

K2 NUCLEOPHILIC SUBSTITUTION

Key Notes

Definition

Nucleophilic substitutions are reactions which involve the substitution of one nucleophile for another nucleophile. Alkyl halides, carboxylic acids, and carboxylic acid derivatives undergo nucleophilic substitution, but the mechanisms for alkyl halides are quite different from those of carboxylic acids and carboxylic acid derivatives.

Mechanism – charged nucleophiles

There are two steps in the nucleophilic substitution of a carboxylic acid derivative with a charged nucleophile. The first step is the same as the first step of nucleophilic addition to aldehydes and ketones. The second step involves reformation of the carbonyl group and expulsion of the leaving group.

Mechanism – neutral nucleophiles

The mechanism of nucleophilic substitution with neutral nucleophiles is the same as the mechanism for charged nucleophiles, except that an extra step is required in order to remove a proton.

Addition vs substitution

Aldehydes and ketones undergo nucleophilic addition rather than nucleophilic substitution since the latter mechanism would require the cleavage of a strong C–H or C–C bond with the generation of a highly reactive hydride ion or carbanion.

Related topics

Organic structures (E4)
Base strength (G3)
Nucleophilic addition (J3)

Preparation of carboxylic acid derivatives (K5)
Reactions (K6)
Nucleophilic substitution (L2)

Definition

Nucleophilic substitutions are reactions which involve the substitution of one nucleophile for another. Alkyl halides, carboxylic acids, and carboxylic acid derivatives undergo nucleophilic substitution. However, the mechanisms involved for alkyl halides (Topic L2) are quite different from those involved for carboxylic acids and their derivatives. The reaction of a methoxide ion with ethanoyl chloride is an example of nucleophilic substitution (*Fig. 1*), where one nucleophile (the methoxide ion) substitutes another nucleophile (Cl^-).

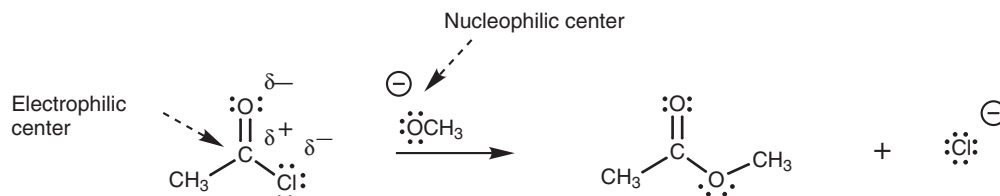


Fig. 1. Nucleophilic substitution.

Mechanism – charged nucleophiles

We shall use the reaction in Fig. 1 to illustrate the mechanism of nucleophilic substitution (Fig. 2). The methoxide ion uses one of its lone pairs of electrons to form a bond to the electrophilic carbonyl carbon of the acid chloride. At the same time, the relatively weak π bond of the carbonyl group breaks and both of the π electrons move onto the carbonyl oxygen to give it a third lone pair of electrons and a negative charge. This is exactly the same first step involved in nucleophilic addition to aldehydes and ketones. However, with an aldehyde or a ketone, the tetrahedral structure is the final product. With carboxylic acid derivatives, the lone pair of electrons on oxygen returns to reform the carbonyl π bond (Step 2). As this happens, the C–Cl bond breaks with both electrons moving onto the chlorine to form a chloride ion which departs the molecule. This explains how the products are formed, but why should the C–Cl σ bond break in preference to the C–OMe σ bond or the C–CH₃ σ bond? The best explanation for this involves looking at the leaving groups which would be formed from these processes (Fig. 3). The leaving groups would be a chloride ion, a methoxide ion and a carbanion, respectively. The chloride ion is the best leaving group because it is the most stable. This is because chlorine is more electronegative than oxygen or carbon and can stabilize the negative charge. This same mechanism is involved in the nucleophilic substitutions of all the other carboxylic acid derivatives and a general mechanism can be drawn (Fig. 4).

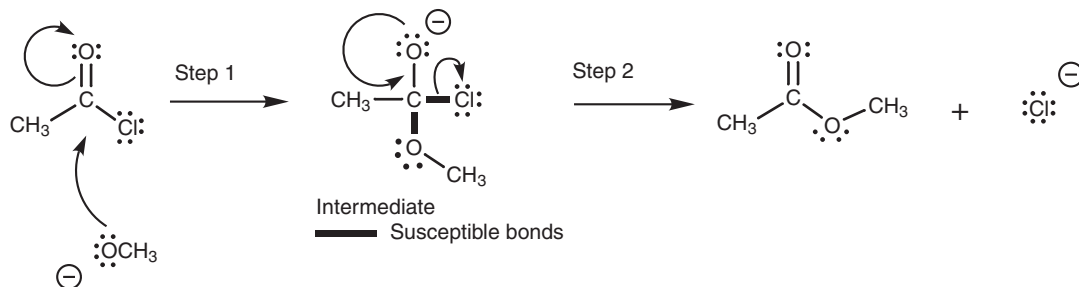


Fig. 2. Mechanism of the nucleophilic substitution.

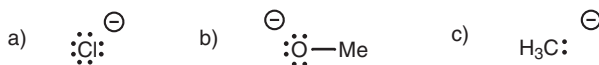


Fig. 3. Leaving groups; (a) chloride; (b) methoxide; (c) carbanion.

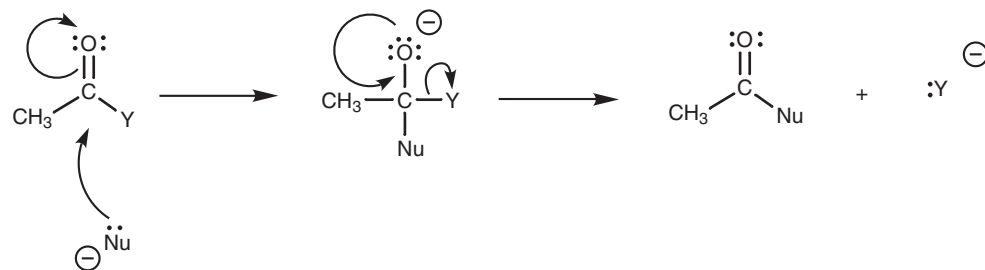


Fig. 4. General mechanism for nucleophilic substitution.

Mechanism – neutral nucleophiles

Acid chlorides are sufficiently reactive to react with uncharged nucleophiles. For example, ethanoyl chloride will react with methanol to give an ester (Fig. 5). Oxygen is the nucleophilic center in methanol and uses one of its lone pairs of electrons to form a new bond to the electrophilic carbon of the acid chloride (Fig. 6). As this new bond forms, the carbonyl π bond breaks and both electrons move onto the carbonyl oxygen to give it a third lone pair of electrons and a negative charge (Step 1). Note that the methanol oxygen gains a positive charge since it has effectively lost an electron by sharing its lone pair with carbon in the new bond. A positive charge on oxygen is not very stable and so the second stage in the mechanism is the loss of a proton. Both electrons in the O–H bond move onto the oxygen to restore a second lone pair of electrons and thus neutralize the charge. Methanol can aid the process by acting as a base. The final stage in the mechanism is the same as before. The carbonyl π bond is reformed and as this happens, the C–Cl σ bond breaks with both electrons ending up on the departing chloride ion as a fourth lone pair of electrons. Finally, the chloride anion can remove a proton from CH_3OH_2^+ to form HCl and methanol (not shown).

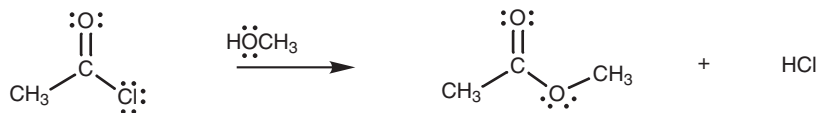


Fig. 5. Ethanoyl chloride reacting with methanol to form methyl ethanoate.

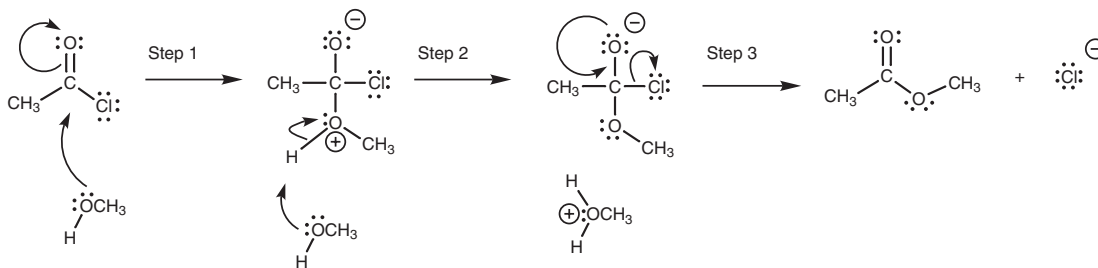


Fig. 6. Mechanism for the reaction of an alcohol with an acid chloride.

The above mechanism is essentially the same mechanism involved in the reaction of ethanoyl chloride with sodium methoxide, the only difference being that we have to remove a proton during the reaction mechanism.

The same mechanism holds true for nucleophilic substitutions of other carboxylic acid derivatives with neutral nucleophiles and we can write a general mechanism (Fig. 7). In practice, acids or bases are often added to improve yields. Specific examples are described in Topic K5.

Addition vs substitution

Carboxylic acids and carboxylic acid derivatives undergo nucleophilic substitution whereas aldehydes and ketones undergo nucleophilic addition. This is because nucleophilic substitution of a ketone or an aldehyde would generate a carbanion or a hydride ion respectively (Fig. 8). These ions are unstable and highly reactive, so they are only formed with difficulty. Furthermore, C–C and C–H σ bonds are not easily broken. Therefore, nucleophilic substitutions of aldehydes or ketones are not feasible.

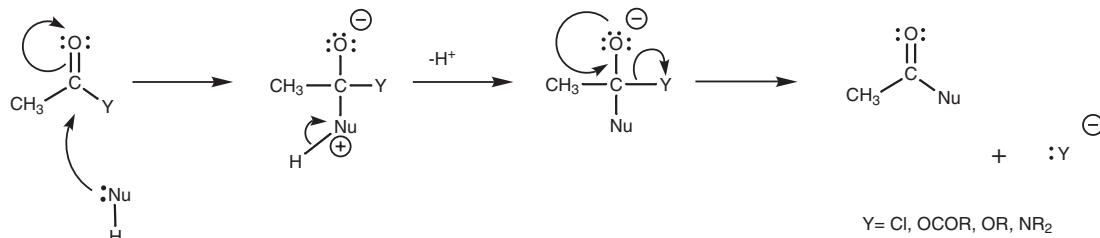


Fig. 7. General mechanism for the nucleophilic substitution of a neutral nucleophile with a carboxylic acid derivative.

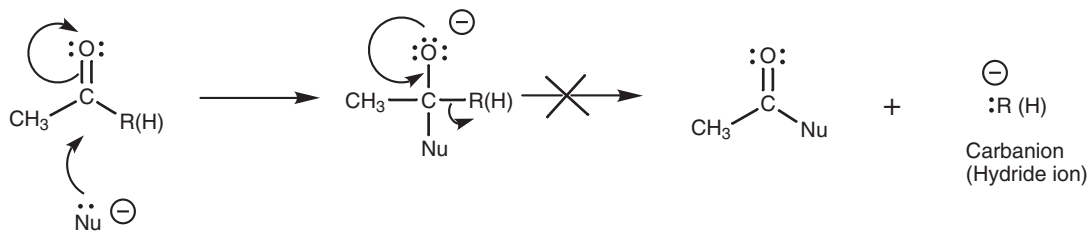


Fig. 8. Unfavorable formation of an unstable carbanion or hydride ion.

K3 REACTIVITY

Key Notes

Reactivity order

Acid chlorides are more reactive than acid anhydrides towards nucleophilic substitution. Acid anhydrides are more reactive than esters, and esters are more reactive than amides. It is possible to convert a reactive acid derivative to a less reactive acid derivative, but not the other way round.

Electronic factors

The relative reactivity of the four different acid derivatives is determined by the relative electrophilicities of the carbonyl carbon atom. Neighboring electronegative atoms increase the electrophilicity of the carbonyl group through an inductive effect. The greater the electronegativity of the neighboring atom, the greater the effect. Chlorine is more electronegative than oxygen, and oxygen is more electronegative than nitrogen. Thus, acid chlorides are more reactive than acid anhydrides and esters, while amides are the least reactive of the acid derivatives. Resonance effects play a role in diminishing the electrophilic character of the carbonyl carbon. Neighboring atoms containing a lone pair of electrons can feed these electrons into the carbonyl center to form a resonance structure where the carbonyl π bond is broken. This resonance is significant in amines where nitrogen is a good nucleophile, but is insignificant in acid chlorides where chlorine is a poor nucleophile. Resonance involving oxygen is weak but significant enough to explain the difference in reactivity between acid anhydrides and esters. Since the resonance in acid anhydrides is split between two carbonyl groups, the decrease in reactivity is less significant than in esters.

Steric factors

Bulky groups attached to the carbonyl group can hinder the approach of nucleophiles and result in lowered reactivity. Bulky nucleophiles will also react more slowly.

Carboxylic acids

Carboxylic acids are more likely to undergo acid–base reactions with nucleophiles rather than nucleophilic substitution. Nucleophilic substitution requires prior activation of the carboxylic acid.

Related topics

Nucleophilic substitution (K2)
Preparations of carboxylic acid derivatives (K5)

Reactions (K6)

Reactivity order

Acid chlorides can be converted to acid anhydrides, esters, or amides (Topic K5). These reactions are possible because acid chlorides are the most reactive of the four carboxylic acid derivatives. Nucleophilic substitutions of the other acid derivatives are more limited because they are less reactive. For example, acid anhydrides can be used to synthesize esters and amides, but cannot be used to synthesize acid chlorides. The possible nucleophilic reactions for each carboxylic

acid derivative depends on its reactivity with respect to the other acid derivatives (Fig. 1). Reactive acid derivatives can be converted to less reactive (more stable) acid derivatives, but not the other way round. For example, an ester can be converted to an amide, but not to an acid anhydride.

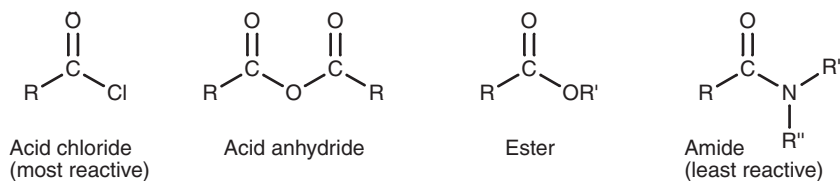


Fig. 1. Relative reactivity of carboxylic acid derivatives.

Electronic factors But why is there this difference in reactivity? The first step in the nucleophilic substitution mechanism (involving the addition of a nucleophile to the electrophilic carbonyl carbon) is the rate-determining step. Therefore, the more electrophilic this carbon is, the more reactive it will be. The nature of Y has a significant effect in this respect (Fig. 2).

Y is linked to the acyl group by an electronegative heteroatom (Cl, O, or N) which makes the carbonyl carbon more electrophilic. The extent to which this happens depends on the electronegativity of Y. If Y is strongly electronegative (e.g. chlorine), it has a strong electron-withdrawing effect on the carbonyl carbon making it more electrophilic and more reactive to nucleophiles. Since chlorine is more electronegative than oxygen, and oxygen is more electronegative than nitrogen, acid chlorides are more reactive than acid anhydrides and esters, while acid anhydrides and esters are more reactive than amides.

The electron-withdrawing effect of Y on the carbonyl carbon is an inductive effect. With amides, there is an important resonance contribution which **decreases** the electrophilicity of the carbonyl carbon (Fig. 3). The nitrogen has a lone pair of electrons which can form a bond to the neighboring carbonyl carbon. As this new bond is formed, the weak π bond breaks and both electrons move onto oxygen to give it a third lone pair of electrons and a negative charge. Since the nitrogen's lone pair of electrons is being fed into the carbonyl group, the carbonyl carbon becomes less electrophilic and is less prone to attack by an incoming nucleophile.

In theory, this resonance could also occur in acid chlorides, acid anhydrides, and esters to give resonance structures (Fig. 4). However, the process is much less important since oxygen and chlorine are less nucleophilic than nitrogen. In these structures, the positive charge ends up on an oxygen or a chlorine atom. These atoms are more electronegative than nitrogen and less able to stabilize a positive charge. These resonance structures might occur to a small extent with esters and acid anhydrides, but are far less likely in acid chlorides. This trend also matches the trend in reactivity.

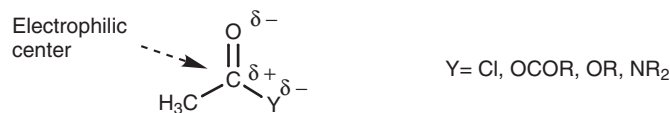


Fig. 2. The electrophilic center of a carboxylic acid derivative.

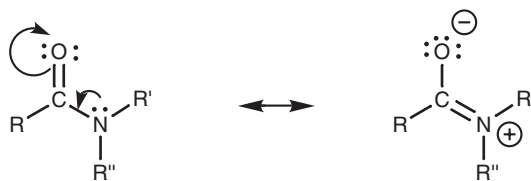


Fig. 3. Resonance contribution in an amide.

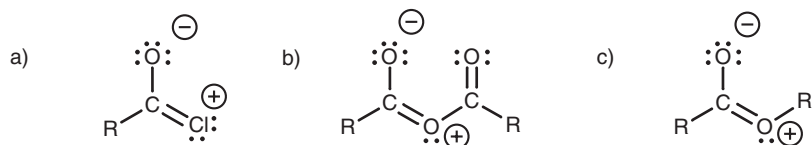


Fig. 4. Resonance structures for (a) an acid chloride; (b) an acid anhydride; (c) an ester.

Although the resonance effect is weak in esters and acid anhydrides, it can explain why acid anhydrides are more reactive than esters. Acid anhydrides have two carbonyl groups and so resonance can take place with either carbonyl group (Fig. 5). As a result, the lone pair of the central oxygen is 'split' between both groups which means that the resonance effect is split between both carbonyl groups. This means that the effect of resonance at any one carbonyl group is diminished and it will remain strongly electrophilic. With an ester, there is only one carbonyl group and so it experiences the full impact of the resonance effect. Therefore, its electrophilic strength will be diminished relative to an acid anhydride.

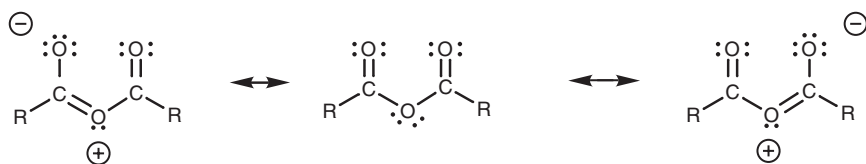


Fig. 5. Resonance structures for an acid anhydride.

Steric factors

Steric factors can play a part in the reactivity of acid derivatives. For example, a bulky group attached to the carbonyl group can hinder the approach of nucleophiles and hence lower reactivity. The steric bulk of the nucleophile can also have an influence in slowing down the reaction. For example, acid chlorides react faster with primary alcohols than they do with secondary or tertiary alcohols. This allows selective esterification if a molecule has more than one alcohol group present (Fig. 6).

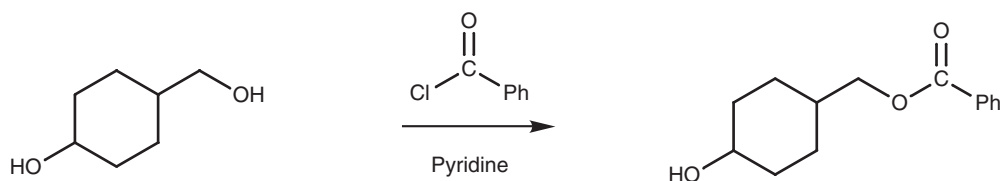


Fig. 6. Selective esterification of a primary alcohol.

Carboxylic acids Where do carboxylic acids fit into the reactivity order described above? The nucleophilic substitution of carboxylic acids is complicated by the fact that an acidic proton is present. Since most nucleophiles can act as bases, the reaction of a carboxylic acid with a nucleophile results in an acid–base reaction rather than nucleophilic substitution.

However, carboxylic acids can undergo nucleophilic substitution if they are activated in advance (Topic K5).