

❖ Ambident Nucleophiles and Regioselectivity

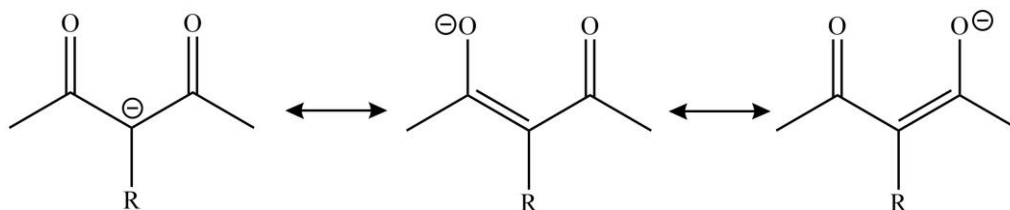
Ambidentate nucleophiles may simply be defined as the nucleophilic species that have more than one atom for the attack to result in different structural isomers; nevertheless, if one isomer is preferred over the other, the phenomenon is called as regioselectivity.

In this section, we will discuss the different types of ambident nucleophiles; and then will try to explain the factors governing the regioselectivity arising from these nucleophiles.

➤ Different Types of Ambident Nucleophiles

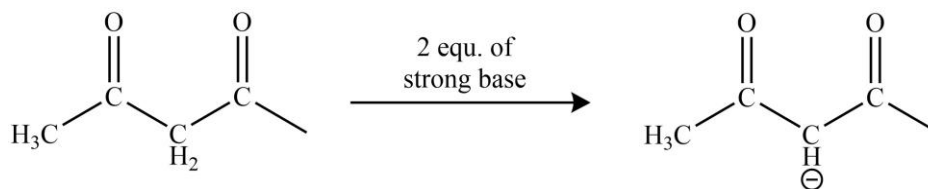
The different types of ambident nucleophiles which are very common in synthetic organic chemistry are discussed below.

1. $[-CO-CR-CO-]^-$ -type ions: The ions of this type are obtained by the elimination of a proton from β -keto esters, malonic esters, or β -diketones, and resonance hybrid structures are needed to depict them.



The possibility of nucleophilic attack arises at the saturated carbon through the oxygen or carbon atoms resulting in O-alkylation or C-alkylation, respectively. However, if the ions are unsymmetrical in nature, three different products can be obtained because either oxygen can show an attacking tendency. Furthermore, the O- or C-acylation can be achieved if the substrate has a carbonyl group.

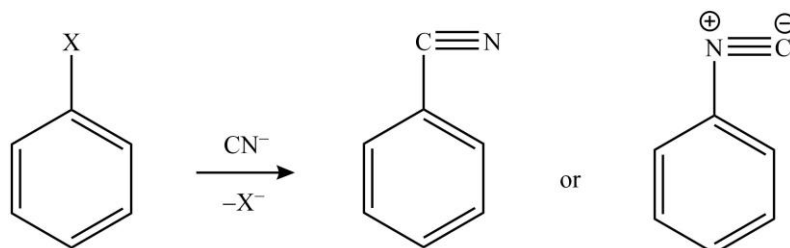
2. $[CH_3CH-CH_2-CO-]$ -type molecules: Upon treating with 2 molar equivalents of a strong base, these types of molecules can release two protons forming a dicarbanion.



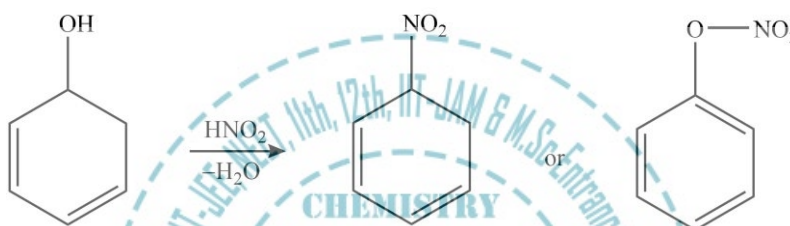
Now although the two atoms bearing negative charge are carbon, these nucleophiles are still called as ambident because they are non-equivalent in nature.; and the possibility of attack by oxygen is also there. Now because the hydrogen at carbon attached to one carbonyl group is less acidic than that of a carbon bonded to two, the CH_2 group should be more basic than the CH group, and therefore, more suitable for the attacks.

All this results in a useful generalization that if there is a stronger acidic group but we need to eliminate a proton from some other carbon to create a nucleophilic site, the removal of both is possible; however, the attack will happen at the weakly acidic position because this conjugate base of the more weak acid. Alternatively, one more acidic proton is needed to be removed if we want to attack a more acidic position.

3. CN^- Ion: This nucleophilic ion can give rise to isocyanides or nitriles depending upon the mode of the chemical bond between carbon and the attacking group.



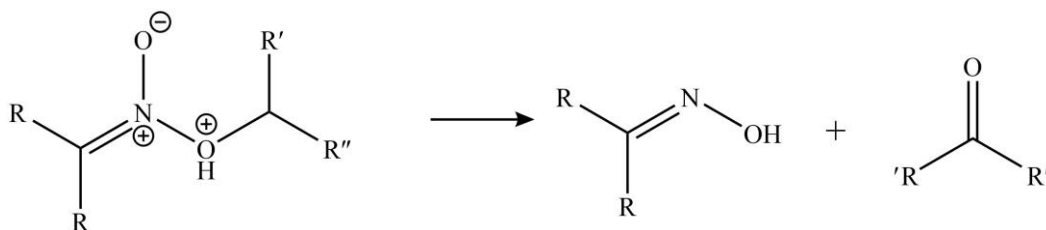
4. NO_2^- Ion: This nucleophilic ion can give rise to nitro compounds or nitrites depending upon the mode of the chemical bond between the carbon and attacking group.



5. Phenoxide Ions: Ions of this type are analogous to enolate anions and can undergo a chemical change to give rise to O-alkylation or C-alkylation.



6. Aliphatic nitro compound's derivatives: In these types of reactions, a carbanion of kind $\text{O}_2\text{N}-\text{R}_2\text{C}^-$ is formed which can be alkylated at carbon or oxygen atom. Furthermore, it is also worthy to remember that the alkylation at oxygen results in the nitronic esters, but these esters would break down to give an aldehyde or ketone or oximes upon simple heat treatment.



➤ **Factors Dictating the Nature of Regioselectivity**

Following the definition of regioselectivity (one product is favored over the other), various factors dictating this preferential attack are discussed below.

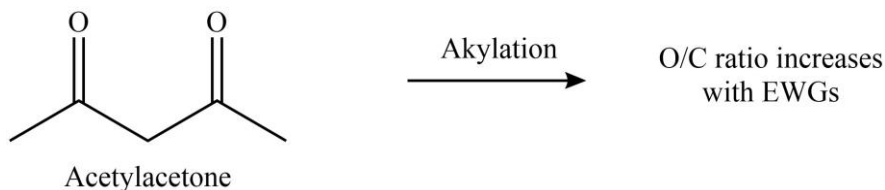
1. Mechanism of the reaction: According to HSAB (hard-soft-acid-base) principle, the hard acids prefer to bind with hard bases whereas soft acids prefer to bind with soft bases. Therefore, we can say that ambident nucleophile uses its more electronegative atom to participate in S_N1 mechanism because the carbocation formed is a hard base; whereas it will use its less electronegative atom to participate in S_N2 mechanism because the carbon center of a molecule is soft acid. In other words, we can say that supporting the S_N2 character of a reaction motivates the nucleophile to attack via a less electronegative group and the vice-versa is also true.

2. Nature of the cation: Since a positive counterion exists for each negatively charged nucleophile, the S_N1 mechanism will be supported if this ion helps the elimination of leaving group (such as Ag^+). On the other hand, if this is a more common type like K^+ or Na^+ , then S_N2 pathway will be supported.

3. Nature of the solvent: The nature of the solvent also affects the site of the attack by making nucleophile more or less free. A freer nucleophile prefers to attack via its more electronegative atom whereas a more engaged nucleophile prefers to attack via the less electronegative atom. The atom with a higher electronegativity is better solvated in protic solvents by the formation of hydrogen bonds. However, neither atom of the nucleophile is significantly solvated in polar aprotic solvents and these solvents are very efficient in solvating different cations making more electronegative atom suitable for attack. Therefore, the higher electronegative end of the nucleophile shows low engagement from both cation as well as from solvent in polar aprotic solvents.

5. Steric effects: It is quite a well-known fact that sterics play a very important role in deciding the final product of a chemical reaction across the domain. If one site surrounded by more bulky groups, is less likely to be attacked in an associative pathway than a less crowded site, and vice-versa is also true. Furthermore, the product with more steric hindrance is less likely to be formed.

4. Electron withdrawing effect: The attachment of more electron-withdrawing groups makes the carbon more electron-deficient and suitable for the attack via more electronegative site, whereas the attachment of more electron-donating groups makes the carbon less electron-deficient and suitable for the attack via a less electronegative site.



For instance, the shift for the attack from carbon to oxygen takes place for the alkylation of acetylacetone's sodium salts.

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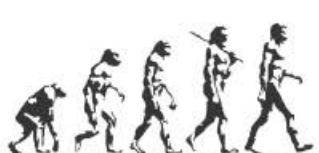
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A TEXTBOOK OF ORGANIC CHEMISTRY

Volume I

MANDEEP DALAL



First Edition

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