acid. Acetic acid belongs to a family of organic compounds known as carboxylic acids. It has one acidic proton attached to the oxygen.



If we measure the pH of a 0.10 – M solution of acetic acid, we find that it is about 2.8. The obvious question is why the pH of a 0.10 – M solution of acetic acid is different from the pH of a 0.10 – M solution of hydrochloric acid? The explanation lies in the fact that acetic acid (CH_3COOH) does not dissociate completely into CH_3CO_2^- and H_3O^+ when it is dissolved in water. A pH of 2.8 indicates that the $[\text{H}_3\text{O}^+] = 10^{-2.8}$. This number can be converted into 1.6×10^{-3} M. About 1.6% of the added acetic acid is ionized (a form known as acetate ion, CH_3COO^-). The rest is in the protonated form (acetic acid, CH_3COOH). The specific molecules that are ionized changes all the time; protons are constantly transferring from one oxygen to another. You can think of this process in another way: it is the system that has a pH, not individual molecules. If we look at a single molecule of acetic acid in the solution, we find that it is ionized 1.6% of the time. This may seem a weird way to think about the system, but remember, many biological systems (such as bacteria) are quite small, with a volume of only a few cubic microns or micrometers (a cubic micron is a cube 10^{-6} m on a side) and may contain a rather small number of any one type of molecule. Thus, rather than thinking about the bulk behavior of these molecules, which are relatively few, it can be more useful to think of the behavior of individual molecules averaged over time. Again, in an aqueous solution of acetic acid molecules, most of the molecules ($\sim 98.4\%$) are in the un-ionized form, so any particular molecule is un-ionized $\sim 98.4\%$ percent of the time.

We can measure the pH of the solutions of many acids of known concentrations, and from these measurements make estimates of the strength of the acid. Strong acids, such as nitric, sulfuric, and hydrochloric are all totally ionized in solution. Weaker acids, such as organic acids, ionize to a much lesser extent. However, given the low naturally occurring concentrations of hydronium and hydroxide ions in pure water, even weak acids can significantly alter the pH of an aqueous solution. The same behavior applies to weak bases.

Conversely, if weak acids or bases are dissolved in solutions of different pH, the amount of ionization of the group may be significantly changed. For example, as we will see in chapters 8 and 9, if we added a weak acid to a solution that was basic (for example at pH9), we would find that much more of the acid will ionize. Many biological molecules contain parts (called functional groups) that behave as weak acids or weak bases. Therefore, the pH of the solution in which these molecules find themselves influences the extent to which these functional groups are ionized. Whether a part of a large molecule is ionized or not can dramatically influence a biomolecule's behavior, structure, and interactions with other molecules. Thus, changes in pH can have dramatic effects on a biological system. For example, if the pH of your blood changes by ± 0.3 pH units, you are likely to die. Biological systems spend much of the energy they use maintaining a constant pH (typically around 7.35 – 7.45).^[17] In addition, the pH within your cells is tightly regulated and can influence cellular behavior.^[18]

? Questions

Questions to Answer

- How would you calculate the molarity of pure water?
- What percentage of water molecules are ionized at 25°C ?
- If the pH of a solution (at 25°C) is 2.0, what is the $[\text{H}_3\text{O}^+]$? What is the $[\text{OH}^-]$?
- If the pH of a solution (at 37°C) is 2.0, what is the $[\text{H}_3\text{O}^+]$? What is the $[\text{OH}^-]$?
- What would be the pH of a 0.01 – M solution of HCl at 25°C ?
- If the pH of a 0.1 – M solution of NH_4Cl is 5.1, what is the $[\text{H}_3\text{O}^+]$?
- Draw out a molecular level picture of what you imagine solutions of NaCl and NH_4Cl look like.
- Why does acetic acid only have one acidic proton (after all, it does have a total of four protons)?
- Why is acetic acid more acidic than ethanol? What is it about the structure of acetic acid that makes it more acidic?

Questions for Later

- Why do you think we keep specifying the temperature in our discussions of reactions?

Questions to Ponder

- Carboxylic acid groups, -COOH , are common in large biomolecules. What would be the effect of raising or lowering the pH on carboxylate side chains?
- What effect do you think that might have on the properties of the biomolecule (solubility, interactions with other molecules, etc.)?
- Amino groups are also common. What would be the effect of raising or lowering the pH on an amino group?

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