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PROFESSOR: OK, OK. The weekend is over. One announcement. Last weekly test will be tomorrow, and it'll be based on homework 11, focused on polymers. And then the following week is the very last week of semester, and there's no testing, no work required of you, when the subject has a final exam. And this one has a big final exam, big celebration, so there will be no weekly test next Tuesday. So this is the last one, so get out the Kleenex.

All right. So today we want to continue the treatment of biochemistry. Last day we started looking at proteins, and the building blocks of proteins are amino acids. And so we looked at the basic structure of amino acids, shown here, which is an  $sp^3$  hybridized central carbon, which I've designated alpha carbon.

And three of the four bonds are the same in every amino acid. Every amino acid has, off the central carbon, an amino group. This is the nitrogen with two hydrogens. It has a hydrogen, a lone hydrogen, and it has a carboxylic acid, which is this COOH. Double bond here, I'm looking at four sticks off the carbon. One, two, three, four. And this proton here is the one that can fall off and go over to the side. And when it does so, then we end up with the acid. It's a proton donor.

And then the fourth bond is this designated R. R is the substituent, and it could be anything. We could put a cyanide up there, if we want. Anything that conforms to this architecture with whatever choice of R is still qualified as amino acid. There are only twenty choices of R that are found in protein.

We also studied chirality, which is handedness. Some of these amino acid molecules are chiral. That is to say, if you put this carboxylic acid in the lower left, and the amino group in the lower right, you have molecules that are seemingly identical, but not superimposable. We call them chiral. And the two forms are called enantiomers. And only the L-enantiomer is found in proteins. And we saw that the L is determined on the basis of polarization rotation of light in an aqueous solution of this.

Except for glycine. In the case of glycine, we have H up here. So we have an H above and an H below. That molecule is not chiral. So nineteen of the twenty amino acids that we find in proteins exhibit chirality.

And later in the lecture we started looking at aqueous solution behavior of the amino acids. And what happens is, when they dissolve in aqueous solution, they form zwitterions. Zwitterions by proton transfer. So the proton goes off the carboxylic acid and joins the amino end, so you have a plus end and a minus end. And then we looked at what happens with the behavior in aqueous solution, and we came up with the Henderson-Hasselbalch equation.

And here it is, plotted. This is the case for alanine. In the case of alanine, we have the methyl group here. So the R is CH<sub>3</sub>. Everything else is the same. So you can see that here's the neutral zwitterion, where the H off of the carboxylic acid, has transferred over to the amino end. We have charge neutrality. The molecule started off net neutral, and now the plus is over here, conferring a positive charge to this end, and leaving this end less a positive charge, and therefore minus. So it's globally neutral, but locally positive and negative. Hence the term zwitterion, because it's essentially dual gender, both positive and negative.

And we looked at the aqueous solution behavior of the zwitterion, and we saw that zwitterion is responsive to its environment. And we reasoned that this is how you start to impart animation to something. How do you get something animated? You get something animated by having it respond to its environment. A rock sits there. You can talk to the rock, nothing happens to the rock. But animated objects, if they're endowed with hearing, if you talk to them, sometimes they respond.

So what's going on there? It to do with the ability to respond chemically. And so what we saw here is, when we went into low pH regime-- low pH means very, very high proton concentration. The zwitterion responds by the Le Chatelier principle to try to minimize that acidity. So it gobbles up protons. And over here we see that it gobbles up protons by attaching to this carboxylic acid end. That's a proton attachment site. And in the extreme, all of the zwitterions have been capped by protons.

So over here we have complete protonation, and that's what we're showing in this graph here, which is just basically the one that's up on the screen, but I'm using different-- see, this is taken from one of the biology readings. They say equivalence of hydroxyl. There's no hydroxyl here. I don't know how these-- you know, the language of some of these branches of science puzzle me. That's equivalence of hydroxyl, but we don't have hydroxyl! It's all about protons.

So here it is, in terms of the equivalence of H plus. So here's the neutral zwitterion. That's this thing here. And this H, if it falls off, it can then become the neutral zwitterion. And then what happens is, as we go to very, very low pH, what happens is that the zwitterion starts attaching protons. So this is a neutral zwitterion to which we've attached the H.

So it's much-- to me this is transparent. What this reads-- I don't know. Equivalence of OH? There's no OH. That's a way of saying it's fully protonated. BUt to me that's sort of a backwards way. Don't tell me what it isn't. Tell me what it is.

So this is fully protonated over here. And as the pH rises, the zwitterion feels less compelled to gobble up the protons, so it sheds protons. And finally the pH gets to a point that's high enough that the zwitterion plays no role,

and it exists as the neutral zwitterion. That's the isoelectric point. We have a 100% concentration of zwitterion.

Then we go to the other extreme. The other extreme is the high pH regime, where it's proton deficient. And so zwitterion responds by-- what? Throwing out hydroxyls? No! In spite of what's written here, there are no hydroxyls. What zwitterion does, is it tries to shed protons to compensate for the proton deficiency. And so some of the HAs become just A minus, because the H's are being liberated. And over here at the extreme, all of the zwitterion has lost its H here. And so now you have something that's net negative. Over here you have something that's net positive. In the center it's net neutral.

So this is the high pH regime, low pH regime, and this is the Henderson-Hasselbalch equation, which answers the question, what is the ratio of neutral zwitterion to either the deprotonated form or the protonated form as a function of pH? You tell me the pH, and I'll tell you what the ratio is.

Last thing that's really cool about this, and shows you the power of this mechanism of attachment or detachment, is as follows. Look at here. This is not exactly to scale, but it's reasonable. You see the pK? This is pK1. This is for the protonating reaction. So over here I have neutral zwitterion, over here I have no neutral zwitterion, all the zwitterions are fully protonated. And in between, I've got-- this is supposed to be sort of halfway across here. So this is 50-50.

But look at what happens. For very, very large changes in ratio of zwitterion to protonated zwitterion, the pH doesn't change that much. The pH changes a lot here, and it changes a lot here. But over a vast expanse of protonation or deprotonation, the pH kind of hovers around pK1.

So the zwitterion is really doing its job. It's trying to hold that solution from shifting pH dramatically. We say that zwitterion, by doing so, acts as a buffer. A buffer holds pH near constant. And the near constant value it's going to hold it to is its pK. So in the acidic regime, in the very low pH regime, over a broad range of protonation deprotonation, it's going to be roughly a pK1. And the same thing happens over here. You see? Over a broad range of A minus to HA, the pH kind of holds around pK2. And then finally, over here, the system gives up and then it shoots up to the 100% deprotonated. So that's the story there, and you see the isoelectric point in the middle.

Now, so far all we've done is we've said what happens when we have a simple amino acid that has just the one proton attachment point on the carboxylic acid and the amino acid. But it can get more complicated. And there is an example in the homework that you might want to look at before the final exam. And that's the case where the R group itself has the ability to protonate or deprotonate. Suppose this R group had a COOH ending here. Can you see that it could also participate? And so then the isoelectric point isn't simply going to be the average of the pK1 and the pK2. Because now there's a pK for this thing, as well.

So this is the example of the tritatable-- that's the term they use. If I could just spell it, I could convey the information. Titratable R group. That's what they're talking about.

Otherwise, if the R group is a neutral, it's just a spectator. Doesn't doesn't participate any more than this. See, here's a hydrogen. Look at this one, people. You see this hydrogen? It doesn't participate at all. Please don't tell me at some point that the zwitterion says, I'm out of hydrogens from here, I'm out of hydrogens for here, I'm going to start shedding this. This is a really strong covalent bond. It's not going anywhere. If you want titration, you've got to put the titratable R group up here. OK? This is so cool.

So now, I'm going to show you an application of this stuff that's used in biology. And I know, because one year they gave a crash course for engineering faculty in biology, and we did we actually did this experiment in the lab. So I'm going to show you how you can use the fact that zwitterion changes in response to its environment in the laboratory.

So what we're going to do is I'm going to make a column here. This is a column, and it's an aqueous solution, a column of varying pH. So it starts at the top, and just for argument's sake, I'm going to put high pH here at the top, and low pH here. So it's an aqueous solution. You can say, wait a minute. He just taught us fixed laws. This is proton deficient this is proton rich. Aren't the protons going to go north and the hydroxyls are going to go south? Yes.

So what are we going to do? We are going to slow down diffusion. We're going to change the diffusion coefficient, and what we're going to do is, we're going to fill this with a solid suspension and turn it into a gel. So what's the function of the gel? Don't say that Professor Sadoway said that he stopped diffusion. Diffusion goes on, but it goes on at a slow rate. So over the time duration of the experiment, for all intents and purposes, the pH changes imperceptibly in comparison to everything else that's going on.

It's all about time scales. You realize, we are all aging. We've been aging ever since I started this lecture. But for all intents and purposes, we can view ourselves as being the age we were when we walked in the room. And even over the semester, chances are. All right? Now if we meet back here in ten years' time, expect to see some changes. Right? But over the time scale of the experiment, we can say we take diffusion out. So that means the high pH is here, the low pH is here.

Now what I want to do, what is it I'm trying to accomplish? I want to separate an amino acid mix. And just for grins and chuckles, we're going to have A1, A2, and A3. Three different amino acids. Which means just three of these things, but three different R values. I'm going to pour them the top. I've got this aqueous solution, got all three amino acids.

So what happens when they fall in here? When they fall in here, they start diffusing, too. Right? Well, first of all, they hit a very, very high pH regime.

So what what's the immediate response to those amino acids in a high pH regime? They're all amino acids. They're all those rescuers. And they say, Hi, pH. It's proton deficient? I can help! And they all start shedding protons. And so within moments, all of those amino acids have been totally-- as they say in California-- totally deprotonated. And here it is. So they're all sitting there, in net negative. They're all sitting there in net negative, right up here.

But I just told you, I shut off diffusion, slowed it down. But I want to get out of here before dinner. So I don't want the protons moving, but I do want the amino acids to get moving.

So what do I do? I put on my electrochemist's hat, because as you know, electrochemistry is the highest form of chemistry, the most noble form of chemistry. It happens to be the area that work in. And so what we do is we electrify the ends. And we'll polarize the top negative and the bottom positive. Well, I just poured in a bunch of amino acids that became net negative, and now they're next to the negative electrode.

So what happens? Now they're in an electric field, and they start moving. They start moving in the electric field, and they're all net negative. But what happens, is they move down here. So this is medium pH. Can you see? I've established the pH gradient. And as they move from high pH to medium pH, the proton deficiency isn't as intense.

So they're responding to their environments. They're saying, you know, back there I had to get rid of all my protons. But now, it doesn't feel so proton deficient, so I can start taking protons on. They respond to their environments. So here, they're all A minuses. And if they ever get down here, they'll all be HAA pluses. And so what are they in here? They're sort of on their way to becoming HAs. Because the pH is continuously variable.

So as they become less negative, what happens to the driving force by the negative electrode? It's weaker. So the protons were, first of all, they're anions. They're net anions. They go, whoa! Negative! And they start moving, and then they get less and less negative, and the field gets weaker and weaker. And eventually, they take on enough protons that they become neutral zwitterions. And what is the response of a neutral ion in an electric field?

Nothing. It stops.

And so let's say, this happens to be the isoelectric point of amino acid number 1. So it gets to the isoelectric point, and it doesn't move anymore. And number 2 and number 3 keep going, and this might be the PI of have number 2, and this might be the PI of number 3. And now I want only amino acid number 1 from this mix, I can now go in-- this is a gel. It's put down on the glass plate, or you can put it in a column. Now you where they are. You come in-- because you've got a pH meter, you know where this is. You know the PI. Bingo. That's where they are. And if I

want number 2, they're right here. And number 3, they're right here.

So this process is called gel electrophoresis. This is the term. It tells you nothing about the process. It tells you how to conduct it. You make a gel, and you polarize the ends. Electrophoresis is simply particles moving in an electric field. You can paint a car this way. Obviously the car, when the car is made of metal. If you have a fiberglass body, you can't use electrophoresis. The car is made of metal, you polarize the car, and the paint, the paint has got dipoles. And so the paint sticks to the car. And then you lift it out, let it drip, and then just get the right amount of paint proportional to the charge you put on the car by electrophoresis.

What's that got to do with this? It doesn't talk about the focusing here. So the mechanism here is called isoelectric focusing. So isoelectric focusing is the principle by which we can separate the amino acids from one another. The gel electrophoresis column is a device in which we do so. And let's be modern, so we'll give it a three-letter initialization. IEF, isoelectric focusing. Isn't that cool? Yeah. I thought so. Anyway. OK.

Everybody's still zoned out from turkey or something. No response. This is brilliant. It's beautiful, and it integrates all of this material, and deadpan. All of this withholding love. You've been with your families, I can tell. All of the old family dynamic, see? It's here. You brought it with you. Leave it! Leave it at the airport.

OK. Now. So we've been talking about the amino acids. We said we're going to use these as building blocks for proteins. Let's build some proteins now. So protein synthesis.

So we're going to make macromolecule. What are we making? We're making a macromolecule. Protein is a macromolecule. You notice I didn't say polymer, because a polymer going to have-- every element along the backbone is going to be the same. But I'm telling you that we can change the choice of R at every station. So it's a macromolecule, but it's not necessarily a polymer.

But we do know, if we're going back a macromolecule, we've got two choices. Addition or condensation polymerization. So I look at the basic structure-- let's put it back the way we found it, so that people don't leave thinking that we have two carboxylic acids. So the most the most general form doesn't have a titratable R group, but it does have an R up here.

So I want to take one of these and link it to another one. So how do I do it? Well, right off the bat, addition polymerization is no good. Because even if I had enough energy in my body to form a radical, what could I do with this? There are no double bonds here! There are no double bonds here. I can't break a double bond and then allow this to bond to its neighbor. So axiomatically, I have to go with condensation polymerization. OK?

Macromolecule formation by condensation reaction. I don't even want to say the word polymerization. By condensation reaction.

OK. So let's look at an example here. An example will be this. I'm going to write, here is the COO R. So I'm going to show this, and then over here-- well, maybe I'd better show some fine structure. I'll give you a little more fine structure. So we'll put the double bond up here, O minus. And then over here, I'm going to put H<sub>3</sub>N plus.

So here's the neutral zwitterion, agreed? And I've got some kind of an R group up here. And I'm going to put next to it a second one of these. So here's the alpha carbon, and we'll go COO. And then over here, I'm going to unpack this nitrogen. It's got one, two, three hydrogens, and it's net positive. So there's the neutral zwitterion.

So now by condensation reaction, what we'll do is we'll take this oxygen off of the left amino acid, and we'll take two of the hydrogens off of this amino acid, and we will eject a water molecule. We'll eject the water molecule. And that's safe. It's compatible with the body.

And now what's left? This carbon is naked. One, two, three. There's a bond sitting here that used to go to the oxygen. And this nitrogen, it's sitting naked too. And so now we can do, is we can make a link between this carbon and this nitrogen. And this bond is called the peptide bond. This is the peptide bond. OK? And we see that the atomic mass of the dipeptide is less than the sum of the masses of the individual components, because we've lost the water.

So I think I've got some slides here. What's here? Oh. This is just the various, pK<sub>1</sub> and pK<sub>2</sub>. And then this side chain here, this is the value of the pK should you have a titratable R group. That's why there's the third column here. So when you see this-- you see, they're all roughly around two for the highly acidic regime, and all around high nines, low tens for the alkaline regime. Roughly the same.

All right. Now connotation polymerization. This is the formation of nylons. You see how you bond this mer to the adjacent mer? Look at this. The nitrogen, that hydrogen is sticking up. There's the nitrogen bonding to the carbon. There's a long pair, and nitrogen-carbon.

Amide bond, peptide bond, same thing. The same bond in the backbone of nylon is the same bond in the backbone of protein. Only, the biologists call this the peptide bond, the polymer scientists call this the amide bond. Think about that when, you know, the holidays are coming, you think you're really special, and you know, the proteins in your body are really bound the same way that nylon is, you know?

All right. So now let's consider-- and here's some examples. Here's a peptide. So it's a long chain here. So it starts, here's the amino group, H<sub>3</sub>N. It's got glycine, and then leucine, and valine, glutamine, et cetera. So there it goes, all the way around, around, around, around, around. And here's another one. There's the amino group, and then, boom, boom, boom.

What's happening here? All of these click stops along here are this.  $\text{H}_2\text{NCHCOOH}$ . And the only thing that's changing is the R group. If this were nylon, it would be the same thing, all the way down. That's how this differentiates itself. All polymers are macromolecules. All macromolecules are not polymers. These are not polymers, but they are macromolecules.

And what else do you see here? Look at this. Cysteine happens to have a double bond. A residual double bond in its R group. Well, where you see a double bond, you go, I can break the double bond, and then I can make another bond. And that's what happens. So we break the double bond with the sulfur, and now we make a disulfide linkage.

What do you think the mechanical properties of this protein are? Mechanically, what do you think this one's like? It's rubbery. This is an elastomer, because you can move the top chain vis-a-vis the bottom chain until these disulfide linkages are flattened. And then if you let it go, it springs back. It's the mechanical properties of, in this case, this is insulin.

Now I want to give you a sense of the variety here. How much information-- because ultimately, it's all about reproduction, right? That's the number one function of any living organism, is to reproduce. That's what makes it life. Right? So it needs an instruction set. And the instruction set doesn't come in the box. It comes inside the organism. And this is the language. This is all we have to work with.

So here's a simple example. This is, how many combinations do you have of dipeptides? So when you start with two amino acids. So this is phenylalanine and aspartic acid. So if I told you, you have A and B, and how many AB mixtures can you come up with? You'd say, well, you've got AA, you've got BB, and you've got AB. You know, it's sort of like calculus, right? If you square A plus B, you'd get A squared, plus 2AB, plus B squared.

But because of chirality, AB is distinguishable from BA. This is cool. This is, again, math serving us, instead of we serving math. All right? So A plus B squared is A squared plus 2AB plus B squared. But no, no, not in biology. Because AB is chiral, and therefore distinguishable from BA. Now you understand chirality. So here's-- you get four. Because see, in this case, phenylalanine peptide to aspartic acid is distinguishable from the one on the right. They're distinguishable. They're different.

OK, so that let's roll with that. Let's say, so if I start with two amino acids, and I want to make dipeptides, well, that's trivial. That's 2 squared, is 4. So I got four different dipeptides, starting with two amino acids.

Now, suppose I said, how many different dipeptides can we make, period? Well, I know I've got a library of 20 amino acids that are found in proteins. So that means the number of dipeptides would be then 20 squared, which is 400. But that's hardly a macromolecule. So let's get into the macromolecule business.



So suppose I took a library of twenty amino acids, and I said, how many kilopeptides could I make? What's a kilopeptide? A kilopeptide is something that's got 1000 peptide bonds in it. So that's going to be 20 to the power of 1000, which is 10 to the power of 1300.

And this is small.  $n$  equals 1000. I'm not stretching the point by pulling something exceptional out. A polymer, if it were polymer, 1000 units long, you'd say, that's sort of fair to middling length. I'm not pulling out the longest polymer ever known. I didn't go to the Guinness Book of Records for this. This is just plain vanilla mer length. So look. How much information can be contained? That's in a single element.

OK. So later on we're going to return to this, and appreciate how we can get to such information density.

And this I think I alluded to on Wednesday. These are the three-letter initializations, and I'll post this at the website. So these are the airports that correspond to the three-letter initialization. Then I showed you the one-letter abbreviation for each of the peptides. You know, it's kind of strange, because the amino acids are what they are. And most airports, they're not like the main ones. It's not like Boston or New York. It's weird places like Australia and Texas and stuff. You know? So-- hey, you've got to have a sense of humor! Come on.

All right. And there's glutamic acid. There's no airport that has GLU as its three-letter--

OK. So here we are. So now we want to do is want to talk about protein structure. And so we're going to look at this as material scientists. We're not going to look at it the way chemists, capital C-chemists, do. And I think by looking at it from a structure perspective, you get some insights into what we can do with these things.

So protein structure. And I'm going to use the terminology that the biologists use. So first of all, they have something they call the primary structure of the protein. And it speaks to composition, the composition. Well, what's the composition? We know that every protein is made of amino acids, and every amino acid is virtually identical, except for the R group. So when you say the composition, you're really saying, what is the R sequence? It's the amino acid sequence down the backbone. Because you've polymerized this thing, or macromolecularized it. Amino acid sequence, which along the backbone. Which is really the R groups. The sequence of R groups, which is going to be the sequence, OK? All right. So here you can see. There's an amino acid sequence.

Number two is the-- these are really-- you know, like the polymer people had conformality. You know, they had nice, powerful words. The first order is the primary, and then the second one is the secondary.

I'm trying to make fun of the biologists, and you're sitting there, you know, with that same Thanksgiving dinner table stoicism.

OK. So what's the secondary? The secondary structure of proteins speaks to packing. And what's the gambit

here? Why do they pack in different ways? Well, just as we saw, you can have a long chain, straight chain. Sometimes things fall back on themselves. It's still a straight chain, but there's a curve, a bend in it, and so on. What proteins are going to do in order to pack, is to try to maximize hydrogen bonding. And this is not even between proteins. This is a protein forming on itself. And you could argue, why do you maximize hydrogen bonding? Because when you make more bonds per unit volume, you decrease the energy of a system. You've been taught that over and over again.

So these are long chain molecules, but they still can loop back on one another. And if you've got a choice of forming a dipole-dipole interaction, an induced dipole-induced dipole interaction, or a hydrogen bond, which is going to give you the most decrease per unit bond? It's hydrogen. So if you can form hydrogen bonds, that gives you the most impact per bond. If you don't have hydrogen bonding capability, then you go for dipole-dipole. And if you don't have dipole-dipole, then it's just the weak van der Waals, or the London dispersion. So that's why this thing goes for hydrogen bonding. Because it wants to. It wants to decrease the energy.

So I have to show you a few cartoons here. All right. So here's a sketch taken from one of the readings. So there's alpha carbon. This is the carboxylic acid, right here. And this is the peptide bond between one carbon and a nitrogen in an adjacent unit. All right? So there's the peptide bond.

The interesting thing is that even though this is  $sp^3$  hybridized, data show that all six atoms lie in a plane. So what happened last time when we came up with this conundrum?  $sp^3$  hybridized, but the data showed it all lies in a plane. That was benzene, remember? And how do we skate with the puck on benzene? Resonance. We said it resonates between two structures, and sometimes the nitrogen lies in the plane. Sometimes the alpha carbon lies in the plane. But thanks to resonance, all six of these can lie in the plane.

OK. So now how do we get to hydrogen bonding? So there's the resonance. All right. Good. So you see, this is free to rotate, right? Once we accept that these six atoms lie in a plane, and these six atoms lie in a plane, and 109 degree angle is fixed, but there's that degree of rotation, which is what gave us the original  $C_{17}H_{36}$  folding back on itself, only we're going to fold back on ourselves in groups of six. So we've got a deck of cards here. I've got six here, six here, six here.

So what am I going to do? I'm going to try to make this blue plane lie relative to the yellow plane in such a way as to maximize hydrogen bonding.

Speaking of energy deficit, we need battery. All right, here we go.

So now we're going to maximize. Look. You see, if I rotate this blue plane in just the right way, I can set up to have a hydrogen bond form between this hydrogen and this oxygen, and on the orange plane, an oxygen and a

hydrogen. So now it becomes a matter of figuring out, what are these angles? You see, there's a phi and a psi here. What are the angles phi and psi to give the maximum hydrogen bonding between these two six-packs of atoms?

And from that, you get secondary structure. It's all about maximizing hydrogen bonding. After that, if you understand what I just said, the rest is trivia.

So here's what happens. Here's one structure. And this was first discovered, if you like, revealed, by Linus Pauling, 1951. Linus Pauling and Corey, 1951, came with the realization that if the protein spirals in a helix, it will line up the maximum number of hydrogen-oxygen hydrogen bonding opportunities, as opposed to going straight. So it doesn't go perfectly straight, it coils.

And this is two different cartoons trying to show. So you can see peptide bonds, and then every so often you get a hydrogen-oxygen bond. Because it spins around, and the idea is, as the helix forms, you can think of it as-- have you ever gone up a spiral staircase? And you think of each subsequent turn of the spiral as a new gallery. And what you've got is hydrogen bonds between the galleries. So you're going up, and there's a hydrogen bond here, and you keep turning, and there's a hydrogen bond here, and there's a hydrogen bond here. That's the way to get maximum hydrogen bonding. There it is.

There's another example. Maybe this is a nicer one. And there's 3.6 residues per turn. That means, per turn is 3.6 R groups, which, it's called residues because historically, when people did the chemical analysis, the residue contained the substituent. That's how they determined what the identity of the protein is. They can't just look at it. And you can't use spectroscopy. Maybe now you can, but in the old days-- I mean, these are all, look. Low mass. Hydrogen, oxygen, nitrogen. They're not distinguishable. They're all low-Z elements. So they had to do wet chemistry, and they would actually peel off the R groups, which were called the residuals. And so 3.6 residuals per turn give you this alpha helix structure.

there's a second structure that works. The second structure is between two chains. So in this case, instead of going coiling by yourself, and forming the galleries, what you do is you take two chains side by side, and you pace them so that you get maximum amount of hydrogen bonding. I showed you this with nylon, how two strands of nylon bond together. They can form hydrogen bonds.

Same thing here. And now, since these are jerking in a motion of six in a plane, six in a plane, six in a plane, six in a plane, what you end up with is this pleating. It's hard to see here. Maybe if your eye can follow along the top here. Here's sort of a cream-colored one, orangey-cream, and it's moving sort of southwest to northeast. And here's one that's sort of a grayish, and it's moving from northwest to southeast. And then up, and then down. And zig and then zag.

And this is called the pleated sheet. This is the beta form. The alpha form is the helix, and the beta form is the pleated sheet. Same thing up here in a different kind of model. Which I look at that and I go, I don't get any information from this thing at all. But they put it in the books. Who cares. This is where you learn something, right here. Once you appreciate that those six atoms have to be in a plane, and how to maximize hydrogen bonding.

So let's put that down. This is all Linus Pauling. So secondary. So you know that six atoms in plane, which leads to resonance. And now, from there, you just need the genius of Linus Pauling, and then you conclude that to maximize hydrogen bonding, you form the alpha helix with hydrogen bonding between galleries. All right? And then the second one is the pleated sheet, or people just call it the sheet. But to me, the sheet means nothing! It's the fact that it's pleated. So I'm going to ignore what the books say. Pleated, pleated sheet. OK. So this is hydrogen bonds between galleries of the same protein. Whereas this is hydrogen bonding between macromolecules.

So if they're both pleated, it's going to work. Or of course, that could be folding back on itself. Remember how I showed you the first day the chain, how the chain wanted to zig-zag, to crystallize? Do you think protein is liable to fold? You've heard of protein folding? Why does it fold? Because it wants to maximize hydrogen bonding! And when it folds, it's not going to maximize hydrogen bonding unless it is in the beta pleated sheet arrangement. Otherwise, what's the point of folding? Because you can't make the link. Because I'm the oxygen, the hydrogen's way over there. If that hydrogen were right over here, we could form the bond.

And then the third one is random.

So let's take a look. I think I've got some images here. Oh, here's another one, showing the-- yeah. I'm trying to, I'm really working hard. Here's six, here's six, here's six, and there's the common carbon. OK? And now you can see the hydrogen bonds forming between. So this could be one protein, this could be another protein, or this could be the same protein that's folding back on itself in a pseudo-crystallization ploy. Yeah.

All right. So if you look in the biology literature, you'll see drawings like this. You've seen these, huh? You look at them and go, what are they talking about? Now you know! This is the secondary structure.

Let's start over here at the amino end. So you're moving along, and it's just sort of random, and now, all of a sudden, look. Round and round and round. What are you looking at? For this run of length, it's in the alpha helix form! And then it kind of goes random for a little bit, and then it goes green. And this green area is pleated sheet. So if the pleated sheet goes this way, and then it goes random, and then the pleated sheet goes this way, what's going to happen? there's going to be hydrogen bonding here, hydrogen bonding here, hydrogen bonding here.

And you know, how is it that this thing decides, oh, somewhere around here, I think. I think I'll just go into an alpha helix arrangement. Why is it alpha helix here, and not alpha helix here? Because of the instant choice of R groups! The instant choice of R groups will dictate whether it can turn around. Because if you've got glycine with its dinky little hydrogen on one side, you're compact and you can move around. But some of these other pendant groups are big, and you can't just shove them one into the other. They'll repel. They won't fit. So this dictates-- so in essence, the secondary structure is set, the table is set by the primary structure, isn't it? This is so cool.

Then there's the tertiary structure. Because random isn't, as they say in California, it's not totally random. There's some order to it. So let's look at the order that comes. See this? Look over here. You see up here? This is supposed to be random coil. But look at it. It's kind of dentate there, isn't it. See, it's sort of tooth-like. Do you think that the artist just did that? Why is it like that? Because of the molecular forces! So let's think on it.

Oh! This is a little piece from *Guys and Dolls*. 1951. The same your Pauling enunciated this. I bet you think that when people talk about the chemistry between folks, that it's a '60s phenomenon. You know, the hippies, drug culture. No. It goes way back. Goes to the '50s. Listen to this. This Sky Masterson, and he's going to tell Sarah-- she's the one that's the, she plays the-- what do you call it-- she works at the Salvation Army mission. And he's a gambler, which in those days was really, you know, like low-life. And he's flirting with her, and she, of course, has nothing to do with him, and eventually, they fall in love, of course. But anyway, so she's told him how she's going to meet the man of her life. And she's very linear. He's got all of these characteristics, and so on and so forth. Real linear. And this guy's a gambler, so he's going to tell her how he's going to find the love of his life.

[BEGIN FILM PLAYBACK]

Do you want to hear how a gambler feels about the big heart drop?

No!

Well, I'll tell you. Mine will come as a surprise to me. Mine, I leave to chance and chemistry?

Chemistry?

Yeah, chemistry.

Suddenly I'll know when my love comes along. I'll know--

[END FILM PLAYBACK]

So there you have it. From 1951. Chemistry, again, chemistry! Chemistry is the central thing. OK. Now let's go forward.

All right. So now let's figure out why-- and now I want to answer the question, why is this forming a tooth-like structure? Why? There's a reason for everything.

All right. So here we are, moving along a length of random coils. So we're in zone three here, random. But it's not completely random. So this is the tertiary structure, and it has to do with interactions between the R groups.

So let's look at number one, zone one here. We've got two cysteines, and cysteine both have sulfur in them. It turns out that the sulfurs can form a covalent bond here. This is between two R groups along a certain length of chain. And once that covalent bond forms, this chain now can't just go flopping any which way, because it's being held in place. It's like you put a prop there.

Over here, what do we have in zone two? We have one R group that's got a hydroxyl. Another one's got an oxygen. There's a hydrogen bond forming between side groups. And in order to form that hydrogen bond, can you see that this coil is actually bent? You see, there's a kink here. This coil should be much longer, if it were straight, distended. But it's actually compressed a little bit in order to facilitate the formation of this hydrogen bond. Which means now, this coil will stay in this configuration.

And then over here, what do we have? Here we have a substituent group that's net positive, here we have a substituent group that's net negative, and we have an electrostatic force. This is coulombic. This is plus attracts minus. And they form.

And over here, this is very interesting. What do we have here? We have a whole bunch of R groups that are all non-polar. And this thing's sitting in an aqueous solution. And what do you know about non-polar groups in water? They're hydrophobic! So I've got this one hydrophobic group sticking out over here. It's just going to have to take it. Because it's bound to the backbone. But I've got another one over here, and the backbone is flexible. And I've got another one over here.

Can you see that if the backbone folds around, I can collect all the hydrophobic entities, and present to the water the hydrophilic opposite side of the backbone. Because if the R group here is hydrophobic, look what's on the other side. These guys. So if I can take all of these and cluster them, then I sort of minimize the energy. Because that there is a repulsive energy term, right? The water doesn't like the non-polar R group. So let's minimize their contact, you know? If you've got two siblings that are fighting, you put them at the other end of the table. You don't sit them next to one another.

So here's what you do. You cluster all of this stuff, and that causes big hairpin turn. So this is called hydrophobic interactions. And that's the tertiary structure. So you see all of those. That's great.

OK. I see we're getting close to the witching hour. So maybe I'll teach you how to do your laundry and send you on your way.

So this interaction I'm just showing you right here is the same thing that's happening when you do your laundry. Now, what's a detergent? A detergent is this long molecule that's got-- you see this zig-zag here? That's the aliphatic. That's the hydrocarbons chain. And it is hydrophobic.

The soil on your clothing is usually some dirt, but it's covered by some grease and oil. So if you just soak it in water, the water can't get at the grease and oil. So what you do, is you put these molecules in that are very long, and then they've got this COO ending, right?

And now what happens? This can form hydrogen bonds to the water, whereas these long hydrophobic tails can bond to the grease and oil. And then you put this in the washing machine, and what's the washing machine do? Mechanically agitate. So you've got these tails, hydrophobic tails, stabbing the grease and oil, bonded to the water, shake the living daylights out of this, and release the grease and oil, which then will release the soil, rinse the whole thing, and you've got clean clothing.

So it's the bonding here. What you've got is an amphipathic molecule with a hydrophobic tail and a hydrophilic head that allows you to do your laundry.

All right. Get out of here. We'll see you on Wednesday.