

Fundamentals of Theoretical Organic Chemistry

Lecture 5

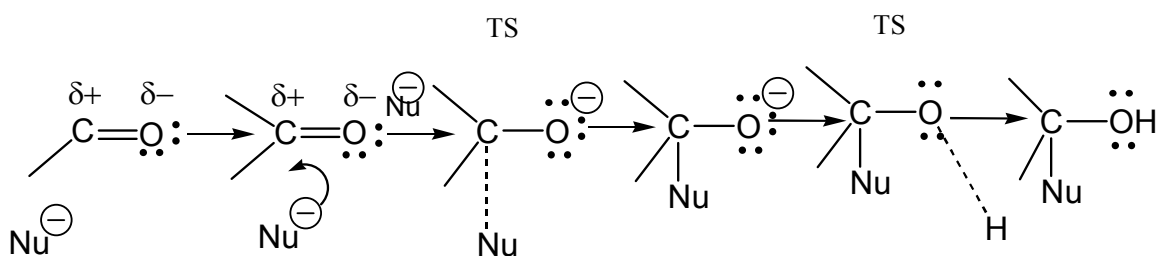
2 Reaction mechanisms in Organic Chemistry

2.2 Addition

2.2.1 Nucleophilic addition

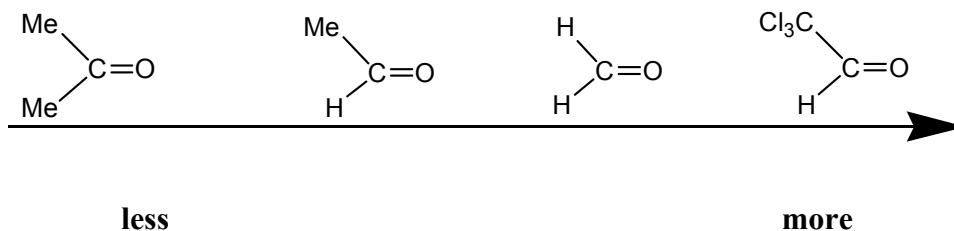
Short summary of nucleophilic addition is given in the chapter of electrophilic addition.

An addition occurs when a molecule containing a double bond is attacked by another molecule having negative (full or partial) charge. Due to the electron richness of the double bond an approach of a nucleophile agent is favourable only if the double bond is asymmetric built up from two atoms with large difference in electronegativity. Such double bond are typically the C=O and C=N bonds. C=C bonds can also subject to nucleophilic addition if one of the carbon atoms is electron poor, such as in acrylonitrile ($\text{H}_2\text{C}=\text{CH}-\text{C}\equiv\text{N}$). Typical nucleophilic agents are negative ions (Cl^- , $^-\text{O}-\text{R}$ etc.) Not like in the case of electrophilic addition the first step of the reaction is not due to the larger reactivity of the π electrons of the double bond, but rather the reactivity of the atom at the relative electron poor side.



The nucleophile group attacks the negatively charged carbon to result the tetrahedral intermediate. Next the oxygen atom acquires an atom or group (e.g. a proton) to stabilize.

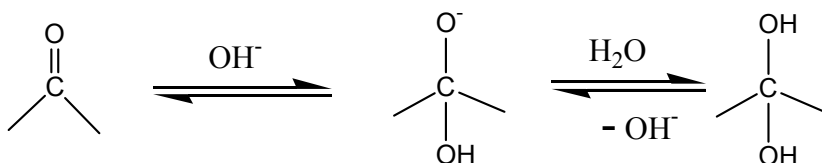
The degree reactivity depends on the polarisation of the double bond. Electron donating groups on the carbon atom side reduce the polarisation and consequently the reactivity.



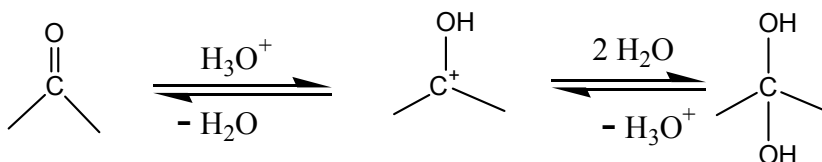
Reactivity

The reaction is catalysed by both acids and bases. Rate constant of the reaction is usually low at $\text{pH}=7$, while high or low pH accelerates the reaction without modifying the equilibrium.

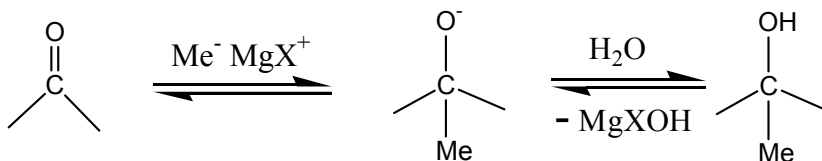
At pH > 7 OH⁻ ions are present in higher concentration, which is a much better nucleophile than water. In this mechanism the OH⁻ attacks the carbonyl carbon atom producing a charged reactant which acquires a proton from the water reproducing the OH⁻ anion.



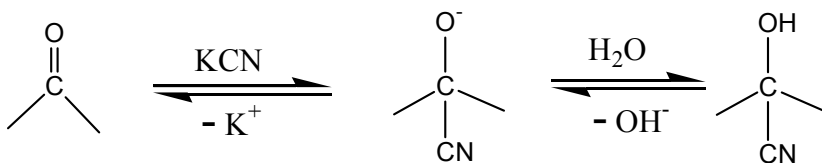
At pH < 7 first the polarisation of the carbonyl group takes place through protonation of the carbonyl oxygen, producing a positively charged carbon which becomes much more sensitive to nucleophilic attack than it was before.



The above reactions resulted the formation of a new C–O bond as the product of the addition. Nucleophile addition can also be used to form a new C–C bond using e.g. a Grignard reagent. Grignard reagents have a structure R–MgX, where the R group has a partial negative charge and can act as a strong nucleophile.

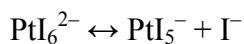


C–C bond formation can be achieved by other C-nucleophiles such as KCN.

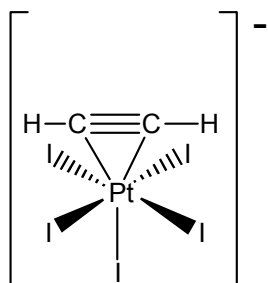
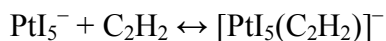


Nucleophilic addition to acetylene (HC≡CH)

Before the nucleophilic addition acetylene has to be activated. Activation is done by PtI₆²⁻ in water. PtI₆²⁻ releases a I⁻ ion in an equilibrium in water:

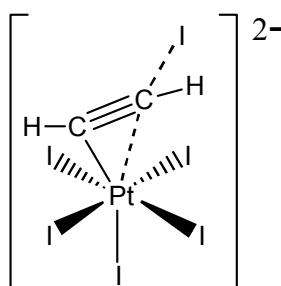


and the resulting PtI_5^- activates the $\text{HC}\equiv\text{CH}$:

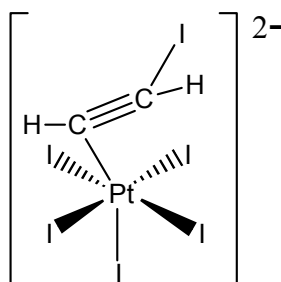


(4)

In this state the acetylene is sensitive to the nucleophilic attack of the I^- ion.



(5)



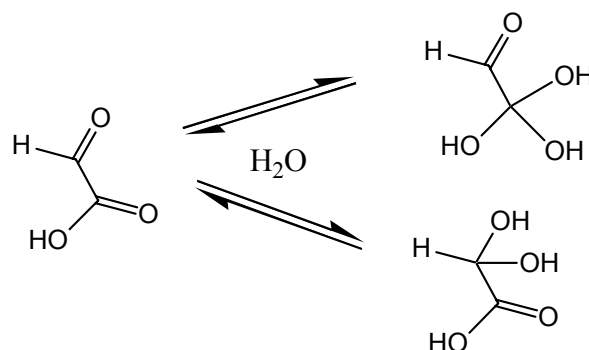
(6).

Through (5) to result (6) According to PCM RB3LYP/BSI calculations the activation energy of this reaction is 5.1 kcal/mol, while the reaction energy is -16.2 kcal/mol. Gas phase calculations of the same system, at the same level of theory gave values 34.3 and 19.2 kcal/mol, respectively, which show the importance of the presence of the highly dielectric environment. (platina ananikov 00 5,6)

Hydration and hydrolysis of alfa-oxo carboxylic acid derivatives

In case of alfa-oxo carboxylic acids, there are two possibilities for nucleophilic addition. Both carbonyl groups can be subject to the reaction. If their molecular environment is different, then the reactions will have different energetics. In the presented case the molecule has a carbonyl group and a carboxylic acid group. Water can be added to both groups. Based on RB3LYP/6-311++G**

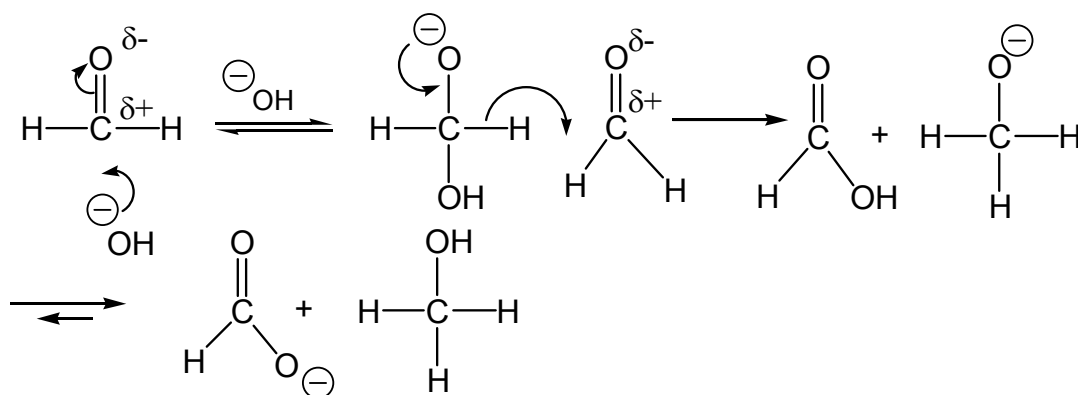
calculations, regarding the reaction energy addition of water to the carbonyl group is favourable ($\Delta E = -7.2$ kcal/mol), while addition to the carboxylic acid group is not favourable ($\Delta E = 5.6$ kcal/mol). The energy barriers of the transition states are 34.2 and 41.0 kcal/mol, respectively. In terms of free energy, however both reactions become unfavourable ($\Delta G = 2.7$ kcal/mol and $\Delta G = 15.6$ kcal/mol).



alfa-oxo-karbonsav janoschek99 7

Cannizzaro reaction

Two moieties of H_2CO form in basic environment a HCOOH and a H_3COH . This is when formaldehyde disproportionate to formic acid and methanol. The first step of this reaction is a nucleophilic addition. The negatively charged OH^- attacks the carbon of the formaldehyde.

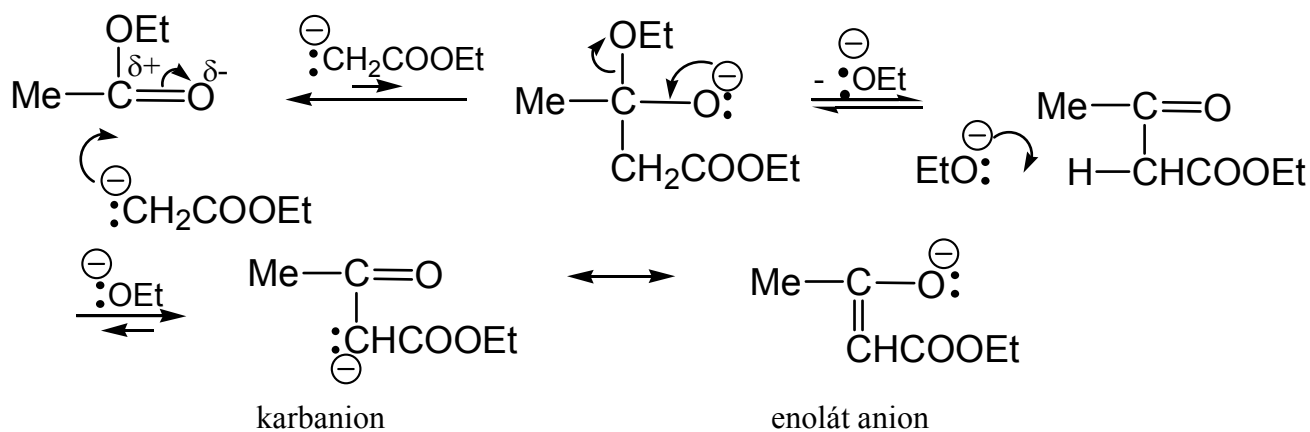


Based on MP3STDQ/6-311++G(d,p)//RHF/6-311++G(d,p) calculations the nucleophilic addition releases 35.3 kcal/mol energy.

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Claisen condensation

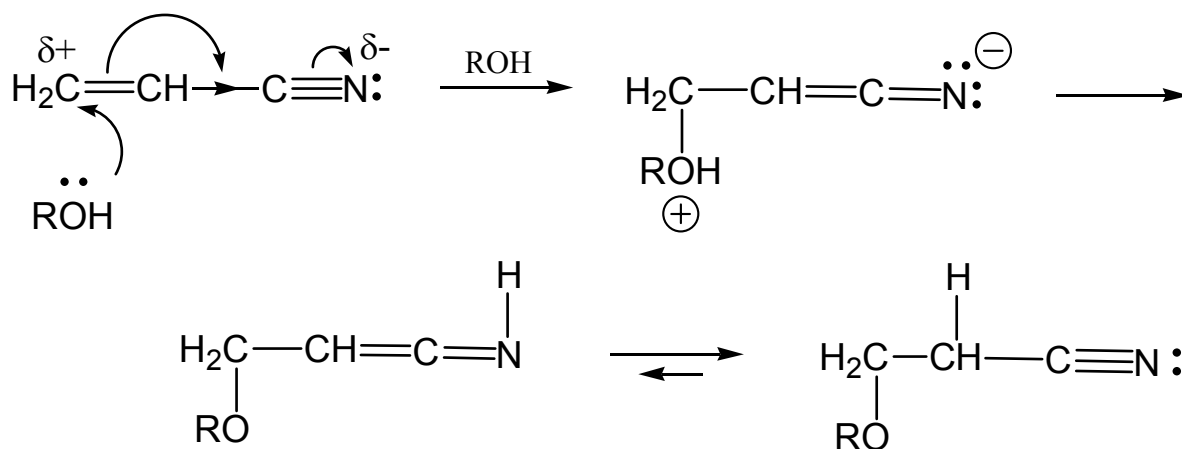
Nucleophilic addition occurs when the deprotonated acetic acid ethyl ester attacks another moiety neutral acetic acid ethyl ester.



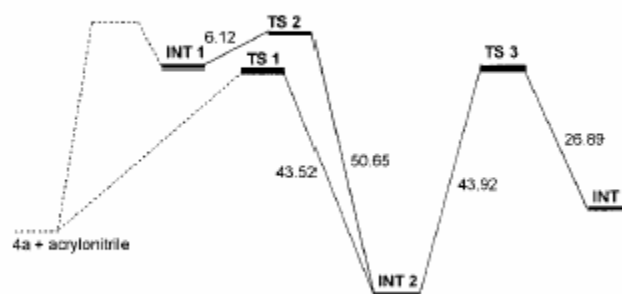
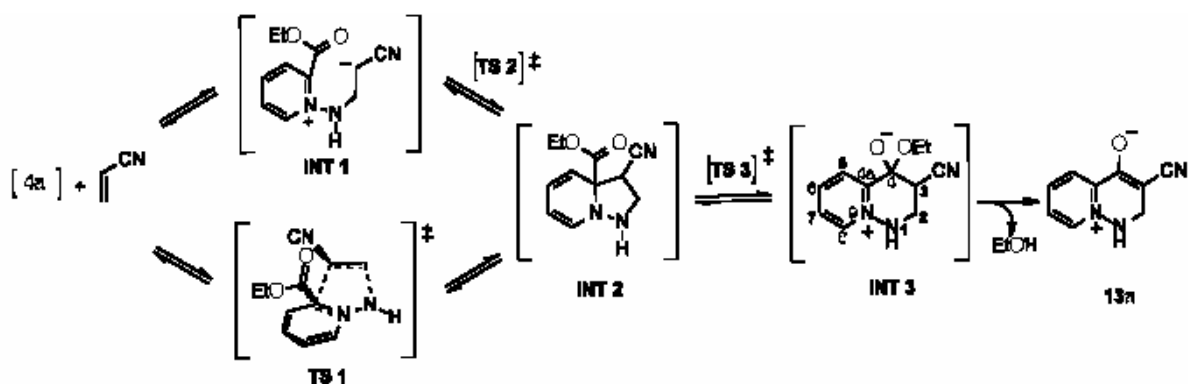
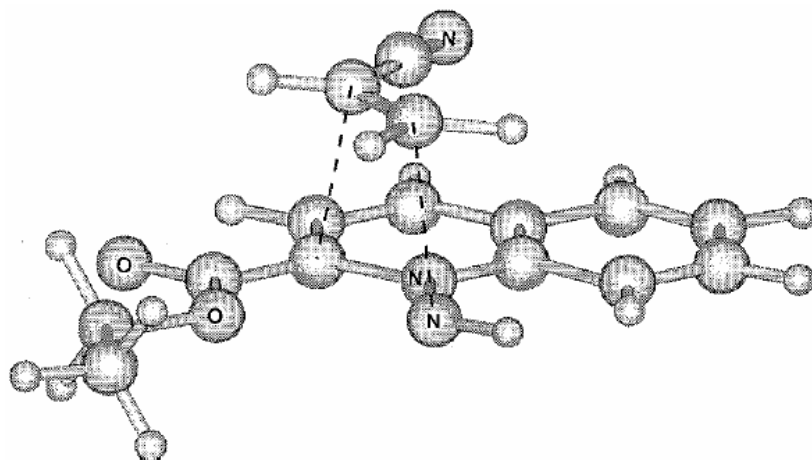
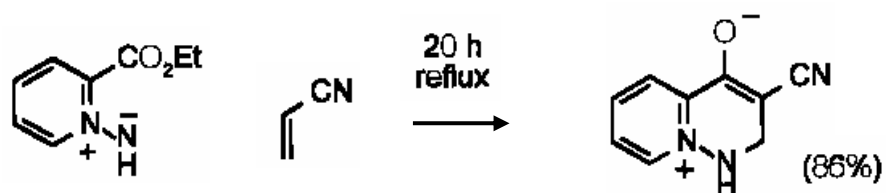
claisen guest 97 9

Nucleophilic addition on C=C bond (acrylonitrile)

Acrylonitrile can be subject to nucleophilic addition as its C=C bond is strongly asymmetric.



An example of such reaction is shown below, where the reaction goes in a concerted mechanism, while the negatively charged nitrogen atom makes a nucleophilic attack on the terminal carbon of the acrylonitrile, the ester carbon exerts an electrophilic attack on the neighbouring carbon of the acrylonitrile. The energetic diagram is shown.



akrilnitril (Valenciano 99) 3,4