

Lecture 23A • 06/13/12

The chiral auxiliary. It all comes down to what do we do with the problem of enantiomers – the problem being that, if we're trying to separate compounds, we need some way to separate them. For example, if we had two different melting points, then we could melt something while the other stays solid if they didn't dissolve in each other. If we had different boiling points, we could do distillation. If they had different densities, and they're not soluble in each other, we could do a simple separation by separatory funnel. There's chromatography, TLC. There's all these different ways that we could separate compounds, but they depend on the compounds having some physical property that's different between the two of them. The difficulty of enantiomers is that they don't have anything different, except optical rotation. Optical rotation, we only that that's different if we pass light through it – that's the key phrase, 'through it', cause it won't do anything to it, so we can't use that to separate the compounds [laser moving molecules one at a time]. The whole idea behind the auxiliary is you make something different.

[Enantiotopic protons] We talked about molecules in which, if you put them in achiral solvents, there are these different positions on the molecule that would not be chemically inequivalent – in other words, by putting it in an achiral environment, these different positions would act the same. Putting them in a chiral environment, then you have a unique interaction going on between the solvent and the molecule you're trying to scan that would change if you used the other enantiomer of the solvent. Then, you had a difference in the scanning behavior of whatever you were trying to analyze.

If we have two different enantiomers, we attach something else to both enantiomers. Let's say that we did this reaction: I have a methyl ester of a compound that's both a ketone and a carboxylic acid. Let's say that I first reduce this with sodium borohydride. Let's say I then saponified and used gentle acid work-up. Sodium borohydride's only going to react with the ketone, so the carboxylic acid survives, but we end up with an alcohol. Under sodium hydroxide, we're not going to get that alcohol to leave, because the alcohol's at the alpha position. In those cases where we're eliminated hydroxide, the alcohol was in the beta position. It will saponify the ester – in other words, we're going to end up with this: two molecules that are enantiomeric, only one stereocenter. They're carboxylic acids. What if you reacted both of them with this amine: a chiral amine. The amine is not going to change its structure, regardless of which of the carboxylic acids it reacts with. It will neutralize the carboxylic acid, so you'll end up with an ammonium ion. In solution, that ammonium ion can float back and forth between the two molecules, but since you're only using one amine to react with both molecules, it doesn't really matter where the reaction occurs versus where that amine ends up. In other words, you're going to have the same type of salt, no matter what. You'll have one salt made from one enantiomer, and then one salt made from the other.

If you remove the solvent and turn these into solids – presumably they would make solids if they're salts – they're now different compounds from each other. What is the configuration of this amine's stereocenter: R or S? R. On the lefthand of the two products, is that R or S? It is also R. Look down below here. Yes, the alcohol is still R on the left, it's still S on the right – but it's also attached to a salt that does not have a different configuration – it's R for both of the salts. If we look at the pair of stereocenters, one is [RR], one is [SR]. Between these, these are diastereomers. Diastereomers have different physical properties than each other. Now they can be separated. When you just have enantiomers, it's [impossible] to separate them because their physical properties are the same. If we can somehow make some new complex that has one more stereocenter in it, and if we used that same stereocenter in making complexes out of both enantiomers, we now produce effectively diastereomers, which can then be separated. In this example of having just made a salt, if we were then to expose these compounds to hydrochloric acid, then we'll release the salts, get back the carboxylic acids, but now they'll be separated. Enantiomers are [impossible] to separate [because of] same physical properties. Diastereomers [can often be] easily separated because they'll have different physical properties. Once we decompose the complex, since we already separated the diastereomers, now the enantiomers are separated.

Methionine

The whole point of the reactivity of methionine is that sulfur is able to be alkylated. When we do that, the sulfur is able to become a leaving group, and we're going to end up making a ring with the oxygen that's over here that's part of methionine itself. We're going to alkylate here and then do a ring closure. It reacts with the cyanogen bromide, kicks off bromide as a leaving group, S_N2 reaction. Nitrogen attack[s], pushing open the carbonyl, which crosses over, kicks the sulfur group out. We make the five-membered ring, which is a nitrogen analog of a lactone. The point here is that, when we hydrolyze, we cleave the polypeptide. Technically, we first turn it into a normal lactone, but that continues to hydrolyze, so what we end up with at the end is a combination carboxylic acid/alcohol. That is the decomposition of a polypeptide chain at methionine. [HVZ][exam – pl, electrophoresis, ion-exchange chromatography, ninhydrin, amino acid synthesis, protein structure, sequence, l versus d, names of amino acids][there's always a last time once there's a first time]

[final review]

[carboxylic acids – relative reactivity of carbonyl compounds: induction, resonance, leaving group; acidic versus basic mechanisms of carbonyls]

[reactions of carboxylic acids – cationic: esterification, hydrolysis; anionic: saponification, diazomethane; reversibility; synthesis of esters and amides]

[alkylation; reduction – DIBAL-H, other, LiAlH₄ versus NaBH₄; lactones; lactams; nitriles; transesterification; stability of carbonates and carbamic acids]

[enolates – pK_as; alpha-halogenation: acidic, basic – haloform; condensations – aldol, mixed aldol, Claisen, Dieckmann; Michael addition; Robinson annulation]

[more enolates – Stork enamine synthesis; alkylations; malonic ester synthesis]

[amines – reductive amination; reduction of imines, nitriles, amides, azides; Curtius and Hofmann rearrangements; acid/base properties; S_N2 – Hofmann elimination; hydrogenation of nitriles; Gabriel synthesis]

[carbohydrates and amino acids]

Structures – Identical to those from lecture 22A (06/11/12) and lecture 22B (06/12/12)