



## Nucleophilic Acyl Substitution Mechanism

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### Transcript

00:00:00:00 - 00:00:13:72

**Dr. Jessie Key:** Hello again, Dr. Jessie Key here to talk to you about the nucleophilic acyl substitution mechanism. The general mechanism for nucleophilic acyl substitution is two steps, nucleophilic attack followed by loss of leaving group.

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**Dr. Jessie Key:** You can show this by starting your curved arrow at the lone pair of the nucleophilic species and ending at the electrophilic carbonyl carbon of the carboxylic acid derivative. This causes the carbon-oxygen pi bond electrons to move up onto the oxygen as a lone pair. A tetrahedral alkoxide anion intermediate is formed, which can then undergo loss of leaving group by moving a lone pair down from the oxygen to reform the pi bond and then break the carbon leaving group sigma bond to eject the leaving group.

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**Dr. Jessie Key:** This generates the desired substitution product where the nucleophile has replaced the leaving group. It should be noted that the leaving group shown here is  $Z$  can never be a hydride,  $H^-$ , or a carbanion,  $R^-$ , in other words, this reaction does not work on aldehydes or ketones. Nucleophilic acyl substitution is commonly performed under acidic or basic conditions, which can often add additional proton transfer steps to the general mechanism.

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**Dr. Jessie Key:** Proton transfers can occur in several places before the nucleophilic attack, after the nucleophilic attack before losing the leaving group, or as the final step in the mechanism. Under acidic conditions, you should use proton transfers to avoid formation of strongly basic species and negative charges. For example, a first step of the mechanism becomes a proton transfer to generate the protonated carbonyl species before nucleophilic attack.

00:01:51:05 - 00:02:21:39

**Dr. Jessie Key:** This increases the electrophilicity of the carbonyl carbon and it helps to avoid formation of the negatively charged alkoxide intermediate later after the nucleophilic attack occurs. Under basic conditions, avoid formation of positive charges or strongly acidic

species using proton transfers only when necessary. This means that when nucleophiles like hydroxide are used, it is okay for the nucleophile to directly attack the carbonyl carbon without first protonating.

00:02:21:39 - 00:02:47:85

**Dr.Jessie Key:** This will prevent forming the formal positive charge on an acidic protonated carbonyl. In the case of neutral nucleophiles, like a means used under neutral conditions, it is also okay for the nucleophile to directly attack the carbonyl carbon without first protonating. There will likely be a proton transfer necessary at the end of the mechanism to obtain a neutrally charged product.

00:02:47:85 - 00:03:08:18

**Dr.Jessie Key:** Let's go through an example for each of these conditions, acidic, neutral, and basic. In this example, we're provided the starting materials of ethanamide, methanol, and a generic acid catalyst as indicated by the  $H^+$  and square brackets. Nucleophilic acyl substitution will occur to generate the product methyl ethanoate.

00:03:08:18 - 00:03:41:14

**Dr.Jessie Key:** The actual acidic species present will be the protonated conjugate acid of the nucleophile methanol. The first step will be a proton transfer, starting at the carbonyl oxygen lone pair to remove a proton from the protonate methanol to generate the protonated carbonyl which is a better electrophile. Next, nucleophilic attack occurs from the nucleophile methanols oxygen lone pair to the electrophilic carbonyl carbon, which causes the carbon oxygen double one to move up as a lone pair.

00:03:46:26 - 00:04:19:06

**Dr.Jessie Key:** A tetrahedral intermediate is obtained, which has a formal positive charge and an additional proton on the oxygen, which just form the new sigma bond to the central carbon of the carbonyl. Next, a proton transfer occurs, and methanol can act as a base to remove the additional proton, which gives a neutrally charged tetrahedral intermediate. Another proton transfer occurs, protonate amine to make it a better leaving group by using the amine lone pair to remove a proton from the protonated methanol.

00:04:23:84 - 00:04:54:32

**Dr.Jessie Key:** The next step is loss of leaving group. We can take the lone pair on the alcohol group down to form a new pi bond, which causes the carbon nitrogen sigma bond to break and those electrons go the nitrogen of the leaving group ammonia. We're now left with the protonated carbonyl with a formal positive charge that can be remedied by one final proton transfer using another equivalent of ethanol as a base to give the final product the ester methyl ethanoate.

00:05:14:21 - 00:05:46:30

**Dr.Jessie Key:** In this example, we're provided the acid chloride, ethanoyl chloride, the nucleophile water, and we generate the carboxylic acid product ethanoic acid. This is an example of the hydrolysis of an acid chloride under neutral conditions. Under neutral

conditions, we have the nucleophile attack first with an arrow going from the lone pair of the water oxygen to the electrophilic carbonyl carbon.

00:05:46:30 - 00:06:25:55

**Dr.Jessie Key:** This moves the carbon oxygen double bonds pi electrons up onto the oxygen, and we now have a tetrahedral intermediate having both a formal negative and formal positive charge. The next step is loss of the chloride leaving group, where the lone pair of oxygen can come back down to reform the carbon oxygen double bond and this causes the carbon chlorine sigma bond to break and those electrons go to the chlorine causing it to leave as the leaving group chloride. In the final step, a proton transfer can occur where the water can act as a base and remove the extra proton from the protonated carboxylic acid intermediate to give the final product ethanoic acid.

00:06:29:35 - 00:06:47:73

**Dr.Jessie Key:** In this example, we again using ethanoyl chloride to form the carboxylic acid ethanoic acid. This time using basic conditions with the nucleophile hydroxide. In the first step, hydroxide performs nucleophilic attack with an arrow going from the oxygen lone pair electrons to electrophilic carbonyl carbon.

00:06:47:73 - 00:07:21:39

**Dr.Jessie Key:** This causes the carbon oxygen double bond pi electrons to go up onto the oxygen, giving the tetrahedral alkoxide intermediate. The lone pair electrons on the alkoxide oxygen come down to reform the pi bond, which causes the carbon chlorine sigma bond to break and those electrons go to the chlorine, allowing it to leave as leaving group chloride. Because we're in the presence of strong base, the ethanoic acid final product will be deprotonated to its carboxylate form.

00:07:21:39 - 00:07:27:59

**Dr.Jessie Key:** To obtain the carboxylic acid again, a subsequent acidic workup step would be required.