

Lecture 23B • 06/19/12

[lab quiz][DCC, BOC, Merrifield resin synthesis, phthalimidomalonic ester synthesis, Strecker synthesis]

A lipid is a naturally-occurring fat-soluble molecule. Fat itself is fat-soluble, but we'll talk about some of the other categories of molecules that can also be found in fat. The first class of compounds we're going to look at are what are known as fatty acids, which are very long-chained carboxylic acids. [saturated carboxylic acids][12, 14, 16-carbon, 18, 20][lauric acid, myristic acid, palmitic acid, steric acid, and arachidic acid] These are found in fats; they occur in lots of other types of molecules as well. Many of them are isolated from both plants and animal sources, particularly the 16- and 18-carbon compounds. [table – olive oil, linseed oil][shampoo bottles] Imagine that you did make ionic headgroups out of just these carboxylic acids, with nothing else on them. Those would become amphiphiles – having these big, long greasy organic bits, but if you did make polar headgroups, then you'd have ionic headgroups, so the salts of these compound or derivatives are often used as soaps. [unsaturated – 18[9], oleic, olive oil; 18[9][12], linoleic acid] If we look from the end of the molecule ... we're very used to using the alpha designation to mean something right next to the carbonyl – just as alpha stands for the first letter, first position, omega stands for the last position, since it's the last Greek letter. If we count from the end of this molecule, we classify this as an omega-6 carboxylic acid, meaning there's an unsaturation at that position. [18[9][12][15], linolenic acid, omega-3 carboxylic acid]. [These last two] are what are referred to as essential fatty acids. You might remember that essential amino acids are ones that cannot be biosynthesized; it's something that we can only get from food sources – same thing with these two fatty acids: they are things that we absolutely need, but we cannot biosynthesize them ourselves. Food sources can be a source of these molecules.

Why might you imagine that the unsaturated molecules, which show up in fats, might be healthier carboxylic acids to incorporate into fats than the saturated fats? They're more reactive. Notice that all these different unsaturation points, in theory, an enzyme would be able to cleave the molecule at that point. The longer carboxylic acid chains, they're not nearly as reactive – carbon-carbon single bonds, much more difficult to break. [relative small number of carbon-carbon bond-breaking reactions] Having the double bond make these more chemically reactive, which allows them to break down. If they didn't break down, what do you think the bad thing would be about having all these big, huge, long carboxylic acids would be? They clump up, they're very, very hydrophobic; we're made of water, so if the stuff clumps together and it happens to be clumping together in a blood vessel, for example, that's not such a good situation. It's a little bit why unsaturated fats, which have these unsaturated molecules, tend to be healthier than the saturated fats that have the less-reactive carboxylic acids. With unsaturated fats, one consequence of those is that they can decompose even in oxygen; they can then be broken down into smaller carboxylic acids. Although this is not exactly a fatty, it is often a by-product of the decomposition of the larger fatty acids. This is butanoic acid, it's systematic name; this is also butyric acid, it's common name. This is [often] encountered [in] butter – think of the smell of rancid, bad butter; that's what this compound smells like. If you think of acetic acid, we're familiar with that with the strong vinegar smell, smell like a salad, may be pungent but doesn't make us necessarily churn in our stomachs. This, is you open up the bottle and smell it, you'd really wish you would not have.

If we were to take one of these really long-chain fatty acids and make an ester out of it with a really long-chain alcohol, then that's where we can get waxes from; they're long-chain esters. One of the major components of beeswax – just to make the point, I'm going to write the [line] structure out: it's a 26-carbon carboxylic acid with a 30-carbon alcohol that it's made the ester from. Big, huge, giant molecule – which helps explain why it's a wax. If we look at this molecule and I ask about polarity, would you classify this molecule as polar or non-polar? Non-polar. Even though the ester group itself might be polar, it's got so much of this non-polar tail on it, the molecule overall very, very non-polar. And yet, it forms a solid at room temperature. There is this interplay between intermolecular forces, the forces that will bring molecules together to from solid and liquid phase, versus kinetic energy, temperature, the energy that's causing the molecules to wiggle and pull apart from each other. Normally, to keep molecules together, to get good, strong intermolecular forces, you need some kind of permanent dipole. Just the middle of this structure would have a little, tiny permanent dipole, but one that's lost in all the rest of the molecule. However, even molecules that don't have permanent dipoles can sometimes get temporary dipoles. There is term dispersion force that's used to describe a lot of these interactions that occur due to temporary or induced dipoles. Because this has got such a long surface to it, temporary deformations in the structure can cause temporary charges to form. Since you have such a huge surface are, that gives you that many more chances that there's going to be some kind of interaction, that many more chances that you're going to be able to bring the molecules together to stick. Even though it's totally non-polar, because of these dispersion forces, because of these attractions due to temporary dipoles, these kinds of compounds are able to make solids. Although waxes are thoroughly non-polar, they have extensive dispersion forces, due to the large size of the molecules. The temporary dipoles due to these dispersion forces are therefore able to hold waxes together as solids at room temperature.

If we make a larger platform, besides just taking one alcohol and putting one of these fatty acids on it, what if we take a polyol – specifically, glycerol – then we're on our way to the traditional type of fat molecule, which can be called a triglyceride, if you want to focus on the carboxylic acid being substituted by glycerol, or you can also call them triacylglycerols, if you want to focus on the fact that glycerol is the center and you're adding these different carboxylic acid substituents to it. A R group attached to a carbonyl, that much of a structure is what's referred to as [an] acyl group.

If we take glycerol, which is a triol, and we add these long-chain carboxylic acids to it, that's going to give us this fat molecule. Fat [is] solid at room temperature; oil [is] liquid at room temperature. [composition of carboxylic acids in oils and fats; plants, unsaturated; animal, saturated]

If we modify a fat molecule just slightly and replace one of the esters with a phosphate group instead, then we get the class of phospholipids. There's several classes of these phospholipids. The general structure is where two of the -OH groups from glycerol retain carboxylic acids as esters; the last group has a phosphate or some other phosphate derivative attached. In these types of system, biologically-active molecules have that middle stereocenter in the R configuration. If you have the same carboxylic acid substituted at each position, that compound is non-stereogenic, because you would have two equivalent substituents.

What are some of the subclasses of this type of structure? If we take a two-carbon molecule that has an alcohol at one end and an amine at the other, that creates one kind of phospholipid known as a cephalin. There's another kind where if you take that same two-carbon molecule, where it has an alcohol at one end and an amine at the other, and if we put methyl groups on the amine, we end up with the molecule choline. [acetylcholine esterase; neurotransmitters] Take that choline, make an ester on the other side of phosphate – because of phosphate's structure, it could actually form esters in more than one direction – leave it attached to the glycerol but attach choline on the other side – this where we get the lecithin structure. Phosphatidyl choline. Why do we care about these? These lecithins are major components of phospholipid bilayers in humans. Cephalins are more commonly found in the phospholipid bilayers of bacteria. Since this is a biological system, the main medium is going to be water, so you have the polar headgroups of these molecules that are arranged so that they're in contact with the water. We're taking this large molecule and representing it as a headgroup that's got a long, forked tail. The organic portion's highly non-polar, wants to avoid water, loves being dissolved with each other, that's why they're drawn to the interior. At high enough concentrations, so you form this structure, but at low enough concentrations so you don't form some complex phase, you end up with this phospholipid bilayer.

Make one more substitution, and we can get a more specialized phospholipid bilayer, one that's primarily found around nerve tissue. Sphingosine has the following structure. It's not glycerol; it's an amino derivative that has and unsaturated, long-chain attachment point at the top of the molecule. In this compound, we end up have R group substitution not on the -OH group this time, but on the amino group. [derivative – attach fatty acid as an amide, includes phosphate and choline – sphingomyelin – nerve sheath][summary]

Terpenes

A molecule such as cholesterol can be derived from simple five-carbon units. Carotene, important in eyesight, used as a source material for the synthesis of retinol, also classified as a terpene. If you like the smell of any flower, almost certainly one of the major components of the fragrance has also been derived from terpene sources. An extraordinarily heavily-exploited biological pathway for building complex molecules. [ATP, pathways]

The essential structural unit in a terpene can be represented by the molecule isoprene – a four-carbon chain that's got a branch at one end. The end that is closer to that branch is referred to as the head of this unit, and the opposite end, furthest from that branch, is referred to as the tail of this unit. If we were to take two of these units and stitch them together somehow, this makes what's called a monoterpene. This was formed by the head of one unit being attached to the tail of another. If we were to take three of these units and put them together, this is the molecule alpha-farnesene, and it's the jumping off point to making a whole host of molecules [variation of functional group and you suddenly change whatever taste, change, or function you're going to get out of that molecule]. This is made up of three of these units [why mono is two units?], [which is called a] sesquiterpene [sesquicentennial]. If you put four units together, it's a diterpene. If you put six units together, and it is a triterpene.

I'm writing a monoterpene attached to a pyrophosphate group, which is where you condense two different phosphates together. Notice that this overall ion has the same -3 charge that a regular phosphate would. That acts like a leaving group in synthesis involving this platform. That monoterpene platform is geranyl pyrophosphate. Let me draw a subset of the molecules [that are generated from it]: [limonene (lemons), alkene; geraniol (geraniums), alcohol and alkene; citronellol (lemons), aldehyde; menthol (peppermint), cyclize with an alcohol]. All of these fragrances and flavors, all of them differ just by the functional groups they have, but they all have the same monoterpene platform. [structural analysis – need to be able to find isoprene units and identify whether heads or tails are connected]

Examples of larger terpenes. Geranyl is the monoterpene platform [farnesyl for sesquiterpenes]. If we take two farnesyl [earthquake!][annalies; LA story] pyrophosphates and we do a tail-to-tail joining, then we get a molecule with the unceremonious-sounding name squalene. Here's why squalene matters at all. I'm going to rewrite squalene. The reason this molecule matters is if you make an epoxide out of it, which is made by the convenient-named enzyme squalene oxidase, we end up with this structure that can undergo acid-catalyzed ring-opening.

Of course, if it undergoes acid-catalyzed ring-opening, this tertiary center's the one that wants to open, which can be attacked from the opposite side of the ring, which then can be attacked by the other ring, which can be attacked by the ring, which can be attacked by the other ring. You have this cascading folding event that zips these four rings up in one shot to create the following 6-6-6-5-membered ring pattern. That pattern forms the core of what are known as steroids, including cholesterol, lanosterol, estrogen, testosterone – all these hugely important biological molecules that all have this central core and just differ by stereochemistry or what functional groups that we put on here. At this point, once it's opened, we've made a ring. After we've done this ring opening that involved a bunch of ring formations, we ended up with a tertiary carbocation. It turns out it would be more stable for some reason if it was at this position, so you get a hydride shift, which causes a hydride shift, which causes a methyl shift, which causes a methyl shift, which causes a hydride shift, because you've got a base that removes this proton. This is the molecule lanosterol, which is a starting material for lots of related molecules. Nineteen steps later, we eventually end up at cholesterol.

Lipids & Terpenes

Lipid – naturally-occurring fat-soluble molecule

Fatty acids – (very) long-chain carboxylic acids

saturated

unsaturated

waxes – long-chain esters: beeswax

Although waxes are thoroughly non-polar, they have extensive dispersion forces due to the very large size of the molecules. The temporary dipoles created by dispersion forces are able to hold waxes together as solids @ RT.

Fats – Triglycerides/triacylglycerols

Fat – solid @ RT

Oil – liquid @ RT

Phospholipids

General structure:

lecithin → major components of phospholipid bilayers in humans

Terpenes

Structures (remaining structures identical to lab 13A)

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