

**Chemistry: Challenges and Solutions**  
**Unit 5: Making Molecules**  
**Lewis Structures and Molecular Geometries**  
Hosted by Beth Taylor

[Tease]

**Water: the most basic need for animals and plants. To form a molecule of water two hydrogen atoms bond with one oxygen atom. But what makes these atoms bond? If we can understand the principles of how atoms bond to form molecules we can figure out how to manipulate them to fight disease.**

CHRISTINA ZIMANYI: If we can stop the reaction from working we can use that to fight cancer.

**Building on the principles of how atoms bond to form molecules, we can predict their shapes. Manipulating these shapes medicinal chemists work to create new cancer drugs.**

ALEX TAYLOR: We're developing compounds to test ideas about new shapes and new types of molecules, to see whether they kill cancer cells.

**Fighting disease starts with understanding how to make molecules.**

[Title: Unit 5 – Making Molecules]

[SEGMENT 1: Lewis Structures and Radicals]

BETH TAYLOR: Hi, I'm Beth Taylor, chemistry instructor at MIT and I'm going to share with you today some of the principles about molecules that I not only use to teach my own students but also that first inspired me to realize that research in chemistry is a really important and really interesting way that we can help others.

Before I became a chemist, I wanted to be a doctor but while taking my pre-med courses I realized that it is essential to think about how our bodies work at the molecular level.

In studying molecules, it is important to be able to visualize where each individual atom and electron are within the molecule. And one way we can do this is using Lewis structures. Let's take water for example. So water is made up of an oxygen atom bound to two individual hydrogen atoms. And oxygen has six valence or outermost electrons, so we can draw these in here. But like any main group element in order to be stable, oxygen would like to have a full octet or eight valence electrons, essentially to fill its valence shell.

So to do this what it can do is make covalent bonds to each of two hydrogen atoms.

And each hydrogen atom has one valence electron. You can see that the oxygen satisfies the octet rule with one, two, three, four, five, six, seven, eight valence electrons. The hydrogens only need two electrons to fill their outermost or 1S shell, and you can see they each have two electrons as well. But typically when we draw Lewis structures we don't draw individual electrons within the bonds, we just draw the bond as a straight line. So each line represents two shared electrons, and these electrons up here belong only to the oxygen, these are called lone pairs.

But what if an atom in a molecule does not have a full octet? An atom within a molecule with an unpaired electron is known as a radical.

A common radical found in our bodies is the hydroxyl radical, which is an oxygen atom bound to a single hydrogen atom. In the hydroxyl radical the oxygen only has one, two, three, four, five, six, seven valence electrons. It doesn't fulfill the octet rule, and because of this it's extremely reactive. Essentially this radical electron is going to react with another molecule, really whatever it bumps into, in order to steal away another electron and typically form a new covalent bond to give the oxygen atom its complete octet.

So, we often think of radicals, or "free" radicals, as being dangerous and that's because they are in many contexts.

For example, this hydroxyl radical can harm our DNA, which leads to aging and even cancer.

However, even the very same radicals that can do us harm, are also essential for life. For example this same hydroxyl radical is used in a very controlled way by white blood cells to kill invading bacteria and viruses. By understanding how radicals work we can come up with solutions to shut down the ones that harm our health.

*[SEGMENT 2: Free Radicals in Cell Replication]*

**Understanding how free radicals react can help researchers in the fight against cancer.**

CHRISTINA ZIMANYI: I'm Christina Zimanyi. I'm a graduate student in the Drennan Laboratory at the Massachusetts Institute of Technology. I am studying the enzyme called ribonucleotide reductase or RNR. It's a very essential enzyme for anything that's alive.

**RNR is required for any cell in the body to reproduce itself. Without RNR, cells have no way of making DNA and thus no way of dividing. Researchers want to understand the structure of RNR and the path of reactions that enable it to help create DNA.**

CHRISTINA ZIMANYI: We want to know how it works, just because we find that interesting on its own, but we also know that if we can stop this enzyme from working we could use that to fight cancer.

**In RNR, an important radical has been identified, an oxygen radical, that is integral in starting the reaction that makes DNA.**

BETH TAYLOR: Let's take a look at this oxygen radical.

This makes this molecule want to react, to pair up this unpaired electron with a source from a nearby atom or bond in order to form a stable octet around oxygen.

CHRISTINA ZIMANYI: We've actually known for a long time that there's an oxygen radical in RNR. And now we're learning more about the pathway that it has to travel to make DNA building blocks, which it needs for cell replication. And if we understand that pathway better, we can understand how to maybe stop it, to help fight cancer cells.

**To investigate the pathway of reactions in RNR, the lab grows crystals that contain RNR enzymes. These crystals contain countless identical copies of the RNR molecule.**

**But looking under a microscope will not reveal the molecular structure of the RNR crystals. Instead Christina uses a technique called x-ray crystallography. First she places the crystal on the end of a pin to be positioned in the x-ray machine.**

CHRISTINA ZIMANYI: Our crystal is here in the path of the x-rays, so we're ready to shoot it. The x-rays travel down this tube, and directly through the crystal. And the electrons from all the atoms, from the enzymes in the crystal are going to interact with those x-rays and make them sort of fly off pathway - it's going to diffract the x-rays, and because it's a crystal, it is going to do that in a very specific way. And the different directions it diffracts are going to be recorded by the detector. And from that information we can figure out where the electrons were in the crystal that caused them to diffract in that particular pattern.

**The detector is hooked up to a computer that reads and interprets the data.**

CHRISTINA ZIMANYI: Over at the x-rays we collected a diffraction pattern. And that diffraction pattern told us something about where the electrons are in our crystal. And that's what we're looking at here. So, where you see big blue blobs, that means there were a lot of electrons there, and where you see black spaces, there were no electrons, and now that we know where all the electrons are we can figure out where all the atoms were. And because we know what atoms make-up the enzyme we can build in all of the pieces. And I can show you what that looks like.

So here we've drawn in all the atoms. For example here, everywhere these yellow lines

meet at a point, that's a carbon atom. And these white lines here that extend off of the carbon atoms here, those are hydrogen atoms, and things that we color red, those are oxygen atoms, and so we can see where exactly in the protein this particular oxygen atom is. And once we've put in all of the atoms we can look and see what the overall structure is of the entire enzyme.

**From the map generated by the diffraction pattern, Christina is able to locate the oxygen free radical. In the case of RNR, the radical must move from the spot where it is generated, the initial site, to the active site, where the reaction takes place that allows the enzyme to help make DNA.**

**So how does the radical actually get from the site where it's generated to the active site?**

BETH TAYLOR: So essentially this free radical, or this lone pair electron, starts its journey by stealing a hydrogen atom from a nearby bond. This single electron forms a covalent bond with the hydrogen, which brings along its electron to make an electron pair or essentially an oxygen-hydrogen bond. But what this means is that this hydrogen is no longer associated with this oxygen atom, and this oxygen now becomes its own free radical. So instead of having the eight electrons, or a full octet, it now has, one, two in this bond here, three, four, five, six, seven. This newly generated free radical then reacts with another hydrogen atom, slowly working its way across the molecule until it hits the active site where it can carry out the DNA synthesis reaction.

**In studying the path of RNR, the team at MIT made essential contributions to a crucial discovery. They found that the radical must travel over 35 angstroms from where it's generated to where it reacts in the active site. An angstrom is equal to one ten billionth of a meter. That may sound small, but in biology, 35 angstroms is really far.**

CHRISTINA ZIMANYI: It was completely unknown when it was first discovered that a radical could travel that far inside of a protein. To give you some perspective, a typical bond length is about two angstroms. So this is many, many bond lengths that this radical needs to travel to perform its function.

**Christina hopes to take advantage of the distance that the RNR radical has to travel to find a way to block its path to the active site.**

CHRISTINA ZIMANYI: Because we know the distance it's traveling is very long, that almost seems like a weakness. And if we could somehow stop the radical along that pathway, we could kill the enzyme, and if we kill the enzyme we can stop cells from dividing. And that is essentially what we want to do to fight cancer.

*[SEGMENT 3: The Geometry of Molecules]*

BETH TAYLOR: Lewis structures are helpful, but they don't tell us about a molecule's geometry. Molecules interact with other molecules based on their shapes, an incredibly important fact for designing medications. In order to predict the geometry of molecules we need to understand that bonds or electron pairs want to get as far away from each other as possible.

So I have two magnets here, and when I try to put the two poles that are the same together, I can't do it, no matter how hard I try. And valence shell electron pair repulsion theory, or "VSEPR," is based on this principle that electrons repel, that they're trying to get as far away from each other as possible. And this theory allows us to predict the geometries of molecules.

DAN ROSENBERG: Today's show is brought to you by valence shell electron pair repulsion theory. And so in this model each balloon is representing a pair of electrons, and these pairs of electrons are mutually repulsive. When there are just two electron pairs, these want to get as far away from each other as possible, and the farthest away they can get is...

I'm the central atom of the molecule and these are my two pairs of electrons, finding the maximum possible distance. But because I only have two arms I'm going to tie these balloons together to form a knot. This knot that holds the balloons together is our model of the central atom. So two balloons mutually repulsive, no matter what you do with them, they form a linear pair.

By tying balloons together we look at the predicted shapes of molecules with a total of two, three, four, five, and six bonds or lone electron pairs surrounding the central atom. We're going to start with six and work our way backwards.

So, six balloons, all mutually repulsive form what we call octahedral. And it's an octahedron because it's got eight triangular faces, all of them are the same, all of the angles are 90 degrees, and it forms what looks like a three-dimensional coordinate axis.

Now, we start getting rid of a few balloons. And with five balloons mutually repelling we've got trigonal bipyramidal: two balloons are at 90 degrees from the plane, that's 90 degrees, and if I tilt them towards you, you can see that three balloons are at 120 degrees - they form a trigonal arrangement.

If we want to get back to four balloons, we have to pop a balloon. The balloons form a geometry called tetrahedral. Three balloons touching the table, one balloon pointing up. All of the faces are triangular, and all of the angles between the balloons are the same 109.5 degrees.

Now, in order to get three balloons from four... Three balloons lie flat on the table, this is the arrangement we call trigonal planar, where each balloon is pushing the other balloons away, and they have 120 degrees between them.

Finally what we have is a linear pair of balloons, when you have two electron pairs around an atom.

And these are the geometries that molecules with a central atom form with their electron pairs, and that is what contributes to the shape of molecules.

*[SEGMENT 4: Penicillin and VSEPR]*

**The geometry of molecules is an important factor in fighting disease. Take the antibiotic penicillin. Penicillin was discovered by Alexander Fleming in 1928. Fleming was studying how to treat bacteria found in infected wounds. He spread plates with this bacteria and then left for summer vacation. And when he returned, what he found was that in addition to growing bacteria, some of the plates were actually contaminated with mold. And wherever this mold was the bacteria didn't grow.**

**So Fleming hypothesized that there was something inside of this mold that was killing the bacteria, and we now know that it was the penicillin within the mold. Scientists eventually figured out how to mass-produce penicillin. This was critical in world war two. Penicillin was used to treat millions of world war two soldiers and saved many lives from death through bacterial infections.**

**Science has won another victory over death.**

BETH TAYLOR: So what is it about penicillin that makes it such a potent anti-biotic? Well for that we need to look at the structure. And it was Dorothy Hodgkin who first solved the structure of penicillin essentially figuring out where every individual atom was in relation to one another.

Penicillin has this four-membered ring called a beta-lactam that's extremely reactive.

Because it's arranged in a square this means that essentially all of these bond angles are going to be 90 degrees. But what we know from VSEPR theory is that in fact these angles would like to be much, much larger.

So let's consider each of the atoms within the beta-lactam. First we have a carbon up top here, and we can see it's bonded to one, two, three, four other atoms.

This means that ideally this carbon atom would like to be in a tetrahedral geometry and have bond angles of 109.5 degrees. But instead it is forced to have a 90 degree bond angle. Similarly with this carbon here we see it's bonded again to one, two, three, four other atoms and would like to have that 109.5 degree bond angle here instead of the roughly 90 degree bond angle that it's forced to have by the four-membered ring.

Then down here we have a nitrogen atom, and the nitrogen is bonded to one, two, three other atoms. But we also know from the Lewis structure that it has a lone pair right

here. So the nitrogen atom also would also like to be in this tetrahedral geometry.

Finally we have this carbonyl carbon, which is bonded only to one, two, three different atoms. It has no lone pairs. So, this would like to take on a trigonal planar geometry and have a bond angle of a hundred and twenty degrees, and again that's much, much greater than what it's constrained to do, which is to be part of this beta-lactam ring at ninety degree angles.

So, essentially this reactivity comes from all of the ring strain created from the beta-lactam. When the penicillin molecule comes into contact with the enzyme that naturally builds the cell wall in bacteria, that enzyme can react with this extremely reactive and strained four-membered ring and eventually break this carbon-nitrogen bond right here.

This releases a whole ton of ring strain because now all of a sudden all of these atoms can take on their ideal geometries, or at least get pretty close. Once the enzyme is covalently bound to the penicillin molecule, it's essentially shut down. It can no longer build the bacterial cell wall, and the bacteria die.

So, when I first studied penicillin, I was amazed, I said 'Wow, like, so this, thinking about the structure right here is how we can actually understand how it works in the body. And this is the point for me where I started that switchover from thinking I want to help people by becoming a doctor to I want help people by studying and understanding how things work on a molecular level.

*[SEGMENT 5: Designing New Cancer Drugs]*

**The geometry of molecules can give us a start in thinking about designing new medications. Researching drug therapies that can successfully target cancer cells is Alex Taylor of Constellation Pharmaceuticals.**

ALEX TAYLOR: We're working to develop new therapies for cancer. We have new biological targets that we're very excited about, and so we're developing compounds that have never been made before to test, to see whether they potentially kill cancer cells.

**In their battle against cancer, the team at Constellation Pharmaceuticals targets a class of proteins whose role in cell growth has only recently been discovered. These proteins are found within cancer cells. Developing a compound to bind with these proteins could ultimately kill cancer cells.**

ALEX TAYLOR: The hope is that by selectively turning off these proteins we could kill the cell, which would lead to a cure for cancer.

**To get the compound to bind with the protein, the team must optimize the shape of the compound.**

ALEX TAYLOR: One approach that we commonly take is to change compounds that are largely flat which can have a lot of liabilities and can be bad for targeting proteins into compounds that are more three-dimensional and have a lot of shape.

**Alex starts with a compound that contains an alkene. Alkenes have at least one carbon-to-carbon double bond. In this molecule the central carbon atom here has 3 other atoms surrounding it, making it trigonal planar, a flat geometry. He hopes to reduce it to an alkane. This will break the double bond and create four atoms around the central atom, making it tetrahedral, a three dimensional geometry.**

ALEX TAYLOR: You may not care if it's flat or if it's three-dimensional, but the protein does. So, one way to think of the protein-binding pocket is kind of like a hand and glove. So there's a very specific shape on the surface of the protein, and then we design compounds to fit in, in that pocket. So, what we're looking at here is a model of the protein with a small molecule inhibitor bound to it.

Here you have the surface of the protein and the pocket that the small molecule fits into. And we know that there is a channel in the back that extends even further into the protein. And through experiments we know that an alkene doesn't fit in there, it doesn't match the surface of the channel quite right. So we're going to change that to an alkane and hopefully fill that space even better and lead to a more potent interaction.

**To create the more three-dimensional alkane from the alkene, Alex must react hydrogen to the alkene, breaking the double bond and adding two new hydrogen atoms to the resulting alkane.**

ALEX TAYLOR: So, now I'm going to set up the reaction that's going to reduce our alkene to our alkanes. We're going to have a catalyst that's going to bind to our alkene and to the hydrogen gas that we're putting in there. And the catalyst will help deliver the hydrogen onto the alkene, turning it into the alkane. So right now in this flask what we have is the solvent to dissolve up the starting alkene. We have the catalyst. It's a palladium catalyst. And we have the starting alkene.

**Alex then fills a balloon with hydrogen to be added to the alkene.**

ALEX TAYLOR: So to get the reaction ready, I use this vacuum line to pull all the air out of the vessel and out of the solution. So you'll see all of the air come out as little bubbles here. And now I am refilling the entire atmosphere with just hydrogen. So now the only thing that is in this tube is hydrogen. And it will diffuse down and get in the solvent. And this will help the reaction, the reduction from the alkene to the alkane go as quickly as possible.

**Once Alex determines that they have made an alkane, he hands it off to the biology team for testing.**



DEANNA A. MELE: Part of our job is to actually take these compounds that the chemists make and synthesize and we put them on cells, which we use as a model system for cancer. And these cell lines are derived from cancer patients, so we actually look at this compound and the effects it has on these cancer cells.

**In addition to shape, another key to predicting if the new compound will bind with the protein is polarity. Polarity is the distribution of electrons around a molecule. If the electrons are distributed evenly the molecule is non-polar. If the electrons are distributed unevenly the molecule is polar. Since electrons are negatively charged the part of the molecule with more electrons is also negatively charged, and the part with fewer electrons is positively charged.**

ALEX TAYLOR: In the proteins that we're trying to target, you have these polar regions and these non-polar regions. And so we know that polar molecules like to interact with polar molecules and non-polar molecules like to interact with other non-polar molecules. And so we try to match those up as well as we can from our small molecules into the protein-binding pocket.

**Many more tests, as well as clinical trials, will have to be completed before this compound can be used as a medicine. But by using the fundamentals of chemistry to influence shape and polarity, Alex and his team move closer to finding specific treatments for cancer.**

ALEX TAYLOR: There are still so many open questions about the best ways to make compounds to treat cancer. But once you get to that point where you've optimized the binding between your small molecule and the protein you've taken the first really big step in fighting cancer.

*[WRAP-UP]*

BETH TAYLOR: We now know that atoms are held together by bonds to form molecules. Understanding how these atoms bond can provide insight into how cells reproduce, whether we're studying healthy cells or cancer cells. And manipulating the shapes and polarities of molecules can help us create new medications to fight disease.

*[END]*