An understanding of the various types of noncovalent forces allows us to explain, on a molecular level, many observable physical properties of organic compounds. In this section, we will concentrate on solubility (especially solubility in water), melting point, and boiling point.

**Solubility**

Virtually all of the organic chemistry that you will see in this course takes place in the solution phase. In the organic laboratory, reactions are often run in nonpolar or slightly polar solvents such as toluene (methylbenzene), dichloromethane, or diethylether. In recent years, much effort has been made to adapt reaction conditions to allow for the use of ‘greener’ (in other words, more environmentally friendly) solvents such as water or ethanol, which are polar and capable of hydrogen bonding. In biochemical reactions the solvent is of course water, but the ‘microenvironment’ inside an enzyme’s active site - where the actual chemistry is going on - can range from very polar to very non-polar, depending on which amino acid residues are present.

You probably remember the ‘like dissolves like’ rule you learned in general chemistry, and even before you took any chemistry at all, you probably observed at some point in your life that oil does not mix with water. Let’s revisit this rule, and put our knowledge of covalent and noncovalent bonding to work.

When considering the solubility of an organic compound in a given solvent, the most important question to ask ourselves is: how strong are the noncovalent interactions between the compound and the solvent molecules? If the solvent is polar, like water, then a smaller hydrocarbon component and/or more charged, hydrogen bonding, and other polar groups will tend to increase the solubility. If the solvent is non-polar, like hexane, then the exact opposite is true.

Imagine that you have a flask filled with water, and a selection of substances that you will test to see how well they dissolve in the water. The first substance is table salt, or sodium chloride. As you would almost certainly predict, especially if you’ve ever inadvertently taken a mouthful of water while swimming in the ocean, this ionic compound dissolves readily in water. Why? Because water, as a very polar molecule, is able to form many ion-dipole interactions with both the sodium cation and the chloride anion, the energy from which is more than enough to make up for energy required to break up the ion-ion interactions in the salt crystal.

The end result, then, is that in place of sodium chloride crystals, we have individual sodium cations and chloride anions surrounded by water molecules – the salt is now in solution. Charged species as a rule dissolve readily in water: in other words, they are very hydrophilic (water-loving).

Now, we’ll try a compound called biphenyl, which, like sodium chloride, is a colorless crystalline substance.
Biphenyl does not dissolve at all in water. Why is this? Because it is a very non-polar molecule, with only carbon-carbon and carbon-hydrogen bonds. It is able to bond to itself very well through nonpolar van der Waals interactions, but it is not able to form significant attractive interactions with very polar solvent molecules like water. Thus, the energetic cost of breaking up the biphenyl-to-biphenyl interactions in the solid is high, and very little is gained in terms of new biphenyl-water interactions. Water is a terrible solvent for nonpolar hydrocarbon molecules: they are very hydrophobic (water-fearing).

Next, you try a series of increasingly large alcohol compounds, starting with methanol (1 carbon) and ending with octanol (8 carbons).

![Methanol, Butanol, Octanol](image)

You find that the smaller alcohols - methanol, ethanol, and propanol - dissolve easily in water, at any water/alcohol ratio that you try. This is because the water is able to form hydrogen bonds with the hydroxyl group in these molecules, and the combined energy of formation of these water-alcohol hydrogen bonds is more than enough to make up for the energy that is lost when the alcohol-alcohol (and water-water) hydrogen bonds are broken up. When you try butanol, however, you begin to notice that, as you add more and more to the water, it starts to form a layer on top of the water. Butanol is only sparingly soluble in water.

The longer-chain alcohols - pentanol, hexanol, heptanol, and octanol - are increasingly non-soluble in water. What is happening here? Clearly, the same favorable water-alcohol hydrogen bonds are still possible with these larger alcohols. The difference, of course, is that the larger alcohols have larger nonpolar, hydrophobic regions in addition to their hydrophilic hydroxyl group. At about four or five carbons, the influence of the hydrophobic part of the molecule begins to overcome that of the hydrophilic part, and water solubility is lost.

Now, try dissolving glucose in the water – even though it has six carbons just like hexanol, it also has five hydrogen-bonding, hydrophilic hydroxyl groups in addition to a sixth oxygen that is capable of being a hydrogen bond acceptor.
We have tipped the scales to the hydrophilic side, and we find that glucose is quite soluble in water.

We saw that ethanol was very water-soluble (if it were not, drinking beer or vodka would be rather inconvenient!) How about dimethyl ether, which is a constitutional isomer of ethanol but with an ether rather than an alcohol functional group? We find that diethyl ether is much less soluble in water. Is it capable of forming hydrogen bonds with water? Yes, in fact, it is—the ether oxygen can act as a hydrogen-bond acceptor. The difference between the ether group and the alcohol group, however, is that the alcohol group is both a hydrogen bond donor and acceptor.

The result is that the alcohol is able to form more energetically favorable interactions with the solvent compared to the ether, and the alcohol is therefore much more soluble.

Here is another easy experiment that can be done (with proper supervision) in an organic laboratory. Try dissolving benzoic acid crystals in room temperature water— you'll find that it is not soluble. As we will learn when we study acid-base chemistry in a later chapter, carboxylic acids such as benzoic acid are relatively weak acids, and thus exist mostly in the acidic (protonated) form when added to pure water.

Acetic acid (vinegar) is quite soluble. This is easy to explain using the small alcohol vs large alcohol argument: the
hydrogen-bonding, hydrophilic effect of the carboxylic acid group is powerful enough to overcome the hydrophobic effect of a single hydrophobic methyl group on acetic acid, but not the larger hydrophobic effect of the 6-carbon benzene group on benzoic acid.

Now, try slowly adding some aqueous sodium hydroxide to the flask containing undissolved benzoic acid. As the solvent becomes more and more basic, the benzoic acid begins to dissolve, until it is completely in solution. What is happening here is that the benzoic acid is being converted to its conjugate base, benzoate. The neutral carboxylic acid group was not hydrophilic enough to make up for the hydrophobic benzene ring, but the carboxylate group, with its full negative charge, is much more hydrophilic. Now, the balance is tipped in favor of water solubility, as the powerfully hydrophilic anion part of the molecule drags the hydrophobic part into solution. Remember, charged species usually dissolve readily in water. If you want to precipitate the benzoic acid back out of solution, you can simply add enough hydrochloric acid to neutralize the solution and reprotonate the carboxylate.

If you are taking a lab component of your organic chemistry course, you will probably do at least one experiment in which you will use this phenomenon to physically separate an organic acid like benzoic acid from a hydrocarbon compound like biphenyl.

Similar arguments can be made to rationalize the solubility of different organic compounds in nonpolar or slightly polar solvents. In general, the greater the content of charged and polar groups in a molecule, the less soluble it tends to be in solvents such as hexane. The ionic and very hydrophilic sodium chloride, for example, is not at all soluble in hexane solvent, while the hydrophobic biphenyl is very soluble in hexane.

Because we are concentrating on the biologically relevant chemistry, let's take a minute to review how to evaluate a compound's solubility in water, the biological solvent:

Summary of factors contributing to water solubility

A: How many carbons? All else being equal, more carbons means more of a non-polar/hydrophobic character, and thus lower solubility in water.

B: How many, and what kind of hydrophilic groups? The more, the greater the water solubility. In order of importance:

1. Anything with a charged group (eg. ammonium, carboxylate, phosphate) is almost certainly water soluble, unless has a very large nonpolar group, in which case it will most likely be soluble in the form of micelles, like a soap or detergent (see next section).

2. Any functional group that can donate a hydrogen bond to water (eg. alcohols, amines) will significantly contribute to water solubility.

3. Any functional group that can only accept a hydrogen bond from water (eg. ketones, aldehydes, ethers) will have a somewhat smaller but still significant effect on water solubility.
4. Other groups that contribute to polarity (e.g., alkyl halides, thiols sulfides) will make a small contribution to water solubility.

**Exercise 2.30:** Rank each set of three compounds below according to their solubility in water (most soluble to least):

- a) [Chemical structures]
- b) [Chemical structures]
- c) [Chemical structures]

**Exercise 2.31:** Vitamins can be classified as water-soluble or fat-soluble (consider fat to be a very non-polar 'solvent'). Decide on a classification for each of the vitamins shown below.

- Vitamin C (ascorbic acid)
- Vitamin B1 (thiamine)
- Vitamin A (retinol)

**Exercise 2.32:** Both aniline and phenol are mostly insoluble in pure water. Predict the solubility of these two compounds in 10% aqueous hydrochloric acid, and explain your reasoning.

- aniline
- phenol

**Exercise 2.33:** Would you predict methanol or 2-propanol (rubbing alcohol) to be a better solvent for cyclohexanone? Why?

Because water is the biological solvent, most biological organic molecules, in order to maintain water-solubility, contain one or more charged functional groups: most often phosphate, ammonium or carboxylate.
Note that the charge on these functional groups depends on their protonation state: spermidine, for example, could be
drawn with three (uncharged) amine groups rather than the charged ammonium groups as shown, and orotate could be
drawn in the uncharged carboxylic acid form. It turns out, however, that these three functional groups are all charged
when in a buffer at the physiological pH of approximately 7.3. We will have much more to say about the acid-base aspects
of these groups in chapter x.

Carbohydrates often lack charged groups, but as we discussed in our 'thought experiment' with glucose, they are quite
water-soluble due to the presence of multiple hydroxyl groups, which can hydrogen bond with water.

Some biomolecules, in contrast, contain distinctly hydrophobic components. Membrane lipids are amphipathic,
meaning that they contain both hydrophobic and hydrophilic components. Cell membranes are composed of membrane
lipids arranged in a 'bilayer', with the hydrophobic 'tails' pointing inward and the hydrophilic 'heads' forming the inner and
outer surfaces, both of which are in contact with water.

The nonpolar interior of the lipid bilayer is able to 'dissolve' hydrophobic biomolecules such as cholesterol. Polar and
charged biomolecules, on the other hand, are not able to cross the membrane, because they are repelled by the
hydrophobic environment of the bilayer's interior. The transport of water-soluble molecules across a membrane can be
accomplished in a controlled and specific manner by special transmembrane transport proteins, a fascinating topic that
you will learn more about if you take a class in biochemistry.

A similar principle is the basis for the action of soaps and detergents. Soaps are composed of fatty acids such as
stearate obtained through basic hydrolysis of triacylglycerols in fats and oils.
Like membrane lipids, fatty acids are amphipathic. In aqueous solution, the fatty acid molecules in soaps will spontaneously form **micelles**, a spherical structure that allows the hydrophobic tails to avoid contact with water and simultaneously form favorable van der Waals contacts with each other.

Because the outside of the micelle is charged, the structure as a whole is soluble in water. Micelles will form spontaneously around small particles of oil that normally would not dissolve in water, and will carry the particle away with it into solution. We will learn more about the chemistry of soap-making in chapter 11.

Synthetic detergents are non-natural amphipathic molecules that work by the same principle as that described for soaps.

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**Boiling point and melting point**

The observable melting and boiling points of different organic molecules provides an additional illustration of the effects of noncovalent interactions. The overarching principle involved is simple: *how well can a compound bind to itself?* Melting and boiling are processes in which noncovalent interactions between identical molecules in a pure sample are disrupted. The stronger the noncovalent interactions, the more energy that is required, in the form of heat, to break them apart.

As a rule, larger molecules have higher boiling (and melting) points. Consider the boiling points of increasingly larger hydrocarbons. More carbons and hydrogens means a greater surface area possible for van der Waals interaction, and thus higher boiling points. Below zero degrees centigrade (and at atmospheric pressure) butane is a liquid, because the butane molecules are held together by Van der Waals forces. Above zero degrees, however, the molecules gain enough
thermal energy to break apart and enter the gas phase. Octane, in contrast, remains in the liquid phase all the way up to 128°C, due to the increased van der Waals interactions made possible by the larger surface area of the individual molecules.

The strength of intermolecular hydrogen bonding and dipole-dipole interactions is reflected in higher boiling points. Look at the trend for hexane (van der Waals interactions only), 3-hexanone (dipole-dipole interactions), and 3-hexanol (hydrogen bonding). In all three molecules, van der Waals interactions are significant. The polar ketone group allows 3-hexanone to form intermolecular dipole-dipole interactions, in addition to the weaker van der Waals interactions. 3-hexanol, because of its hydroxyl group, is able to form intermolecular hydrogen bonds, which are stronger yet.

Of particular interest to biologists (and pretty much anything else that is alive on the planet) is the effect of hydrogen bonding in water. Because it is able to form tight networks of intermolecular hydrogen bonds, water remains in the liquid phase at temperatures up to 100°C despite its small size. The world would obviously be a very different place if water boiled at 30°C.

Exercise 2.34:

Based on their structures, rank phenol, benzene, benzaldehyde, and benzoic acid in terms of lowest to highest boiling point. Explain your reasoning.

Answer

By thinking about noncovalent intermolecular interactions, we can also predict relative melting points. All of the same principles apply: stronger intermolecular interactions result in a higher melting point. Ionic compounds, as expected, usually have very high melting points due to the strength of ion-ion interactions. Just like with boiling points, the presence of polar and hydrogen-bonding groups on organic compounds generally leads to higher melting points. The size of a molecule influences its melting point as well as its boiling point, again due to increased van der Waals interactions between molecules.
What is different about melting point trends, that we don't see with boiling point or solubility trends, is the importance of a molecule's shape and its ability of pack tightly together. Picture yourself trying to make a stable pile of baseballs in the floor. It just doesn't work, because spheres don't pack together well - there is very little area of contact between each ball. It is very easy, though, to make a stack of flat objects like books.

The same concept applies to how well molecules pack together in a solid. The flat shape of aromatic compounds allows them to pack efficiently, and thus aromatics tend to have higher melting points compared to non-planar hydrocarbons with similar molecular weights. Comparing the melting points of benzene and toluene, you can see that the extra methyl group on toluene disrupts the molecule's ability to pack tightly, thus decreasing the cumulative strength of intermolecular van der Waals forces and lowering the melting point.

![Molecular structures of benzene and toluene](image)

Note also that the boiling point for toluene is significantly above the boiling point of benzene! The key factor for the boiling point trend in this case is size (toluene has one more carbon), whereas for the melting point trend, shape plays a much more important role. This makes sense when you consider that melting involves 'unpacking' the molecules from their ordered array, whereas boiling involves simply separating them from their already loose (liquid) association with each other.

**Exercise 2.35**: Which would you expect to have the higher melting point, 2,3-dimethylbutane or hexane? Explain.

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**Physical properties of lipids and proteins**

**Lipids**

An interesting biological example of the relationship between molecular structure and melting point is provided by the observable physical difference between animal fats like butter or lard, which are solid at room temperature, and vegetable oils, which are liquid. Recall that fats and oils are triacylglycerols: fatty acids linked to a glycerol backbone. In vegetable oils, the fatty acid components are unsaturated, meaning that they contain one or more double bonds. Solid animal fat, in contrast, contains mainly saturated hydrocarbon chains, with no double bonds.
The double bond(s) in vegetable oils cause those hydrocarbon chains to be more rigid, and 'bent' at an angle (remember that rotation is restricted around double bonds), with the result that they don't pack together as closely, and thus can be broken apart (melted) more readily.

In a related context, the fluidity of a cell membrane (essentially, the melting point) is determined to a large extent by the length and degree of unsaturation of the fatty acid 'tails' on the membrane lipids. Longer and more saturated fatty acids make the membrane less fluid (they are able maximize van der Waals interactions), while shorter and more unsaturated fatty acids cause the membrane to be more fluid.

**Proteins**

The very same noncovalent forces we have just learned about are also integral to protein structure: when a protein folds up, it does so in such a way that very specific non-covalent interactions form between amino acid residues on different regions of the chain, each one becoming part of the 'molecular glue' that holds the chain together in its correctly folded shape. Hydrogen bonds and charge-charge interactions are particularly important in this respect. In general, the interior of a folded protein is relatively hydrophobic, while the outside surface, which of course is in constant contact with water, is very hydrophilic - many charged side chains such as aspartate, glutamate, lysine, and arginine point out of the surface of a protein structure.

Most of the proteins of 'mesophilic' organisms (those who thrive in intermediate temperatures, including humans) will denature - come unfolded - at high temperatures, as the heat disrupts the specific noncovalent interactions holding the protein chain together. Unfolded proteins usually are not water soluble because the more hydrophobic interior regions are no longer hidden from the solvent, so denaturing is accompanied by precipitation. Obviously, an unfolded protein also loses its functionality.

In the last few decades, we have become aware that a wide variety of microbes naturally inhabit extremely hot environments such as the boiling water of hot springs in Yellowstone National Park, or the base of a deep-sea thermal
vent. How do the proteins of these 'thermophiles' hold up to the heat? There is nothing extraordinary about these proteins that makes them so resistant to heat, other than the fact that they have evolved so that they simply have more molecular 'glue' holding them together - in particular, more ionic interactions between oppositely charged residues. In just one of many examples, the three-dimensional structure of an enzyme from *Pyrococcus horikoshii*, a microbe isolated from a thermal vent deep in the Pacific Ocean, was compared to a very similar enzyme in humans. The thermophilic protein has a stabilizing charge-charge interaction between the terminal carboxylate group on the last amino acid in the chain and an arginine residue near the beginning of the chain.

This interaction is not present in the human version of the protein because the terminal carboxylate group is angled away from the positively-charged group on the arginine. The single charge-charge interaction is not by itself responsible for the thermostability of the *P. horikoshii* protein - other similar interactions throughout the protein structure also contribute (see the original report at *PLOS Biology* 2011, 9, e1001027).

Conversely, proteins from 'psychrophilic' organisms - those which live in extremely cold temperatures, such as in arctic soils or in small water pockets in polar ice - have fewer stabilizing charge-charge interactions. This gives them the flexibility to function at temperatures in which mesophilic human or *E. coli* proteins would be frozen and inactive. On the other hand, a typical psychrophilic protein will rapidly unfold, precipitate, and lose its functionality at room temperature.

Scientists are extremely interested in thermostable proteins, because the ability to function at high temperatures can be a very desirable trait for a protein used in industrial processes. In fact, thermostable DNA polymerase from *Thermus aquaticus* (the enzyme is known to molecular biologists as 'Taq polymerase') is the enzyme that makes the PCR (polymerase chain reaction) process possible, and has earned billions of dollars in royalties for drug company Hoffman La Roche, the patent owner. Many research groups are searching for useful enzymes in thermophilic species, and others are working on ways to engineer heat stability into existing mesophilic enzymes by tinkering with their amino acid sequences to introduce new stabilizing charge-charge interactions.

Kahn Academy video tutorials on solubility, boiling point