

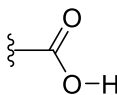
Organic Chemistry
Semester-4, CBCS
Course: CEMG CC-4/GE-4

Course taught by: Kaushik Basu, Department of Chemistry, SPCMC, Kolkata

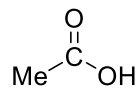
email: chiralkaushik@gmail.com

Lecture Note prepared by Kaushik Basu, SPCMC

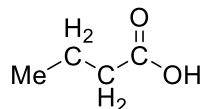
Carboxylic acids are compounds with a -COOH group.



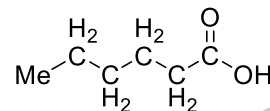
These compounds are abundant in nature, where they are responsible for some familiar odours.



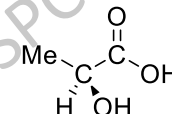
acetic acid
(pungent smell of vinegar)



butanoic acid
(rancid odour of sour butter)

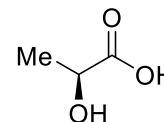
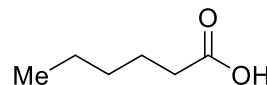
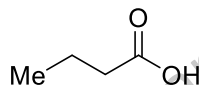
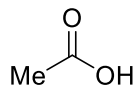


hexanoic acid
(odour of dirty socks)

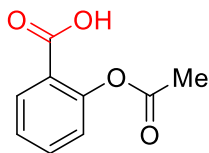


lactic acid
(odour of sour milk)

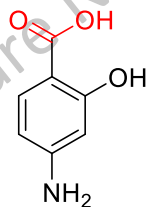
These molecules may also be drawn in the following way (line structure):



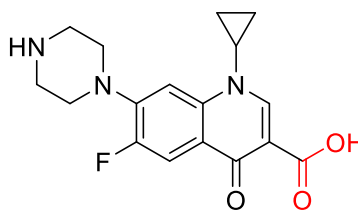
Carboxylic acids are also found in a wide range of pharmaceuticals that are used to treat a variety of conditions.



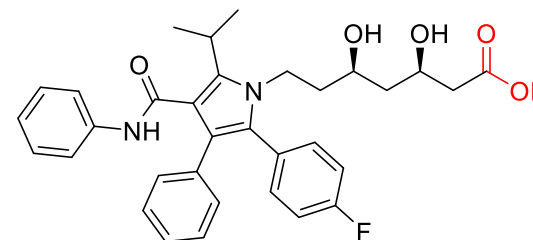
acetylsalicylic acid
(aspirin, analgesic)



4-aminosalicylic acid
(for tuberculosis treatment)



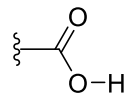
ciprofloxacin
(antibiotic)



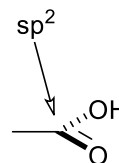
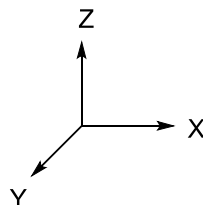
atorvastatin
(for cardiovascular disease)

Structure and property:

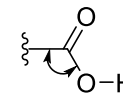
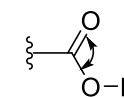
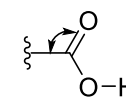
Carboxylic acids are compounds with a -COOH group.



The carbon atom of a carboxylic acid group is sp^2 hybridized and therefore exhibits trigonal planar geometry with bond angles that are nearly 120° .

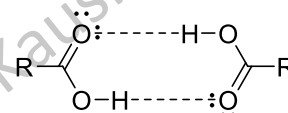


planar, resides on the XY plane



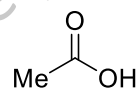
All bond angles
~ 120°

Carboxylic acids can form two intermolecular hydrogen-bonding interactions, allowing the molecules to associate with each other in pairs.

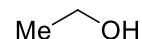


carboxylic acid dimer

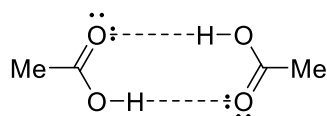
These hydrogen-bonding interactions explain the relatively high boiling points of carboxylic acids. For example, compare the boiling points of acetic acid and ethanol. Acetic acid has a higher boiling point as a result of stronger intermolecular forces.



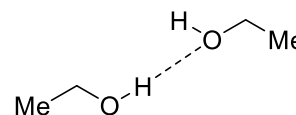
acetic acid, b.p. 118°C



ethanol, b.p. 78°C



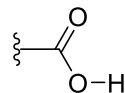
stronger H-bonds



relatively weaker H-bonds

Structure and property: Acidity

Carboxylic acids are compounds with a -COOH group.

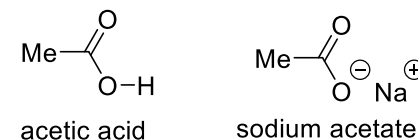


As their name implies, carboxylic acids exhibit mildly acidic protons.

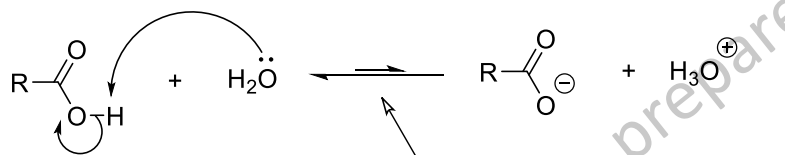
Treatment of a carboxylic acid with a strong base, such as sodium hydroxide, yields a carboxylate salt.



Carboxylate salts are ionic and are therefore more water-soluble than their corresponding carboxylic acids. Carboxylate ions are named by replacing the suffix "ic acid" with "ate"; for example:



Even in water, carboxylic acid is partly ionized:



In most cases, the equilibrium significantly favours the carboxylic acid, i.e. it favours the LHS.

Note the direction of the equilibrium arrow

To quantify the relative acidity of different species, we use something known as the pK_a .

This is the negative log value of K_a , where K_a is the acid ionization constant

$$pK_a = -\log K_a$$

What exactly is the acid ionization constant?

Structure and property: Acidity

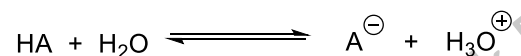
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$$pK_a = -\log K_a$$

What exactly is the acid ionization constant?

Consider the following equilibrium where HA is an acid, A^- is the corresponding conjugate base, H_2O is the base and H_3O^+ is the conjugate acid



The equilibrium constant for this reaction can be defined as:

$$K_{eq.} = \frac{[H_3O^+][A^-]}{[HA][H_2O]} \quad [X] \text{ implies eqm. concentration of species X}$$

as water is the solvent as well as the base here, its concentration is essentially constant.

Thus, we have,

$$K_a = K_{eq.} [H_2O] = \frac{[H_3O^+][A^-]}{[HA]} \quad \text{at a fixed T}$$

Recall that,

$$pK_a = -\log K_a$$

As the acidity increases, the HA molecules have a greater tendency to ionize, $K_{eq.}$ increases, so does K_a

As K_a increases, $-\log K_a$ decreases, i.e. pK_a decreases.

Therefore, *higher* the acidity of an acid HA, *smaller* is the value of its pK_a .

Structure and property: Acidity

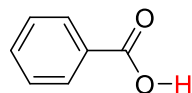
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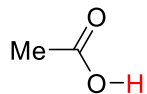
Higher the acidity of an acid HA, smaller is the value of its pK_a .

Carboxylic acids generally have K_a usually around 10^{-4} or 10^{-5} . In other words, the pK_a of most carboxylic acids is between 4 and 5.



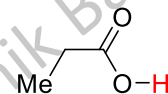
benzoic acid

pK_a 4.19



acetic acid

4.76

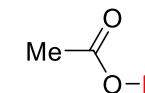


propanoic acid

4.87

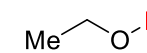
When compared to inorganic acids, such as HCl or H_2SO_4 , carboxylic acids are extremely weak acids.

But when compared to most classes of organic compounds, such as alcohols, they are relatively acidic. For example, compare the pK_a values of acetic acid and ethanol.



acetic acid

pK_a 4.76

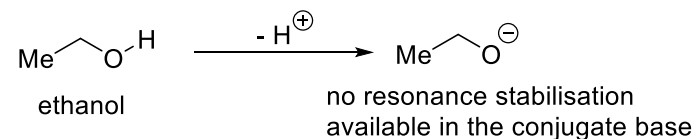
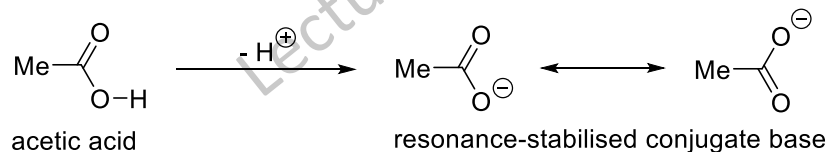


ethanol

16

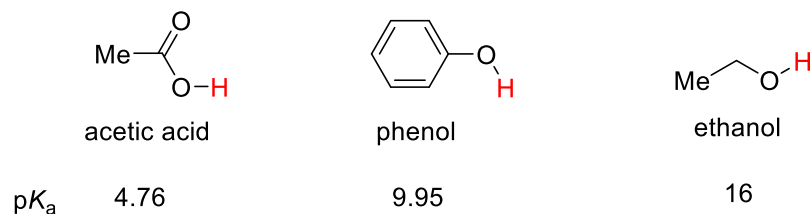
Acetic acid is 11 orders of magnitude more acidic than ethanol (over a hundred billion times more acidic).

The acidity of carboxylic acids is primarily due to the stability of the conjugate base, which is resonance-stabilized.

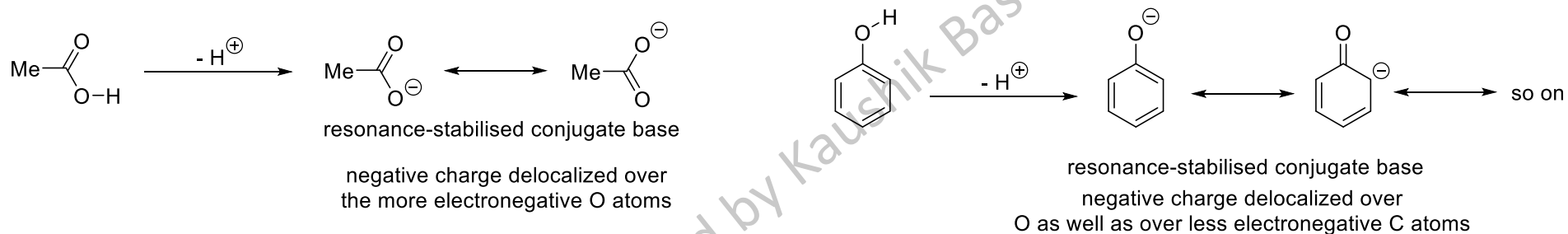


In the conjugate base of acetic acid, the negative charge is delocalized over two oxygen atoms, and it is therefore more stable than the conjugate base of ethanol.

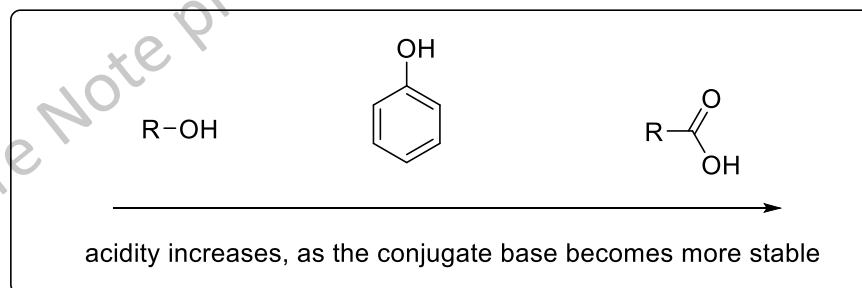
Structure and property: Acidity



The conjugate base of phenol is also resonance-stabilized, but its stabilization is less than that of carboxylates.



Thus acidity order of the three classes of compounds:

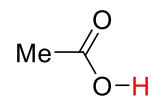


The key to increasing the acidity is therefore to stabilise the conjugate base. This implies delocalizing the negative charge on the conjugate base. Either via resonance or via some other mechanism.

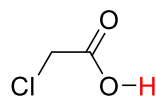
Structure and property: Acidity

Substituent Effect on Acidity:

The presence of electron-withdrawing substituents can have a profound impact on the acidity of a carboxylic acid.

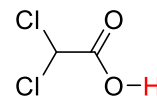


acetic acid

pK_a 4.76

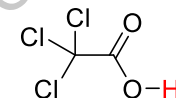
2-chloroacetic acid

2.9



2,2-dichloroacetic acid

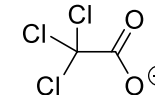
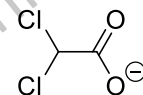
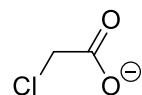
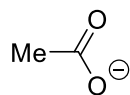
1.3



2,2,2-trichloroacetic acid

0.9

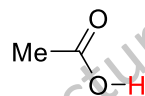
conjugate base:



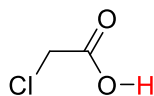
pK_a decreases with each additional chlorine substituent at the α-carbon.

Cl is an electron-withdrawing group (EWG). It draws away the electron density from the carboxylate group by inductive withdrawal. As the number of the EW Cl atoms increases, the conjugate base become progressively more stable. Therefore acidity increases with the increase in the number of Cl atoms at the α-carbon.

As the EW capacity of the EWG increases, the conjugate base becomes more stable and the acidity increases.

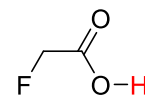


acetic acid

pK_a 4.76

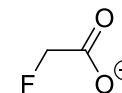
2-chloroacetic acid

2.9

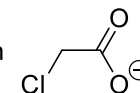


2-fluoroacetic acid

2.6



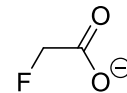
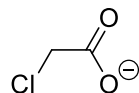
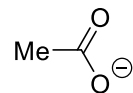
is more stable than



F is more electronegative than Cl

pK_a decreases with increase in the EW capacity of the substituent

conjugate base:

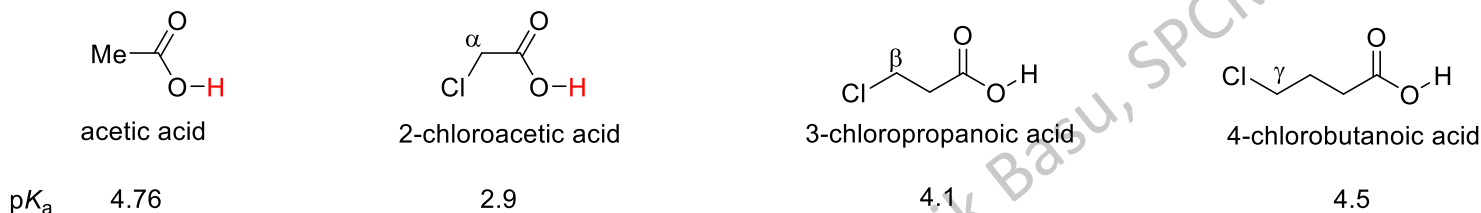


Structure and property: Acidity

Substituent Effect on Acidity:

The presence of electron-withdrawing substituents can have a profound impact on the acidity of a carboxylic acid.

The effect of an electron-withdrawing group depends on its proximity to the carboxylic acid group.



The EW effect is most pronounced when the electron-withdrawing group is located at the α -position (C-2).

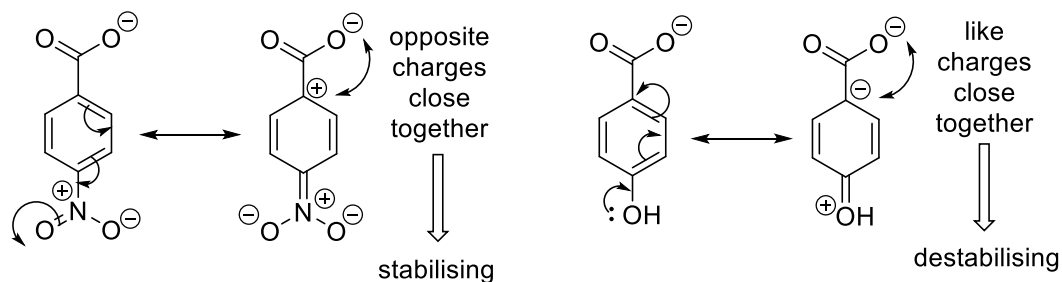
As the distance between the chlorine atom and the carboxylic acid group increases, the EW effect of the chlorine atom is diminished, acidity decreases.

pK_a increases with increasing distance between the EW substituent and the carboxylate group

The effects of electron-withdrawing substituents are also observed for substituted benzoic acids.

		EWG			ERG	
	Z	NO_2	CHO	Cl	H	Me
pK_a	3.4	3.8	4.0	4.2	4.3	4.5

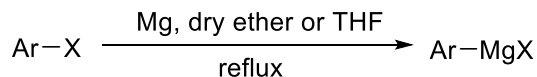
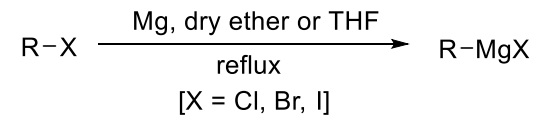
A nitro group is a powerful electron-withdrawing group (-I, -R effect). Consequently, the presence of the nitro group on the ring will stabilize the conjugate base, giving a low pK_a value (relative to benzoic acid). In contrast, a hydroxy group is a powerful electron-donating group (+R > -I effect), and therefore, the presence of the hydroxy group will destabilize the conjugate base, giving a high pK_a value (relative to benzoic acid).



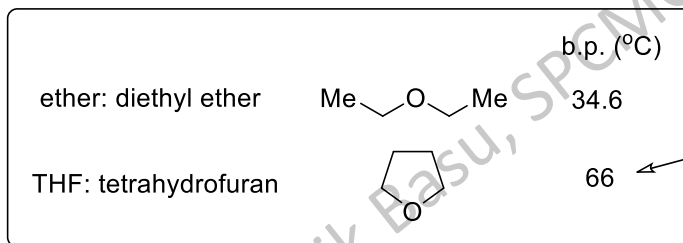
Preparation: Carboxylic acids from Grignard reagents

Grignard Reagents: Organomagnesium compounds of general formula RMgX or ArMgX .

Typically made from organohalides and Mg metal, in inert solvents such as ether under N_2 atmosphere.

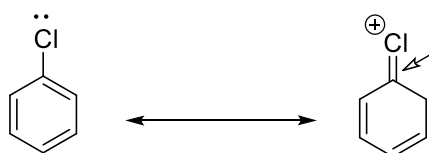


[For X=Cl, THF has to be used, for X = Br, I, we can use ether]

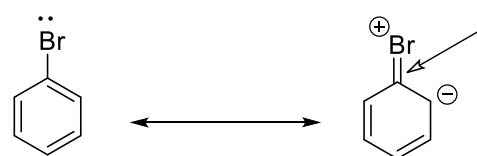


can do the reaction at high temp.s

Mg is oxidatively inserted into the C-X bond; weaker the C-X bond, easier is the reaction:



partial double bond character, stronger C-Cl bond, more difficult to break.

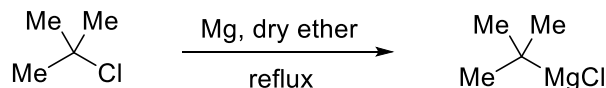
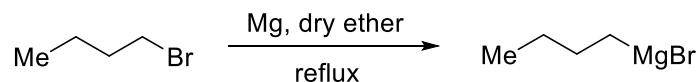
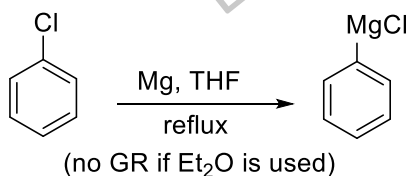
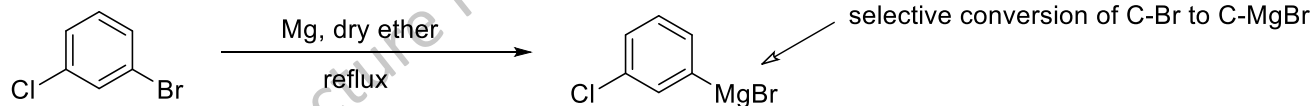


less effective resonance, C-Br orbital size mismatch, C-Br bond relatively weak, easier to break.

must use high boiling THF

can use low boiling ether

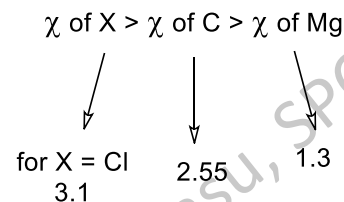
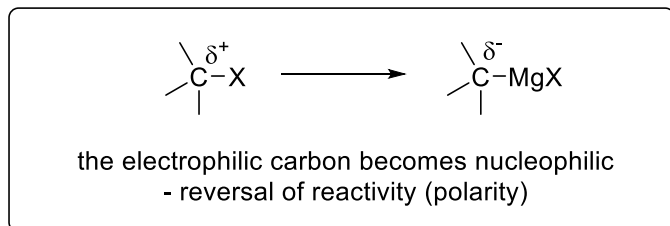
Illustrative examples:



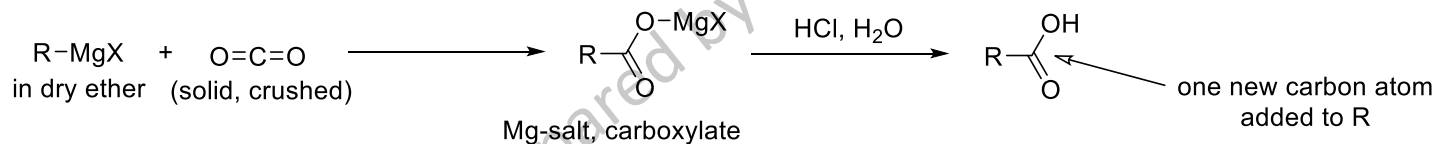
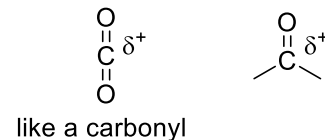
(For aliphatic organochlorides, there is no possibility of conjugation, C-Cl is pure single bond, can use ether as solvent)

Preparation: Carboxylic acids from Grignard reagents

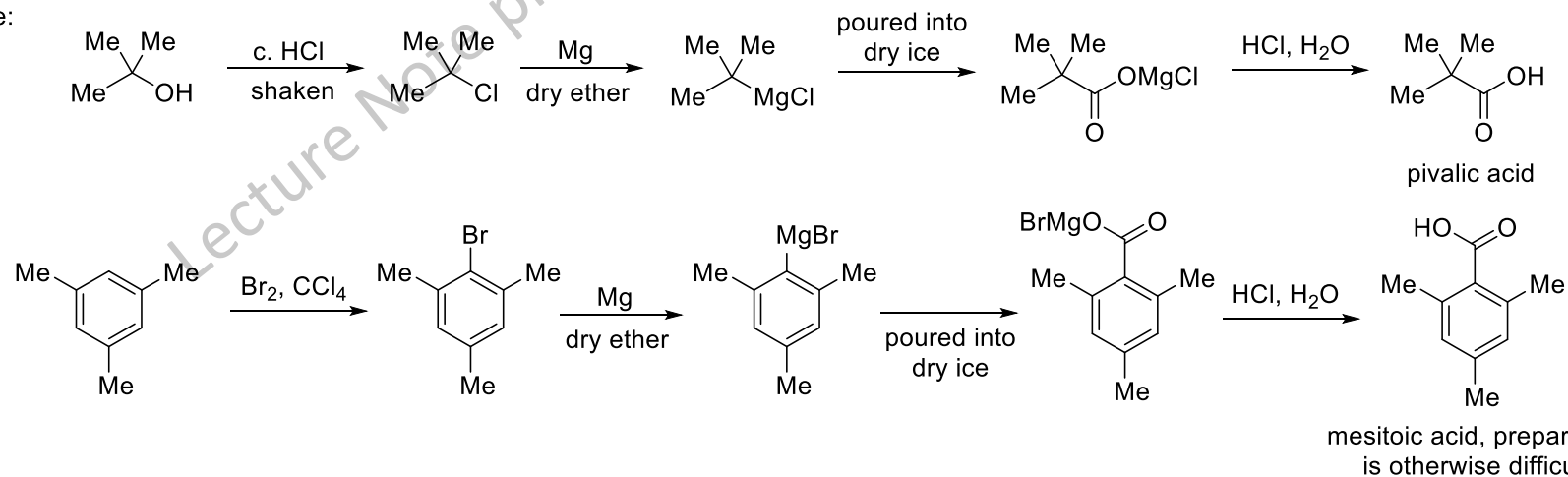
Utility of Grignard reagents: Source of carbanions - negatively polarised carbon - extremely useful for construction of new C-C bonds,



Grignard reagent can thus act as a nucleophile and react with a variety of electrophiles to generate various products. One such electrophile is carbon dioxide. The product is a carboxylate salt, upon work up we get a carboxylic acid.

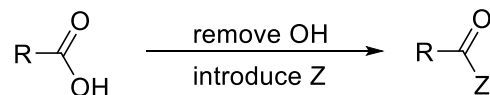


Example:

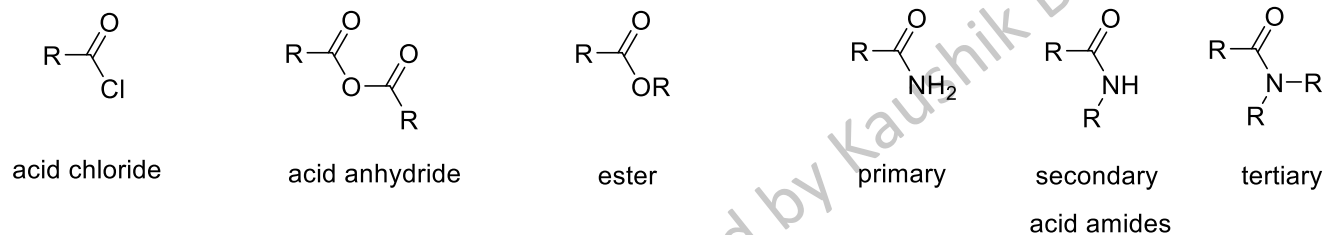


Introduction to carboxylic acid derivatives:

Carboxylic acids can be converted into several derivatives that still contain the acyl group:



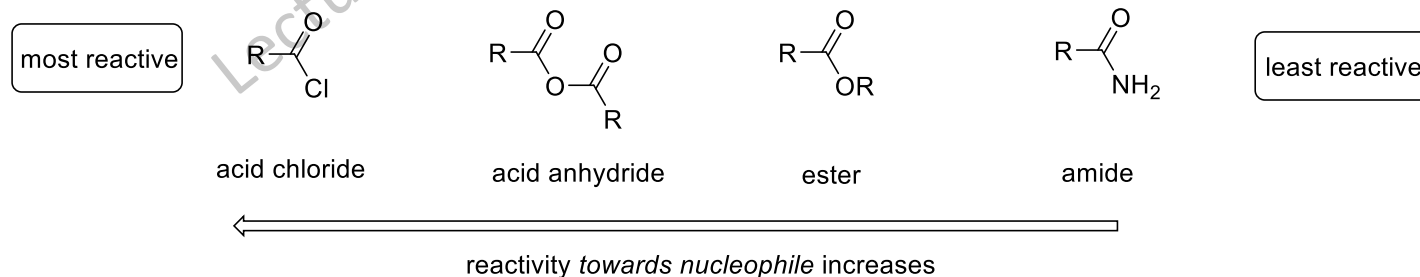
Replacement of the OH group with a different group (Z) does not involve a change in oxidation state if Z is a heteroatom (Cl, O, N, etc.). Compounds of this type are called carboxylic acid derivatives. The four most common types of carboxylic acid derivatives are shown below.



The carbon atom of a carbonyl group is electrophilic as a result of both inductive and resonance effects.

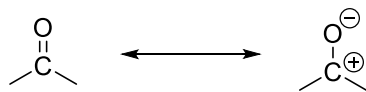


The same is true of carboxylic acid derivatives, although there is a wide range of reactivity among the carboxylic acid derivatives, illustrated in the following figure:



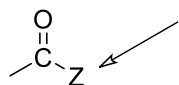
Introduction to carboxylic acid derivatives:

Explanation of relative reactivity:



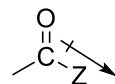
The larger the electron deficiency on the carbonyl carbon, higher is the electrophilicity and higher is the reactivity towards nucleophiles

Electrophilicity of acid derivatives:



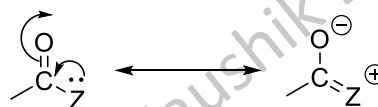
an electronegative heteroatom, has two effects

- I effect - electron-withdrawing inductive effect - enhances electrophilicity of carbonyl carbon,
- +R effect - electron-releasing resonance effect - decreases electrophilicity of the same carbonyl carbon



-I effect

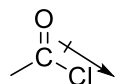
because Z is an electronegative heteroatom



+R effect

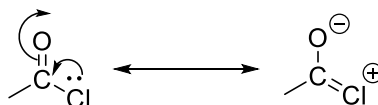
because Z has unshared electron pairs

Case of acid chloride:



-I effect

because Cl is an electronegative heteroatom



+R effect

because Cl has unshared electron pairs

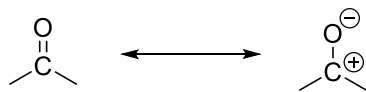
The inductive EW effect of Cl is higher than its resonance ER effect.

Because the C(2p) orbital and the Cl(3p) orbitals are different in size - there is significant size mismatch between C and Cl orbitals; this compromises the delocalization of the Cl lone pair over the C=O. This reduces the +R effect of Cl. However, as inductive EW effect operates through the sigma bond network and Cl is a more electronegative element than C, the -I effect is strong enough to overcome the +R effect.

An acid chloride is thus extremely electrophilic

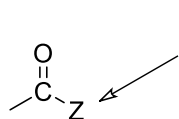
Introduction to carboxylic acid derivatives:

Explanation of relative reactivity:



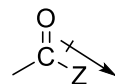
The larger the electron deficiency on the carbonyl carbon, higher is the electrophilicity and higher is the reactivity towards nucleophiles

Electrophilicity of acid derivatives:



an electronegative heteroatom, has two effects

- I effect - electron-withdrawing inductive effect - enhances electrophilicity of carbonyl carbon,
- +R effect - electron-releasing resonance effect - decreases electrophilicity of the same carbonyl carbon



-I effect

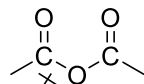
because Z is an electronegative heteroatom



+R effect

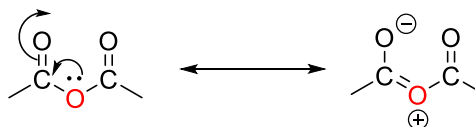
because Z has unshared electron pairs

Case of acid anhydride:



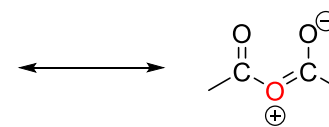
-I effect

because O is an electronegative heteroatom



+R effect

because O has unshared electron pairs



The red O is conjugated with both C=O, but it must interact with either one, cannot donate electrons simultaneously to both C=O, this is cross-conjugation.

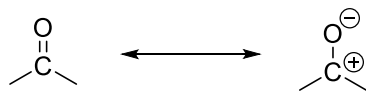
The inductive EW effect of O is higher than its resonance ER effect.

The cross conjugation of O l.p. reduces the +R effect. In addition, O is highly electronegative so does not particularly like to donate electrons. Inductive EW effect of O operates through the sigma bond network and the -I effect is strong enough to overcome the +R effect. The orbital sizes between C and O match, so electron donation is not as poor as in case of Cl, but not strong enough to overcome the strong -I effect.

The acid anhydride is thus moderately electrophilic.

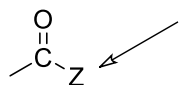
Introduction to carboxylic acid derivatives:

Explanation of relative reactivity:



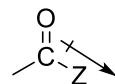
The larger the electron deficiency on the carbonyl carbon, higher is the electrophilicity and higher is the reactivity towards nucleophiles

Electrophilicity of acid derivatives:



an electronegative heteroatom, has two effects

- I effect - electron-withdrawing inductive effect - enhances electrophilicity of carbonyl carbon,
- +R effect - electron-releasing resonance effect - decreases electrophilicity of the same carbonyl carbon



-I effect

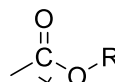
because Z is an electronegative heteroatom



+R effect

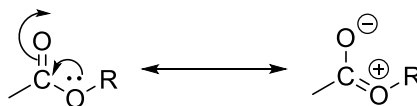
because Z has unshared electron pairs

Case of ester:



-I effect

because O is an electronegative heteroatom



+R effect

because O has unshared electron pairs

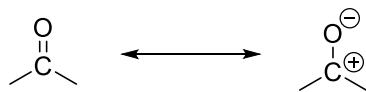
The inductive EW effect of OR is higher than its resonance ER effect.

O being more electronegative than C shows a strong -I effect, but it also has a +R effect. The donation is better than that seen in anhydride as there is no cross conjugation, but the much greater electronegativity of O implies that the -I effect is still strongly operating. And because O is highly electronegative, it does not like to share its e-pair easily.

The ester is thus considerably electrophilic.

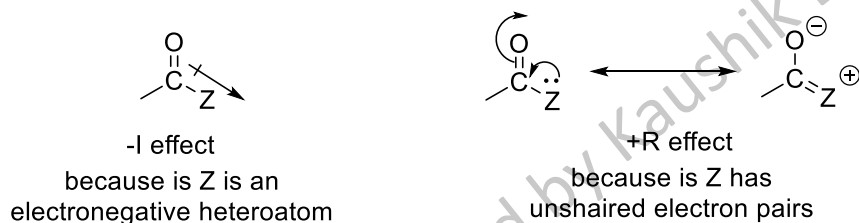
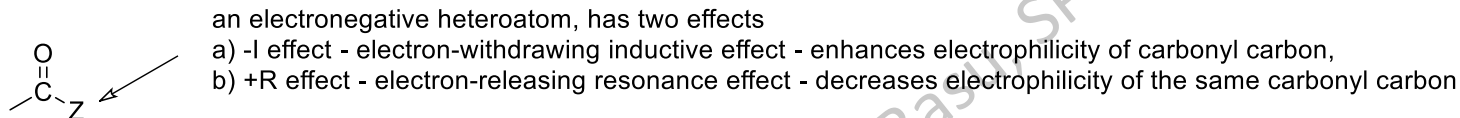
Introduction to carboxylic acid derivatives:

Explanation of relative reactivity:

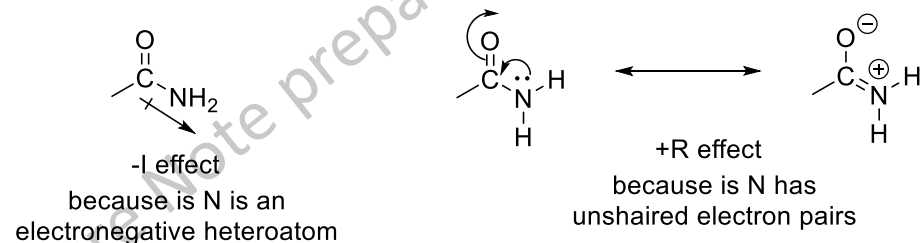


The larger the electron deficiency on the carbonyl carbon, higher is the electrophilicity and higher is the reactivity towards nucleophiles

Electrophilicity of acid derivatives:



Case of amide:



The inductive EW effect of NH_2 is higher than its resonance ER effect.

O being more electronegative than C shows a strong -I effect, but it also has a +R effect. The donation is better than that seen in ester, and N is less electronegative than O. Because of this - a) N tolerates positive charge better than O does, the +R effect is very strong, and b) NH_2 has a much lower inductive EW effect than OR or OCOR or Cl.

The acid amide is thus the least electrophilic of the lot.