Lab 5A • 04/30/12

A Fischer projection is an alternate way of representing in two dimensions a three-dimensional molecule, specifically to show what kind of configuration it has for its stereocenter. [Let's] start with a molecule that has just one stereocenter, a nice, simple molecule. There is more than one type of stereochemistry out there. If we have an alkene that has four [different] substituents on it, if you move the position of two substituents, rotate the two around, you get a different molecule, even though in that specific example you'd have all of the same atoms hooked up to all of the same atoms, it's just they differ in position in space. That's the definition of stereoisomerization – you have multiple molecules that are identical in formula, identical in connectivity, but have their atoms arranged differently in three dimensions. Double bonds have stereoisomerization, but I'm going to be focusing on tetrahedral centers, or what are called asymmetric carbons.

What's the quick and dirty rule that we use in order to determine whether a molecule has an [asymmetric carbon]? If it has four different substituents attached to it, which we've got in this case. There is this system by which we can assign what's called an absolute configuration – we can call it R or S. What is the proper way to determine whether this is R or S? We want to visualize this in such a way that the H is [oriented] away from our point of view. If there's a way that we can manipulate the molecule to do that, or, we can ascribe a visualization point, a point of reference. I use an eye symbol, where the eye is looking a something, and that little line on the top is the eyebrow, [because] it can matter whether we we're looking at something down like this or whether we're looking 180° upside-down like that. I'm oriented in this way looking down on the molecule, looking down at that carbon hydrogen bond. What I see is that the bromine is directly in front of me, and bromine is the highest atomic number of all of these atoms, and it is the atomic number that determines the order of priority – at least, that's the first of the Cahn-Ingold-Prelog priority rules. Bromine is priority number one; chlorine's number 2; fluorine's number 3; hydrogen is the least important. So, although yes, in this case, we want to visualize this with the hydrogen pointed away from us, there will be cases where hydrogen is not the least important atom, so there'll be cases where it's not hydrogen that you're trying to orient away.

Focusing on this example: bromine is in the plane of the board, the same place I'm looking through, and it's oriented up. Then, I look at the chlorine, the second group, and it is in the back of the board, it's got a dash, so from my viewpoint perspective that means it's down and to the left. If I then look at the fluorine, it is down and to my right. So, up, left, right – if I turn around so that you're looking the same way I would be at that hydrogen, what way of rotation does it appear that we have? Couterclockwise, which means this is going to be an S stereocenter.

What if we did want to rewrite this molecule in such a way that that hydrogen – the least important group – is explicitly pointed away from us? How could we rewrite this so we put hydrogen as a dash? Switch three groups – rotate them in order, or precess them. If you have a hydrogen currently in the plane of the board, and one of the halogens is also in the plane of the board, there's one halogen coming at you, one halogen coming away from you. The one that's coming at me, I want the hydrogen to be in its place instead, so all I do is rotate that bond in 3D space. What happened when I did that? Three atoms moved, because one bond stayed constant, and the other three switched positions.

There is another way that we could do this that has the exact same result. What would happen if I swapped the position of any two groups? What if I took the chlorine and hydrogen and reversed them? What would that do to the stereocenter? Invert it. Any time you switch two groups, it's like you have taken the mirror image, so it inverts the configuration of that stereocenter. If you are going to try to read things directly off of the structure, this is what you'd want to do. Look at where the hydrogen was originally. Hydrogen was in the plane of the molecule. If we ignored the hydrogen and looked a the order of the priorities, the way they're written right now, would it appear to have been R or S? It looks R if we ignored where the hydrogen really is. This is why you've got to be careful when doing visualization that you really do put it firmly in the back position. I've now done that, but done it in an inappropriate way, by just switching two groups. Switching two groups is going to invert the configuration of that stereocenter. If you switch a pair once, that inverts it. What happens if we take any pair and again invert; then won't I switch right back to where I started from? In this case, a double negative is a positive – if I've inverted once and inverted again, I get back to the original stereocenter configuration. I'm going to leave the hydrogen alone this time, because I want the hydrogen in that place, so I'm going to choose two other groups to swap - I'll choose the fluorine and chlorine. Before I flip these two a second time, see that the bromine is position 1, chlorine's position 2, fluorine's priority 3, hydrogen's in the back the way it's supposed to be, so it both looks like and it really is R. But now I'm going to swap those two groups again because I want to figure out what the original molecule's configuration is. I'll put fluorine on the right; I'll leave the hydrogen in the dash position; and chlorine has now moved to be on the left. We now have hydrogen in the back, the way it's supposed to be. We can put our priorities in [and] see that they go counterclockwise, which means it is again S.

Now look at the original molecule and compare it to the one we just ended up with. If I took the fluorine and rotated around to where the hydrogen is, which rotates to where the chlorine is, which rotates back to where the chlorine started, that's exactly what I just showed you a moment ago with this model set, that I'm just rotating around one bond. What does that mean? That means that, for tetrahedral geometry, reflection twice is the same as rotation once.[group theory] By swapping two groups twice, for tetrahedral geometry, that is the same thing as rotating them around once. Same molecule: R or S? It's still S, isn't it? The hydrogen's still in the back. But it looks different than the molecule that I just wrote, doesn't it?

But it's not a different molecule. I've got this blue and this green substituent on the model I'm looking at. I could arrange it in such a way where I'm looking at it from an angle here, and from my perspective it looks like the green's on the left and the blue's on the right. If I keep the molecule still and walk a couple of inches this way, now it looks like the green's on the right and the blue's on the left. The molecule didn't change at all, did it? So the only difference between these two representations is which way, which angle I'm viewing the model from. Otherwise, these are perfectly identical. This is another reason why, if you're going to read the configuration directly from the molecule, you want to make absolutely sure that that hydrogen's in the back, because, not to confuse you, but what that means as far as writing down the structure, this fluorine and chlorine on the very original molecule, I could flip their positions and it's the same molecule – not change the dash and the wedge, just change where I write I dash, where I write the wedge. I could put the wedge here with fluorine where chlorine is, and I could put the chlorine with a dash where the fluorine, and it's the same molecule; it's just whether I'm looking at it from here or from here. But if I flipped those two groups and you didn't put the hydrogen in the back, you would have thought that stereocenter was R, or maybe S as it is, because right now (ignoring the hydrogen) it looks R. You've got to be very careful with your visualizations. Double inversion of a tetrahedral geometry is the same as rotation. Swapping and substituents on a tetrahedral center twice – and not [necessarily] the same substituents each time – causes the same result as rotation around one bond once, which can also be accomplished by rotating the positions of three substituents.

Now getting to Fischer projections themselves [same Fischer as Fischer esterification and the Fischer stereochemistry proof, Nobel prize]. Why do we care about Fischer projections? To give a little bit of historical context, it was only 20 years that he came up with [them] (Fischer projections) that there wasn't even agreement that there was such a thing as a tetrahedral carbon. The existence of the geometry of carbon was an invention of the mid-1850's. Before then, Dalton and other researchers had gotten people convinced there was [such a thing as] an atom. It was in the 1850's or 60's that they realized that carbon was tetrahedral. The mathematicians then said: oh, well that means, it's going to do this, this, this, and this – including having stereocenters, places where geometry could be inverted. Fischer wanted to come up with a way to write these things down. His specialty field was in carbohydrates, and that's still where these Fischer projections are most frequently used. I need to show you the standard form, the way we represent a sugar or carbohydrate on paper, which means I have to introduce what is a carbohydrate.

As the name sounds, a carbohydrate is something that has carbon and water, effectively, as its overall formula, multiplied by some number x, the whole darn formula. To give an example, here's what a Fischer projection looks like. This is the molecule d-glucose. What does that d mean? Dextrose, which has to do something with rotation. If you have two molecules that are enantiomers, what does the term 'enantiomer' mean? Mirror images, ok. If you have two molecules that are mirror images but otherwise identical, what physical properties do they share and what physical properties are different? Their melting points, boiling points, indices of refraction, denisties – everything about the two molecules – identical – all physical properties are identical, except [two]: optical rotation [and some new property]. That's where the term racemic comes up, because if you have two compounds that are enantiomers, that are equal in concentration, one turns light one way, one turns light the other way – that's what a racemic mixture is. If we know that one form turns light to the right, one form turns light to the left, what we could do is look it up in a table and figure out which one of the compounds it is. What if you're the guy inventing optical rotation and it's never been measured before. If you measure optical rotation, how do you know which one is R and which one is S? You don't; it is impossible to tell. The d and I do relate to optical rotation, but don't relate to R and S, there is no relationship – except, if d is R, I is S, if d is S, I is r.

Why have that crazy system? Because nobody knew for sure ... there wasn't such a thing as R and S, that didn't get invented until the [19]50's, that's the first time we knew which one is which. Back in the 1870's/80's when Fischer was working on this, these symbols d and I were used to represent rotation. There's another molecule that this is all based on. But he took a guess – he guessed that the d form was one particular configuration of that molecule – and every other molecule he synthesized from it, and he said that's the d configuration. All of organic chemistry had these d and I designations – but nobody knew if they were right. In the 1950's when the experiment was finally done that showed it, they could have found out that he was wrong, which means every structure in every book that had a d or I in it would have to be reversed for its next edition, because everybody would have known that the wrong answer had been there for decades. He just happened to guess correctly. What we write as the d form is what he wrote, because we proved he was correct. How? By taking a crystal of a certain material and taking an x-ray pattern of it. You can take x-rays, shine them at a crystal, see what bounces back, and mathematically figure out where the points are, and figure out where the atoms had to be that generated that pattern – that's called x-ray crystallography – that's the same that Watson, Crick, and Rosalind [name? used to determine the structure of DNA]. X-ray crystallography, same thing – you could see the positions of the atoms, and so somebody figured out: oh, that really was the right configuration. This d is related to stereochemistry, is still used cause we know which one is which, but it's a relative configuration, not absolute like R or S

Here's d-glucose. What's this Fischer projection thing mean? When we see Fischer projections of carbohydrates, we tend to put the carbonyl portion — whether it's an aldehyde or a ketone — at the top, and then the rest of the molecule, we make a backbone out of it. Having shown you the complicated version, let me show you a simple version of a Fischer projection. This is the molecule d-glyceraldehyde; here's the molecule glycerol that it's related to [athletic use of glycerol, triglycerides]. What is a triglyceride?

It's nothing more than the triester of glycerol – if you take three long carboxylic acids and put them onto glycerol, that's fat, that's what simplest form of fat in our body is, nothing more than the ester of glycerol. Turn one of those oxygens into a phosphorus group and then we get lipids that show up in these cell linings that form phospholipid bilayers – same root platform, just with a few tweaks. Glyceraldehyde, we get form oxidizing one end of the molecule or the other; it is the simplest sugar. What do these cross bars mean? Any group written in vertical orientation on a Fischer projection, by definition, is pointed away from us. Any group that's written on what you could call the arms, the horizontal rungs on this ladder, those are by definition pointed towards us. Up and down, that's away; the arms are towards us.

How do we interpret this Fischer projection? The backbone, everything is pointed away; the arms, everything is oriented towards. This is not the normal way we write a stereocenter. In a normal stereocenter, you only have two things normally written as the plain line, and only one each a wedge and a dash. But there's more restriction to it than that. Normally, the two things that are in a plane must form some kind of simple angle with each other just like this. Notice that those two plain lines are leading to a point. By convention, you must draw the wedge and the dash facing that same direction away from the point. If you, for example, move the wedge to be in the same place the plain lines, then if you're doing a quick reading of R and S, you're could get the wrong answer, cause it could appear to be in the wrong place. But we've now purposely defined a structure in this way, but there's a reason for that, because everything that's vertical is always pointed away from us; everything that's on the arms is always pointed towards us, so you never have to guess.

Is this the R or the S form of glyceraldehyde? Which of the four groups – the carbonyl, the CH2OH, the -OH group itself, or the hydrogen – which of those is highest priority? The oxygen, cause it doesn't matter what carbon's got on it, it's still carbon, and the first rules says it's highest atomic number that matters. Oxygen, the one directly connected to the stereocenter, that's the highest priority; it's the highest atomic number, so it gets priority. How would we handle the priority of the carbonyl? We have to write phantom atoms. The way that we do phantom atoms is to add one of each of the atoms that part of that double bond; if it's a triple bond, we're going to add two of each. First, you write the bond that was originally there. We had a carbon-oxygen bond; on the carbon, we add an oxygen, on the oxygen, we add a carbon. That's the process of doubling done for phantom atoms. If we end up in a position where we have to do a comparison, then the oxygen with the carbon – that new phantom carbon - that carbon counts, but it doesn't have any attachments to it, so past that point, there's nothing to compare; something else would automatically win out, you could say. On the bottom, we have an [O, H, H] attached; on the top, once we've expanded it use the phantom atoms, you could see that we have [O, O, H] attached. Since at this first point we find a difference – oxygen being more important than hydrogen – we can decide that this top group is more important. If we got [O, O, H] and compared to [O, O, H], then we'd have to go one more positions out. That top group is number 2 in priority; the bottom group is therefore number 3; and the hydrogen is least important. So is this R or S? R. Why? Doesn't it look counterclockwise? But it's still R, why? Because the hydrogen's pointed towards us. Whenever the hydrogen's pointed towards us, we're doing it backwards, which means whatever answer you get, you take the reverse answer. Since this appears to be counterclockwise, it's really R. In this case, they hydrogen is pointed towards the viewer, which we know, because it's on one of the arms, which, by definition, is always pointed towards us. So whatever apparent orientation the remaining groups have must be reversed – in other words, it looks counterclockwise, but is really R.

Instead of having to do this flip-flip thing, if we wanted to get that hydrogen in the right position, couldn't we just turn the Fischer projection by 90°? No. Why? Because right now, the arms are on the left and right, and they're pointed towards you. If I turned the Fischer projection 90°, I'd still have the arms pointed towards you, but by definition, the Fischer projection must be so that the vertical part, the backbone, are pointed away from you. If you took a stereocenter and rotate it, you're not just rotating it if you do it with a Fischer projection, you're inverting it. In other words, in normal 3D space, I could take this and of course turn it to the right – nothing happens. This is not normal space. This has a very firm definition of what left and right mean, and what top and bottom mean. When you take a Fischer projection and turn it 90°, you do that. You [do] not just rotate it, but at the same time you flip it. But we're not flipping the orientation of where we actually write the substituents; that means, you invert the stereocenter. It's called improper rotation, because we're not just rotating, we're reflecting at the same time. A Fischer projection turned 90° is an invalid operation for a Fischer projection. A slightly simpler way of saying it is: since a Fischer projection has a firm definition of what's facing towards and away, it may not be rotated by any angle. Fischer projections cannot be rotated because there's a firm an immutable definition for what the vertical and the horizontal positions mean. If a Fischer projection is rotated 90°, it inverts the stereocenter. Vertically means pointed away; horizontal means pointed towards – and it never, ever changes.

Back to my question though: what if we wanted to get the hydrogen pointed away from us in a Fischer projection? We could see that we could flip two groups twice or rotate three of them; that is still perfectly valid, because no matter how we view three-dimensional space, if we hold one bond and just rotate, we're just going to precess the positions of those substituents. Even on a Fischer projection, if you hold one atom constant and rotate the other three, it gets you back the same stereocenter again. I'll take that original – we don't normally write the wedges and dashes on a Fischer projection – we just write a simple cross like this. I'm going to take three groups and precess them, just like a pinwheel [definition of pinwheel]. I'll move those three groups around. Now, the hydrogen's on the bottom, the way we want; we still have the same priority orders of -OH being priority 1, the carbonyl being priority 2, CH2OH being priority 3. It's now in the right position, so we can just automatically jump to calling that R.

We should practice taking a molecule and putting it into a regular Fischer projection. I'll take that same starting molecule, the haloalkane, and we'll project it into a Fischer projection. Recognize that there's an awful lot of freedom for single-stereocenter molecules as far as how are we going to do the Fischer projection. The only restriction that the things top and bottom are away, and the things left and right are towards you. That means I could make the bromine and hydrogen towards me, the hydrogen and chlorine towards me, the bromine and chlorine, the fluorine and chlorine – there's all these different combinations, so we need to establish where we want to put out perspective. I usually think it's a heck of a lot easier if you make the two things that are plain lines one of the pairs – either the arms or the backbone – and then automatically make the other two things whatever you didn't make the first two. I usually prefer normally to make the things that are plain lines the backbone. Why? Because then you've got something that's obviously pointed one way – we could figure out later on if that's left or right – and something obviously pointed the other way, and figure out if that's left or right. [don't have to do it that way]

Would you prefer that I make the bromine and the hydrogen the backbone? If so, there's only one other choice that we need to make: because if I say that the bromine and the hydrogen are going to be the backbone, that means you have to be observing from below and left here, cause those are above and to the right. Would you like my eyebrow on top, so bromine looks to be on top, or would you like my eyebrow to be on bottom, so that the hydrogen look like it's on bottom? On the bottom? OK. If I'm looking at the molecule that way, then what is on top? The hydrogen, right? So hydrogen's up top here, which is down from everybody else's perspective, and the bromine, from my perspective, is the bottom, but from yours, it's the top. Would you like me make this simple on everybody and just switch where the eyebrow goes? [No] If you are looking at it from that perspective, like this, from my perspective, is the fluorine on my right or my left? [how many forms of inversion are going on here] May we make this the easy way for everybody's benefit?

Doing the sane thing here, we're going to put the bromine on top, the hydrogen just the way it looks like right now. Now from everyone's more natural perspective, that fluorine is a wedge, which means it's out here; my perspective is this way – is this my right or my left? The right. The means the fluorine is going to go on the righthand side of the projection, and chlorine is going to go on the left. I'm looking at the molecule this way: bromine is in the same plane as I am, hydrogen is in the same plane as I am. By making the logical choice to put the eyebrow up top, that makes the bromine, which is pointed up, going to be on the top part of that backbone, because, by definition, those things [are] pointed away from me on the backbone. The hydrogen is down here, but it's still part of the backbone, pointed away from me, but it's down, that's why I put it at the bottom of the Fischer projection. When I'm looking at it this way, what's throwing some of you off is fluorine, from this side view, looks like it's on the left, but it's not at all; this is a two-dimensional projection. Realize that if I look at that, the fluorine is really on the right here, isn't it? That means we put it on the right. It doesn't matter how we wrote it, what does it look like in 3D space? That's why the choice of perspective is so important, and knowing where a dash and a wedge go. That's why I recommend putting the plain lines in the backbone, so you make less errors when transcribing the arms, the parts that are pointed towards you. That fluorine is coming at me, but it's on my right, and that chlorine is coming at me, but it's on my left; that's why I put the fluorine right and chlorine left in the Fischer projection.

We already know from back before what the correct answer to this being R or S is: it's S. What is it now? Bromine is priority 1, chlorine is priority 2, fluorine is priority 3. Hydrogen is pointed towards us or away from us? Away – by definition, those things on the bottom of the Fischer projection are pointed away from us. That means whatever orientation is remaining can be read directly – that's another beauty of the Fischer projection, no matter which [of the] four positions we keep still and call the least important group, the rest can be read directly to determine if it's R or S. This is still S, exactly the way we want it. [could write out CH2OH as a rung on ladder, but don't because it's at the end and it's not a stereocenter]

Glucose [molecules that must be memorized][no lone pairs for sugars]

This is d-glucose. By convention, Fischer projections of carbohydrates are drawn so that the carbonyl is on top – I say carbonyl because some sugars are aldehydes – those are aldoses – some sugars are ketone – which are ketoses. [enantiomer – mirror image; diastereomer – not mirror image; epimer – subset of a diastereomer; anomer – subset of epimer, position where where that carbonyl is; what anomeric position is] We need to be able to put this back into a dash-wedge structure. Let me show you the correct way to do this. We have a total of six carbons. But, by definition, everything in the backbone is supposed to be pointed away from us. That means that this carbon is pointed away from that one, this one is pointed away from that one ... but how could we have things that are all pointed away from each other – unless it was like they were in a wheel. In other words, I could take this paper and I'll write the Fischer projection on it. By definition, every group [in the backbone] on here is supposed to be pointed away from each other, so the real way to write it down is to view it like this – in other words, like this. The bottom carbon is not a stereocenter, so I'm not worried about my dashes and wedges there. Whether I write the wedge on the right or the wedge on the left – the left being what I did here – it doesn't matter, it's which side of the molecule are you peering at – but what you do for one stereocenter, do for all of them, so you don't confuse your reader, your grader. Which way am I going to visualized it? I'm going to pretend I'm looking at the Fischer projection the way we're all at, from the top down, which means all those -OH groups are pointed at me, all those hydrogens are pointed at me, which means, as I come around the molecule here, if I'm looking here, now the groups are pointed at me.

How do we translate these groups onto here? If, by convention, this is the top of the molecule, everything's pointed at me, that means that all these groups are on my right. [-OH, -OH, -H, -OH] will go on each of these wedge positions because they're also one that would be on the right if I'm looking down at the molecule, as I must be for the Fischer projection. The other side would then all be on the dashes. I've written all of my wedges and dashes in. The first carbon closest to the carbon: should the wedge or the dash get the -OH group? Look at the original FIscher projection to make that determination. -OH on the wedge, because at that carbon, in order for the arms to be pointed at us, we have to be looking down at the molecule. If we're looking down, wedge, which is out of the plane of the board, is on my right; dash, which is into the plane of the board, is going to be on the left then. The next carbon: will the -OH group be on the wedge or the dash? The dash, because in order for the arms to be pointed towards us, we must now look up at the molecule. From that perspective, when looking up, my left is pointed towards you, which means the left is now a wedge; my right, which is into the plane of the board from your perspective, that's a dash. The -OH group is on the right; it must therefore be on the dash. Back up to the top again, the next carbon, we have to visualize from the top, again to make those arms pointed towards me, so the next -OH group, is it going to be a wedge or a dash? A dash. The final group will also be a dash.

In other words, if we had this molecule [I-allose], I've got all of these -OH groups on the left, all on one side of the Fischer projection, when I move to being a dash-wedge ... notice what I've done, I've made this one step more complicated. In this problem, I arbitrarily chose to put the carbonyl on the righthand side of the paper, and I had the carbonyl pointed down. Generally, when you point it down like that, it means the dash-wedge structure, the zigzag's going to be exactly the way that I've drawn it. On the other structure here I'm about to do, I've chosen to point the carbonyl up, which means the first carbon, its groups are pointed down. When the groups are pointed down, my left is now pointed towards you, and that is a wedge, because I'm looking up like this, then my right is your dash. The -OH group that is on the left will be a wedge first, which means the next one's a dash, which means the next one's a wedge, which means the next one's a dash. You can just choose one visualization perspective and just invert as you go from carbon to carbon to carbon. That means though, if you do your first one wrong, the whole molecule's wrong, and you've got the enantiomer. Some people do better picking the proper visualization point at each point as you go.

You need to be able to do it from both directions. In other words, if I had this molecule, d-mannose, you need to be able to draw a Fischer projection for it. Will the -OH group on the first carbon be on the right or the left? Left. By definition, [a] Fischer projection must be written in such a way that the side groups are pointed towards me, in order to get the hydrogen and -OH group pointed towards me, I need to view the molecule from above, like this. If I'm viewing the molecule from above, the -OH group is on my left, the hydrogen is on my right, cause -OH is wedge, hydrogen's dash. I now have two choices: I can either go to the next position, still looking from above, I can see that the hydrogen is on my left, that the -OH group is on my right, but because I'm looking the wrong way, I have to invert what I've got; hydrogen used to be down here on my left, when I rotate it around, but I'm still looking the same way, that means it's on the opposite side. Instead, [you can] just look up like that. Now, the hydrogen is on my left. What is the position of the next one: right or the left? Hydrogen on the [right] because it is a wedge, which from look looking down would be on my [right], and then the -OH group, which is a dash, into the plane of the board, which would be on my [left]. The eyebrow has to be here, because by definition, the carbonyl goes at the top of a Fischer projection. Whether I'm looking from above or below, the eyebrow is always in the same place. That'll put that hydrogen on my [right]. Now the bottom one, the -OH group is still going to be on the [right], the hydrogen is on the left. [popping of model sets]

[lab directions]

When two groups on a stereocenter are exchanged, it inverts the configuration of that stereocenter.

Swapping any two substituents on a tetrahderal center twice (does not have to be the same two substituents) causes the same result as rotation around one bond once – which can also be accomplished by rotation of 3 substituents.

Carbohydrate - [CH2O]x

By definition, any group written on the "backbone" (vertical) is oriented away from the view, and any group written on the "arms" (horizontal) is oriented towards.

The hydrogen is pointed towards the viewer, so whatever apparent orientation the remaining groups have must be reversed. (looks counterclockwise, but is really R)

Fischer projections cannot be rotated, since there is a firm and immutable definition for what the virtical and horizontal positions represent

If a Fischer projection is rotated 90°, it inverts the configuration.

By convention, FIscher projections of carbohydrates are drawn so that the C=O is on top.

Structures