Carbonyl Chemistry

Substitution

Introduction

Leaving groups are anions that can be expelled from molecules taking their negative charge with them

If, however, the intermediate is unstable and there are any good leaving groups around it, they'll be expelled

When a nucleophile attacks a carbonyl group, it forms a tetrahedral intermediate

The re-forming of a C=O double bond by far compensates the loss of the leaving group

This is a nucleophilic substitution mechanism

The reaction goes Trigonal Planar --> Tetrahedral --> Trigonal planar

ImPoRtAnT nOtE - this is **NOT** an **Sn2** mechanism - the *p* system prevents the correct approach of the nucleophile. Therefore, **all** the steps of this mechanism have to be drawn

Radioisotope labelling studies have shown the "swapping" of the oxygens

We know that the tetrahedral intermediate exists because...

Carboxylic acid derivatives

Examples

All have the formula RCOX

Acid - X = OH

Acid/Acyl chloride - X = Cl

Ester - X = OR

Amide - X = NH2

Anhydride - X = RCOO

Nitrile - RC≡N

The nature of X is very important for substitution

Leaving groups

A good leaving group must be a **stable** anion, and a convenient guide to the stability of anions is **the pKa of their conjugate acids**

The **lower** the pKa of its conjugate acid, the **more stable** **the base** and the **better** the leaving group

pKa is a measure of stability only with respect to the protonated form of the anion

Here, we're looking for a measure of the stability of the conjugate acid plus leaving group with respect to the negatively charged tetrahedral intermediate

However, this is only a **rough guide**

R- **50**

NH2- **35**

RO- **16**

RCO2- **5**

Cl- **-7**

Learn these five values, of pKa of conjugate acid

If the attacking nucleophile happens to be the best leaving group, then no reaction will occur

Nucleophiles

Again, pKa values are a good indication

Good nucleophiles are **poor leaving groups**

A species that will readily form new bonds to hydrogen will probably also readily form bonds to carbons

Therefore, the **higher** the **pKa value** of the **conjugate acid**, the *better* the nucleophile

NH3 **9**

ROH **-5**

We add two values to the list above

Electrophiles (i.e.: reactivity of the acid derivative)

It depends on how good the leaving group is

And on how good a nucleophile the attacking thing is

We can class acids with the most reactive at the top and the least at the bottom - transformations are always possible moving **down** the series

This is because the *p** orbital is raised

Also because electron density donated to carbonyl carbon - less polarised

(Ironically, this weakens the C=O bond)

Delocalisation *stabilises* the acid derivative, and makes it **less reactive** towards nucleophiles

Amides show the greatest degree of delocalisation, **esters** less so, **anhydrides** less so and **acyl chlorides** less so

This can clearly be seen in IR stretching frequencies

If the attached group is **electronegative**, it increases the +ve charge on the carbonyl carbon and makes it a better electrophile

There is, however, also an **inductive** effect

Thus, the attached group has two effects - **inductive** and **conjugative**

Reactions

Interconversions between acid derivatives

A **base** is used to remove the proton from the alcohol as it attacks the carbonyl group

Pyridine is often used

Acid anhydrides and acid chlorides react with alcohols to make esters

If this is done under **basic conditions**, it is **irreversible**

This is because the final deprotonation step is irreversible

This reaction is reversible, the opposite being called **ester hydrolysis**

The lone pair on the carboxyl group can be protonated by strong acids (see before) protonated carbonyl groups are then **extremely** powerful nucleophiles

It also makes the leaving group much better

Carboxylic acids react with alcohols to make esters, under acid catalysis

The mechanism is as follows

Proton protonates carbonyl

Alcohol attacks

Proton transfer from alcohol to solvent

Proton transferred to the leaving OH

H2O leaves

The position of the equilibrium is determined by which reagents are in excess

This is very similar to ester formation

A second molecule of amine has to act as the base, to remove the extra hydrogen on the amine

It results in a Amine+ Cl- ionic by-product

A way round this is the Schotton-Baumann method

Amines react with acid chlorides to produce amides

NaOH can't be used as the base because it also attacks the acyl chloride to give carboxylic acid

The NaOH and the organic layers are kept separate using a heavy solvent in which the organic stuff can dissolve, but the NaOH can't

The HCl released by the reaction can diffuse into the NaOH layer, and be neutralised there

Notes

All that happens is that the acid is deprotonated

Once that happens, substitution is prevented because (almost) nothing can attack the (stable) carboxylate anion

Carboxylic acids do not undergo substitution reactions under basic conditions

This means that if we want to make esters from alcohols and carboxylic acids, we *must* use acidic conditions, because alcohols by themselves just aren't reactive enough, and we can't use a base

Reduction of esters

The mild reducing agent NaBH4 will not reduce esters

First by substitution of -OR for a hydrogen to make an aldehyde

Then by the reduction of the aldehyde all the way to an alcohol by addition

The stronger LiAlH4 reduce esters all the way to the corresponding alcohol

Esters and organometallics

Esters react **twice** with organometallics

First time in a substitution to make an aldehyde or ketone

Second time to add to that one and make an alcohol

Note that the initial product is more electrophilic than the starting material, so even with one equivalent of organometallic, the final product will be formed

Addition

Mechanism

Nucleophilic attack on carbonyl group (SLOW)

Protonation of the **anion** that results **(FAST)**

The first step is the most important - it forms a new C-C *sigma* bond at the expense of a C=O *p* bond

Orbital explanations

The attack at C is favoured

The polarisation gives the carbon atom some degree of positive charge, and this attracts the negative nucleophile

The attack involves the movement of electrons from the HOMO of the nucleophile to the LUMO, which is the *p** antibonding orbital - the coefficient of which is greater on the C, meaning a better HOMO-LUMO interaction there

Mechanism

The nucleophile approaches and the electron pair in its HOMO start to interact with the LUMO (*p**) to form a new *sigma* bond

Filling this antibonding orbital breaks the *p* bond, the electrons of which end up on the electronegative oxygen

The **trigonal planar, sp2** carbon changes to a **tetrahedral, sp3** carbon in the product

Trajectory

Nucleophile attacks at the **Burgi-Dunitz angle**, **107°** from the C-O bond

This is a compromise between

Maximum overlap of the HOMO with *p**

Minimum repulsion of the nucleophile HOMO by the electron density in the **carbonyl *p* bond**

Any group which hinders this trajectory will greatly reduce the rate of addition - causing **steric hindrance**

Factors affecting

Steric hindrance

As the carbonyl carbon moves from sp2 to sp3, its bond angles get smaller - in other words, the substituents move **closer together**

The least bulky the substituents, therefore, the easier this will be, and the more favoured the reaction

This is why these reactions are usually faster for aldehydes then for ketones

Ring structures

Small rings also favour those types of reactions

Bond angles change from 120 to 109 in the first step of the addition

In a three-membered ring, bond angles are forced to be 60, so the ring is very strained

However, *less* strain is involved when the carbon atoms are sp3 (ideal angle 109) than when they're sp2 (ideal angle 120)

Similar results, to a lesser extend, apply to four and five ring structures

Electronegative groups

Electronegative groups make the carbon atom even more polarised, and makes the attack of the negative nucleophile even easier

The electronegative effects are greater than the steric hindrance ones

Such effects can have a large influence on the equilibrium

Addition of water to aldehydes and ketones

The formaldehyde in water 13C NMR shows a peak at 83ppm (C-O) rather than at 150-200 (C=O)

Water has **added** to the carbonyl group to form a **hydrate**, or **1, 1-diol**

In the reaction, a proton has to be transferred from one oxygen atom to another, mediated by water molecules

This is an **equilibrium** between starting materials and products

Reaction of the hydrate in water with a trace of NaOH can produce the starting aldehyde (OH- acts as a **base** and deprotonates one of the hydrate OHs)

It is affected by the factors described above

Examples

Nucleophilic attack by "hydride"

Nucleophilic attack by a simple hydride H-anion (for example, from NaH) does *not* occur

H- is very small, and has a very high charge density

The small 1s orbital is of an ideal size to interact with the H atom's contribution to the *sigma* orbital of an H-X bond

It only ever reacts as a base

Much too small to interact easily with carbon's more diffuse 2p orbital contribution tot he LUMO (*p**) of the C=O group

The orbital interactions that would be involved if it were to act as a nucleophile are very poor

However, it would be rather useful to be able to add H- to a carbonyl group, because we would then have a reduction

Nucleophilic attack by "hydrides"

It turns out that this can be done using compounds that contain nucleophilic hydrogen atoms

This is **isoelectronic** with methane, and contains a negative charge since boron has one less proton

However, the boron does *not* have a lone pair, and it is **WRONG** to draw an arrow showing the negative charge coming from the boron - that would imply that the boron originally had 10 electrons in its outer shell, impossible for a first row element

Instead, all the electrons (including the one represented by the negative charge) are in the C-H *sigma* bonds

It is then one of these *sigma* bonds that interacts with the *p** MO - a much better match than H-

As a result, the boron becomes trivalent and neutral again, with an empty *p* orbital

The oxyanion produced is then likely to stabilise the electron deficient BH3 by donating a pair of electrons into the empty p orbital

The most important is NaBH4, a water-soluble salt containing the **tetrahedral** BH4- ion

This is very weak - it can even be used in water

Usually, a water/ethanol mixture is used as the solvent

Much stronger H- donors, such as **lithium aluminium hydride** can be used

Reacts violently with water, produced flamable H2

Sodium borohydride reacts with

Aldehydes

Ketones (slower)

NOT with less reactive carbonyl compounds such as ester or amides

Good selectivity if the molecule contains several groups

Addition of organometallic reagents

Li-C or Mg-C bonds are highly polarised towards carbon

They are therefore very powerful nucleophiles, and attack the carbonyl group to give alcohols, forming a new C-C bond

It is important that water not be present in the first step, as it destroys the organometallic compound

the second step, in which water is added, in known as the **work-up**

Hemiacetal formation

Hemiacetals are the result of the addition of alcohols to carbonyl compounds

This really only ever occurs if the product is cyclic, which gives it extra stability

Catalysis

Acid

The first step is the protonation of the carbonyl oxygen's lone pair

The positive charge makes the carbon much more electrophilic and so the reaction is faster

The proton is regenerated

Base (for reactions involving alcohols)

The first step is deprotonation of the alcohol by the base

This makes the reaction faster by making the alcohol more nucleophilic

Again, the hydroxide is regenerated at the end

Bonding in carbonyl compounds

Sigma system

Formed between two sp2 hybrids on carbon and oxygen

The two other sp2 hybrids on carbon form two *sigma* bonds to the substituents

The two other sp2 hybrids on the oxygen contain lone pairs

The sp2 hybridisation means that the carbonyl group has to be **planar**, with bond angles nearly **120°**

p system

The *p* bond results from the overlaping of the resulting two p orbitals on C and O

The *p* bond is skewed towards oxygen, because oxygen is more electronegative than carbon

Similarly, the *p** antibonding orbital is skewed towards the carbon, with a larger coefficient there

Consequences

The bond is rather shorter than a typical C-O single bond, and over twice as strong

The polarised C=O gives the carbon atom some degree of positive charge