Lecture 7   Imines, Hydrazones and Oximes

Objectives:

By the end of this lecture you will be able to:

- draw the mechanism for imine formation;
- account for the decreased electrophilicity of C=N compounds;
- use frontier molecular orbitals to account for the increased nucleophilicity of hydroxylamines and hydrazines over alkoxides and amines;
- draw the mechanism for oxime and hydrazone formation;
- use 2,4-dinitrophenylhydrazones for characterising aldehydes and ketones;
- use the Beckmann rearrangement for preparing amides from oximes.

Introduction

The carbonyl group (C=O) is the most important C=X functional group. However X can be other heteroatoms such as N and S. In this lecture we will examine the formation of a variety of C=N functional groups and compare their reactivity with their oxygen analogues.

Imines

The reaction of primary amines with aldehydes and ketones under dehydrating conditions generates the corresponding imine. The mechanism is a variation of the nucleophilic addition-elimination reaction that we have discussed for carboxylic acid derivatives.

- You should compare the first few steps with those in the hydration of aldehydes and ketones; the mechanisms are identical.
- The reaction is normally acid-catalysed (Lewis or Brønsted). Whilst primary amines are relatively good nucleophiles, without some activation of the carbonyl group, nucleophilic addition is generally slow.
- Note that primary amines are also much more basic than the carbonyl oxygen ($pK_a(RNH_3^+)$ ~ 11; $pK_a(R(C=OH)^+R)$ ~ -6) so for the most part the amine will be protonated making it non-nucleophilic).
- Under acidic conditions, the rate-determining step is not surprisingly the addition reaction to form the first tetrahedral intermediate.
- Imine formation can also be carried out under neutral or basic reaction conditions. In these cases, the dehydration step is rate-determining.
- The reaction is an equilibrium process and if anything, thermodynamically uphill (C=N bond is weaker than C=O bond). Therefore to drive the reaction over to product it is normal to use an excess of amine and remove the water from the reaction mixture as it is formed in the

dehydration step. This can be achieved in a variety of ways including using a dehydrating agent in the reaction mixture (*e.g.* $MgSO_4$), or by azeotropic removal of water using Dean-Stark apparatus.
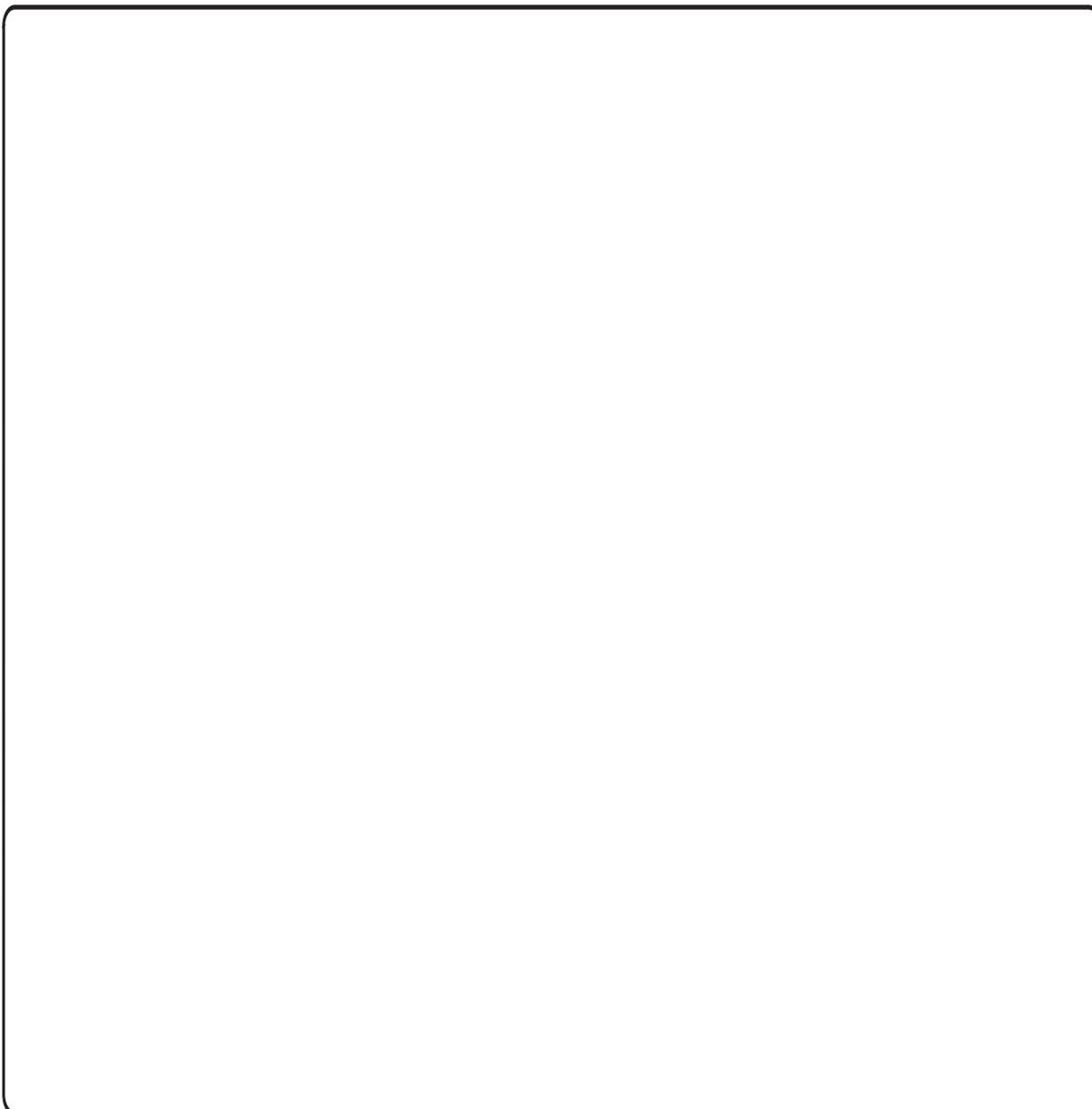
Imines are less electrophilic than aldehydes and ketones

The decreased electrophilicity of imines is readily accounted for by the lower electronegativity of nitrogen compared with that of oxygen.

Electronegativity of oxygen on the Pauling scale = 3.44

Electronegativity of nitrogen on the Pauling scale = 3.04

Electronegativity of carbon on the Pauling scale = 2.55

As a result of the reduced electronegativity of the heteroatom, the double bond in an imine is less polarised. There is therefore a weaker dipole moment across an imine than across the corresponding carbonyl group.

There is therefore less $\delta+$ charge at the imine carbon atom which makes it less electrophilic; thus whilst imines do react with nucleophiles in a similar fashion to carbonyl groups, they tend to require strong nucleophiles and more forcing reaction conditions.

Note that under acidic conditions imines can be activated in a similar way to aldehydes. Furthermore since the imine nitrogen is more basic than the oxygen in a carbonyl group, the equilibrium lies more towards the reactive iminium species, than it does in the corresponding carbonyl series:
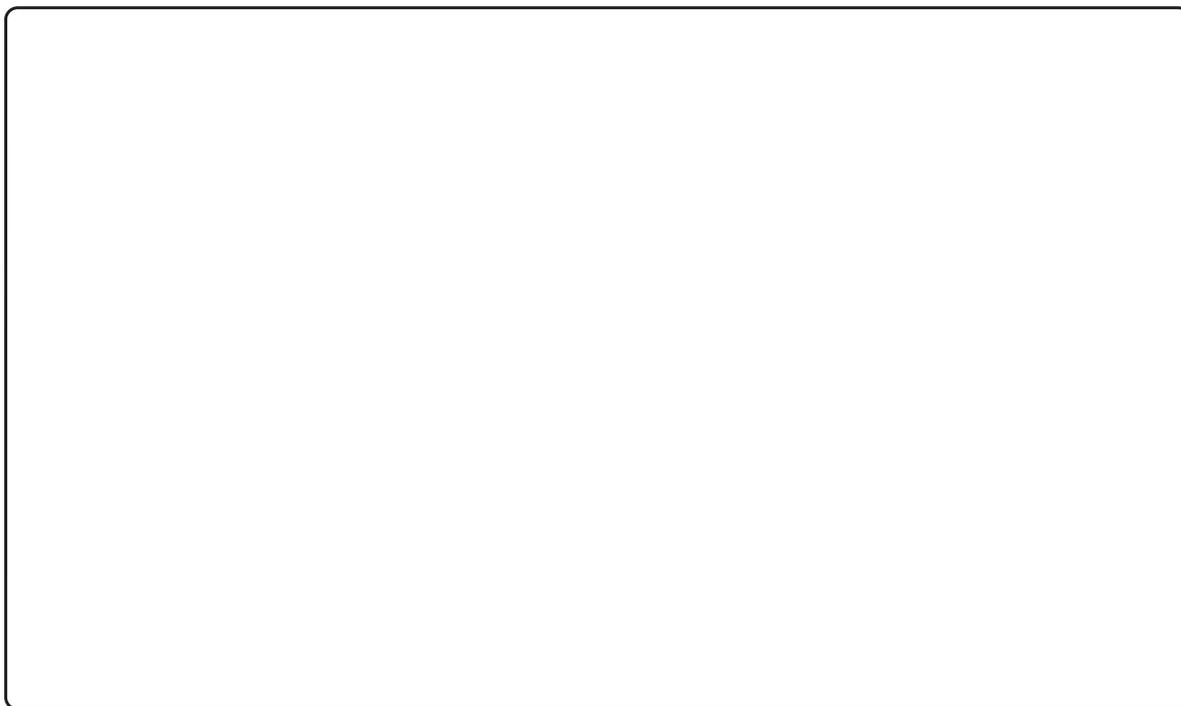
Hydrazones and Oximes

Hydrazines and hydroxylamines both react with aldehydes and ketones to provide hydrazones and oximes, respectively. Although both these reagents are more nucleophilic than the parent amine, they still react better under acid or base catalysis. The mechanism is analogous to that used to form imines.

An Issue of Stereochemistry

Since imines, hydrazones and oximes have substituents off both ends of the C=N double bond, there is an issue of stereochemistry that needs to be considered, just as there is for any unsymmetrically substituted double bond.
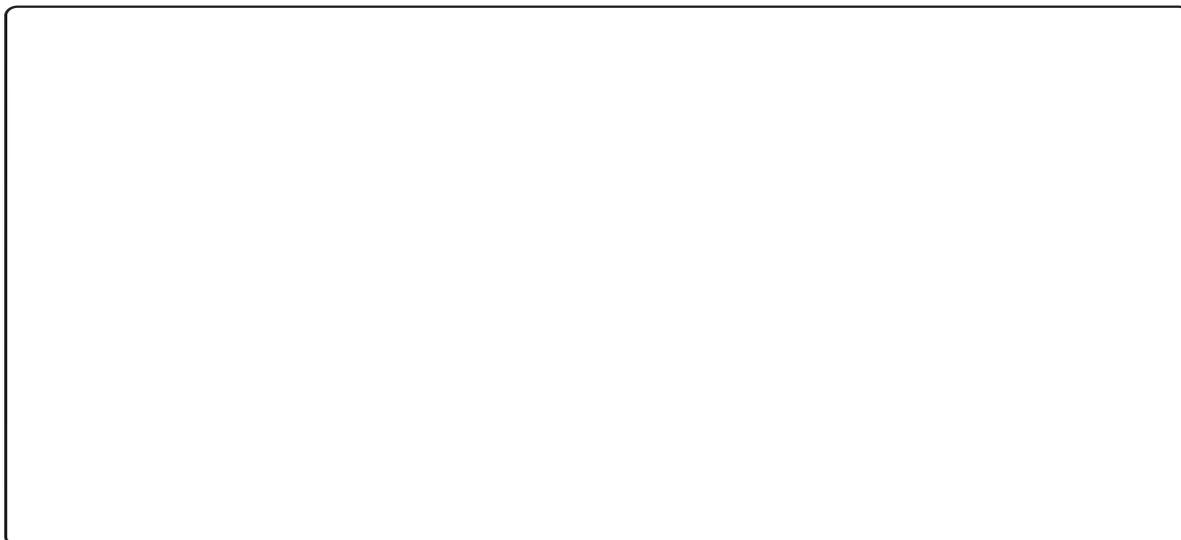
For imines and hydrazones the energetic barrier to (*E*)-(*Z*) isomerisation is sufficiently low for it to be relatively difficult to isolate (*E*)- or (*Z*)-stereoisomers. That is not to say, of course that one stereoisomer does not predominate in the equilibrium. On steric grounds the (*E*)-stereoisomer is normally the major product.

In the case of oximes, the barrier to interconversion between the two stereoisomers is much higher and allows the isolation of the two stereoisomers. As before, minimising steric hindrance normally ensures that one stereoisomer predominates.

2,4-Dinitrophenylhydrazones

Before the advent of modern analytical techniques such as NMR spectroscopy and mass spectrometry, chemical derivatisation was commonly used to identify unknown compounds. Simple aldehydes and ketones are usually liquids. Reaction with 2,4-dinitrophenylhydrazine generates the corresponding 2,4-dinitrophenylhydrazone (2,4-DNP derivative) which is usually a bright yellow crystalline solid possessing a characteristic melting point. Comparing the melting point of an unknown 2,4-DNP derivative with those in lists of tables of known DNP derivatives allows the identification of the parent aldehyde or ketone.

Reactions of Oximes

Consider the reaction of two stereoisomeric oximes with *para*-toluenesulfonyl chloride (TsCl). The outcome is strongly dependent on the *configuration* of the oxime. When the (*E*)-stereoisomer is used, an amide is obtained through a reaction known as the **Beckmann rearrangement**. When the (*Z*)-stereoisomer is used, an elimination reaction proceeds to provide the corresponding nitrile.

The outcome of the reaction is determined by the type of group that is antiperiplanar to the alcohol.

Mechanism of the Beckmann Rearrangement
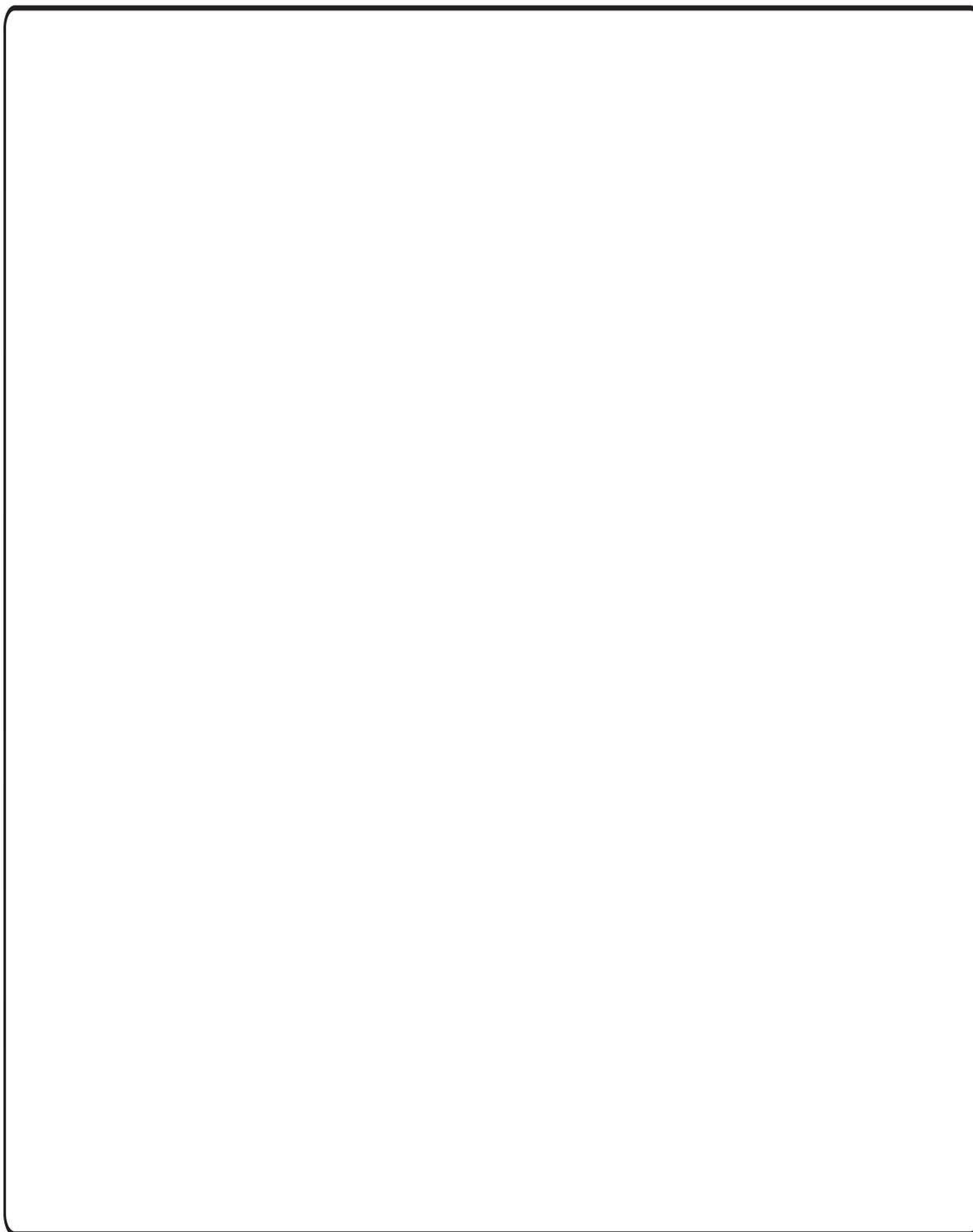
The key step in the reaction is migration of the antiperiplanar group on to the nitrogen with concomitant displacement of the tosylate leaving group. The incipient positive charge is then trapped with water and a series of proton transfer steps provides the corresponding amide.

Formation of a nitrile from the (Z)-stereoisomer

This reaction is effectively an E_2-elimination reaction. The antiperiplanar group is a hydrogen substituent, which, rather than migrating, is abstracted by an external base:

Why are hydrazines and hydroxylamines more nucleophilic than amines?

It is a general observation that heteroatoms bonded directly to another heteroatom (*e.g.* hydroxylamines and hydrazines) exhibit increased nucleophilicity compared with the parent system where the heteroatom substituent is replaced with a carbon substituent.

We can rationalise this observation by examining the important frontier molecular orbital of the nucleophile, specifically the **H**ighest **O**ccupied **M**olecular **O**rbital (HOMO).

In general the higher is the energy of the HOMO of a nucleophile the greater is its reactivity as a nucleophile. The presence of a heteroatom substituent possessing a lone pair of electrons in an orbital that can overlap with the lone pair of electrons on the adjacent heteroatom raises the energy of the HOMO and therefore renders it more nucleophilic. This is a general observation and is known as the **α-effect**.

Summary

Replacing the carbonyl oxygen with a nitrogen atom affords a related class of compounds: imines, hydrazones and oximes. All three can be prepared from the parent aldehyde or ketone and a nitrogen nucleophile: primary amines provide imines, hydrazines provide hydrazones, and hydroxylamines give oximes.

The mechanism for forming of C=N derivatives is similar to the nucleophilic addition-elimination processes seen with carboxylic acid derivatives. An initial nucleophilic addition step is followed by dehydration. The reaction is catalysed with acid or base. The rate-determining step depends on the pH of the reaction. Under acidic conditions, the RDS is the initial addition reaction to form the tetrahedral intermediate, whilst under basic conditions dehydration is rate-determining.

C=N derivatives are less electrophilic than their carbonyl analogues owing to the decreased electronegativity of nitrogen compared with oxygen. This renders C=N derivatives less susceptible towards nucleophilic attack.

The presence of a substituent on the nitrogen of imines, hydrazones and oximes means that two stereoisomers are possible for compounds derived from aldehydes and unsymmetrically substituted ketones. In the case of imines and hydrazones, the energy barrier to interconversion is relatively low such that stereoisomerically pure derivatives are not easy to isolate - the

stereoisomers are not configurationally stable. In contrast, the barrier to interconversion between oxime stereoisomers is high and the two stereoisomers can often be separated and isolated as stereoisomerically pure species. The (*E*)-stereoisomer is normally the predominant species.

2,4-Dinitrophenylhydrazones have been widely used in the past for elucidating the structure of aldehydes and ketones. The advent of modern spectroscopic and spectrometric techniques means that this method of structure elucidation is now uncommon.

Oximes undergo rearrangement reactions or elimination reactions on treatment with acids (Brønsted or Lewis) or when the alcohol is made into a good leaving group. The reaction pathway that is followed depends on the substituent that is antiperiplanar to the leaving group.

Hydrazines and hydroxylamines are more nucleophilic than simple amines. This is a result of the second heteroatom raising the energy of the HOMO rendering the group more nucleophilic. This is called the α-effect.