Rearrangements and Reactive Intermediates

1A Organic Chemistry

Handout 2  - Carbenes and Nitrenes

http://burton.chem.ox.ac.uk/teaching.html
Carbenes

- neutral divalent carbon species – 6 electrons around central carbon atom – highly reactive, generally electrophilic

- structure – singlet carbenes

  ![Singlet Carbenes Diagram](image)

  singlet carbenes have three electron pairs and an empty orbital to place around the central atom - a similar case to carbocations (carbenium ions)

- singlet carbenes are bent with the bond pairs and lone pairs in sp² hybridised orbitals, along with a vacant p-orbital

  - typical bond angle range for singlet carbenes are 100° - 110°

- structure – triplet carbenes

  ![Triplet Carbenes Diagram](image)

  triplet carbenes are bent with a typical bond angle range of 130° - 150°

- carbene structures from spectroscopy, in low pressure gas, and in low temperature matrix (<77 K)
  - electronic spectra with rotational structure
  - infra red analysis
  - electron spin resonance (for triplets)
Why are triplet carbenes bent?

- imagine a linear geometry for the triplet carbene
  - there will be a central sp hybridised carbon atom with the two bonding pairs of electrons are in sp-hybrid orbitals (50% s-character)
  - the unpaired electrons are in the two orthogonal 2p orbitals

  - this linear arrangement means that the unpaired electrons have no s-character — the more s-character the more stable the electron

  - bending the linear state leads to one of the unpaired electrons gaining some s-character and being lowered in energy — here one of the p-orbitals becomes an sp\(^n\) hybrid orbital (a σ-orbital)

  - the more bent the carbene is the greater the difference in energy between the p and σ-orbitals

  - due to electron electron repulsion there is an energy cost in pairing electrons (Hund’s rule)

  - if there is a small energy gap between σ and p-orbitals the electrons will remain unpaired i.e. triplet
Walsh diagram for \( \text{CH}_2 \) gives a more sophisticated analysis and accounts for electronic structure of \( \text{CH}_2 \). See Prof McGrady “Bonding in Molecules” course 2nd year.

Simplified Walsh diagram for \( \text{CH}_2 \):

- Beginning with linear \( \text{CH}_2 \), MO diagram predicts a triplet ground state.
- Slight bending should be stabilising as one of the electrons is now in a bonding MO.
- With further bending, the lower energy of the bonding MO overcomes electron-electron repulsion and the singlet carbene becomes more stable.

Take home message:
- Triplet carbenes and singlet carbenes are bent – we will consider them both to be \( \text{sp}^2 \) hybridised.
- Triplet carbenes have a larger bond angle than singlet carbenes.
- The above representations are adequate for our purposes.
- Neither Walsh diagram nor hybridisation allows us to predict the ground state for any particular carbene.
methylene (CH₂) has a triplet ground state – the singlet state is ca. 38 kJmol⁻¹ higher in energy

134° 102°

methylene (CH₂) has a triplet ground state – the singlet state is ca. 38 kJmol⁻¹ higher in energy

dialkylcarbenes, arylalkylcarbenes and some diarylcarbenes have triplet ground states

heteroatom substituted carbenes have singlet ground states due to delocalisation

carbene or ylid? c.f.

N-heterocyclic carbene

increasing carbene stability
- The majority of carbenes are electrophilic – there are six electrons around the central carbon and hence they are electron deficient.

- N-heterocyclic carbenes (and related carbenes) are nucleophilic - they are widely used as ligands for transition metals.

- Nature was here before us with nucleophilic carbenes – thiamine pyrophosphate (vitamin B1) – more next year.

some methods for carbene formation

- direct irradiation normally produces a carbene in the singlet excited state
- irradiation or heating diazo or diazirine compounds forms singlet carbenes
- relaxation of the singlet state to the triplet state (if it is lower in energy) can occur but requires collision with other molecules
- direct formation of the triplet state can occur by irradiation in the presence of a triplet sensitisier
- reactions of carbenes
- insertion into C-H bonds – generally unselective, occurs with very reaction carbenes, not Cl₂C⃗.
- for singlet carbenes reaction occurs with retention of configuration – with triplet carbenes stereochemistry is lost
- example – the Bamford Stevens reactions – solvent dependent product formation

![Diagram of carbenes reactions and rearrangements](image)

- remember on treatment with 2 equivalents of an alkyllithium, tosylhydrazones undergo the Shapiro reaction
- **insertion reactions**

  \[
  \text{POMe}_2\text{Cl} \xrightarrow{n-\text{BuLi}, t-\text{BuOK}} \text{POMe}_2\text{LiCl} \rightleftharpoons \text{POMe}_2\text{HMe} \xrightarrow{\text{Schlosser’s base – a very strong base}} \text{carbenoid}
  \]

- **insertion reactions into adjacent C-H bonds is the equivalent of a 1,2-shift**

  \[
  \text{PhMe} \xrightarrow{\text{h} \nu} \text{PhH} \xrightarrow{1,2-\text{migration}} \text{PhMe} \\
  \text{R} \rightleftharpoons \text{H} \xrightarrow{\text{high temperature}} \text{alkylidene carbene}
  \]

- **insertion into XH bonds is common using transition metal catalysis**

  \[
  \text{MeO} = \text{C} = \text{O} \xrightarrow{\text{Rh}_2(\text{OAc})_4} \text{C} = \text{O} \xrightarrow{\text{C-H insertion}} \text{C} = \text{O}
  \]

  - **rhodium carbenoid is equivalent to a carbene**

  - **here the (rhodium) carbene is attacked by the nucleophilic alcohol followed by proton transfer**
- Wolff rearrangement
  \[ \text{hv or heat or metal catalyst} \]
  - concerted or stepwise mechanism – depends on substrate and reaction conditions
  - as a rule of thumb, the thermal reactions are concerted and the photochemical reactions proceed via carbenes
  \[ \text{concerted} \quad \text{stepwise via carbene} \]
  - the acyl carbenes are also in equilibrium with an oxirene in some cases (\(=^{13}\text{C}\))
  \[ \text{oxirene mixture} \]
  - Arndt-Eistert homologation
  \[ \text{Ag(I) cat.} \]
  \[ \text{hv or heat or metal catalyst} \]
- Wolff rearrangement – a look at the orbitals
- with cyclic ketones the reaction is likely to be concerted under most conditions

\[
\text{Wolff rearrangement} \quad \text{hv, MeOH} \quad \text{99%} \\
\text{mechanism in more detail correct orbital overlap required for migration}
\]

- migration with retention of configuration

- some other rearrangements
- Doering-LaFlamme allene synthesis

\[
\text{R} = \text{CHBr}_3, \text{NaOH} \\
\text{Skattebol rearrangement}
\]

\[
\begin{align*}
\text{C-H insertion}
\end{align*}
\]
carbene addition reactions

- addition to C=C bonds: i) stereospecific for singlet carbenes; ii) non-stereospecific for triplet carbenes; iii) distinguishes between triplet and singlet carbenes

- singlet carbene – concerted reaction

- triplet carbene – non-concerted radical reaction – spin inversion (requires molecular collision) may be slower than bond rotation leading to stereochemical scrambling
- Reimer – Tieman reaction

\[
\begin{align*}
\text{benzene} & \xrightarrow{\text{CHCl}_3, \text{NaOH}} \text{benzoic acid} + \text{phenol} \\
\text{dichlorocarbene} & \xrightarrow{\text{CHCl}_3, \text{NaOH}} \text{chloroformaldehyde} + \text{phenol}
\end{align*}
\]

- dichlorocarbene adds to pyrrole followed by rearrangement

\[
\begin{align*}
\text{pyrrole} & \xrightarrow{\text{CHCl}_3, \text{NaOH}} \text{chloroformaldehyde} + \text{phenol}
\end{align*}
\]

- very electrophilic carbenes will add to benzene

\[
\begin{align*}
\text{ethoxycarbodiimide} & \xrightarrow{\text{heat in benzene}} \text{benzene} + \text{ethoxycarbonyl} \\
\text{ethoxycarbonyl} & \xrightarrow{\text{heat in benzene}} \text{benzylic anion}
\end{align*}
\]

6π electrocyclic ring opening
Simmons Smith cyclopropanation

metal catalysed addition reactions of diazocompounds - common catalysts include: Cu, Cul, Rh$_2$(OAc)$_4$, Cu(OAc)$_2$
Carbenes readily react with nucleophiles.

Nucleophilic carbenes are useful catalysts.

- N-heterocyclic carbene catalyses the benzoin reaction
  - acts like cyanide:
    - good nucleophile
    - stabilises adjacent negative charge
    - good leaving group
Nitrenes

- neutral monovalent nitrogen species – 6 electrons around nitrogen atom, isoelectronic with carbenes
- similar chemistry to carbenes, some differences and nitrenes are generally more reactive

\[
\begin{align*}
\text{singlet } \text{sp}^2 & \quad \text{triplet } \text{sp} \\
R-N: & \quad R-N^+ \\
& \\
\end{align*}
\]

- nitrenes are by definition linear, as with carbenes they have singlet and triplet states
- nitrenes have a larger energy separation between the triplet and singlet states – triplet is usual ground state
- as with carbenes, good π donor substituents can give singlet ground states

most common method for generation is thermolysis or photolysis of azides

\[
\begin{align*}
\text{R-NN} & \quad \text{hv or heat} \quad \text{R-N}^+ + \text{N}_2 \\
\text{R-N} & \quad \text{Et}_3\text{N} \quad \text{R-N}^+ \text{OTs} \quad \text{OTs} \quad \text{R-N}^+ \\
& \quad \alpha\text{-elimination}
\end{align*}
\]

- a number of methods for nitrene generation, analogous to the methods for carbene generation, are known
- free nitrenes are not always formed under these conditions
- generation by reduction of nitro compounds

\[
\text{ArNO}_2^+ \xrightarrow{\text{PR}_3} \text{ArN}^+ \xrightarrow{\text{heat}} \text{ArN}_2^+ \xrightarrow{-\text{Ph}_3\text{PO}} \text{ArN}_2^+ \xrightarrow{\alpha-\text{elimination}} \text{ArN}_2^+ \xrightarrow{\text{PR}_3} \text{ArN}_2^+ \xrightarrow{-\text{Ph}_3\text{PO}} \text{ArN}_2^+ \xrightarrow{\text{PR}_3} \text{ArN}_2^+ \]

- carbazole synthesis

\[
\begin{align*}
\text{ArNO}_2^- & \xrightarrow{\text{PPh}_3} \text{carbazole} \xrightarrow{\text{heat}} \text{ArN}_3^- \\
\end{align*}
\]

- generation from isocyanates

\[
\begin{align*}
\text{ArN}_2^+ \xrightarrow{\text{h}_\nu} \text{ArN}_2^+ \\
\text{ArN}_2^+ \xrightarrow{-\text{CO}} \text{ArN}_2^+
\end{align*}
\]
addition to C=C bonds
- as with carbenes, addition of nitrenes to alkenes is stereospecific with singlet nitrenes, and non-stereospecific with triplet nitrenes

- with high concentration of olefin singlet nitrene reacts stereospecifically to give aziridine products – trans-olefin gives trans-aziridine; cis-olefin gives cis-aziridine
- with low concentration of olefin singlet nitrene undergoes intersystem crossing to ground state triplet and reacts non-stereospecifically with each alkenes (diradical mechanism) to give mixtures of aziridine products
- photochemical generation of nitrene gives analogous results
insertion reactions

\[
\begin{align*}
\text{singlet} & : \quad R'\text{N} \quad + \quad H\text{R} \quad \rightarrow \quad \overset{\text{concerted}}{\text{R'}}\text{N} \quad + \quad H\text{R} \\
\text{triplet} & : \quad R'\text{N} \quad + \quad H\text{R} \quad \rightarrow \quad \overset{\text{radical reaction}}{\text{R'}}\text{N} \quad + \quad H\text{R}
\end{align*}
\]

Retention

\[
\begin{align*}
\text{singlet nitrene} & \quad \xrightarrow{\text{heat}} \quad \text{retention}
\end{align*}
\]

Nitrenoids frequently give better yields of C-H insertion reactions under milder conditions

\[
\begin{align*}
\text{iodonium ylid} & \quad \xrightarrow{\text{PhI(OAc)}_2, \text{cat. Rh}_2(OAc)_4} \quad \text{rhodium nitrenoid} \quad \xrightarrow{\text{Rh}^{\text{II}}} \quad \text{C-H insertion} \\
& \quad \xrightarrow{86\%} \quad \text{products}
\end{align*}
\]

In a similar manner transition metal nitrenoids react with alkenes to give good yields of aziridines.
- rearrangement of nitrenes

- photolysis of alkyl azides yields imines – nitrenes are most likely not intermediates in such reactions

\[
\begin{align*}
\text{R} & \quad \text{N} & \quad \text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{R'} & \quad \text{N} & \quad \text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{hv} & \quad \text{R'} & \quad \text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \\
\end{align*}
\]
concerted 1,2 shift

- Curtius rearrangement or acyl azides

\[
\begin{align*}
\text{R} & \quad \text{Cl} & \quad \text{O} & \quad \text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{NaN}_3 & \quad \text{hv} & \quad \text{h} & \quad \text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{ROH} & \quad \text{or} & \quad \text{water} & \quad \text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \\
\end{align*}
\]
there are two plausible mechanisms

\[
\begin{align*}
\text{R} & \quad \text{N} & \quad \text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \\
\text{RO} & \quad \text{R} & \quad \text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \\
& \quad \text{conc} & \quad \text{stepvia nitrene}
\end{align*}
\]

- the thermal reaction is concerted; the photochemical reaction may proceed via a nitrene, but may be concerted

- the Curtius rearrangement proceeds with retention of configuration in the migrating group
- other rearrangements to electron deficient nitrogen – these rearrangements are unlikely to involve nitrenes

- Hoffman rearrangement

\[
\begin{align*}
\text{R} & \text{NH} \quad \xrightarrow{\text{Br}_2, \Theta \text{OH}} \quad \text{RNH}_2 \\
\text{R} & \text{N} \quad \text{O} \quad \text{O} \quad \xrightarrow{\Theta \text{OH}} \quad \text{R} \text{N} \text{O} \\
\text{R} & \text{N} \quad \text{O} \quad \text{O} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{R} \text{N} \text{O}
\end{align*}
\]

- Lossen rearrangement

\[
\begin{align*}
\text{R} \text{N} \text{O} \quad \text{O} \quad \text{R}' & \xrightarrow{\Theta \text{OH}} \quad \text{R} \text{N} \text{O} \quad \text{water} \quad \text{RNH}_2 \\
\text{R} \text{N} \text{O} \quad \text{O} \quad \text{R}' & \xrightarrow{\Theta \text{OH}} \quad \text{R} \text{N} \text{O} \quad \text{water} \quad \text{RNH}_2
\end{align*}
\]
Schmidt rearrangement

\[ \text{Rearrangement of } \text{RCONH}_2 \text{ to } \text{RCO}_2 \text{H} \]

Schmidt rearrangement with ketones (aldehydes give nitriles)

Intramolecular Schmidt rearrangement with alkyl azides
**Beckmann rearrangement**

The group anti to the leaving group migrates ($\sigma_{CC} \text{ to } \sigma^*_{N-O}$)

Oximes can undergo E/Z isomerisation under the acidic reactions conditions

Migration with retention of configuration

**Beckmann rearrangement – synthesis of caprolactam, precursor to nylon 6**

Keto-enamine formation:

- $\text{NH$_2$OH}$
- $\text{H$_2$SO$_4$}$

Caprolactam

Most stable oxime with bulky groups trans

**Neber rearrangement – substituent possessing most acidic hydrogen migrates**

**Stieglitz rearrangement**
Baeyer-Villiger

- conversion of a ketone into an ester by oxygen insertion

- order of migration A.K.A migratory aptitude
  3° alkyl > 2° alkyl > aryl > 1° alkyl > methyl
  i.e. the group which best supports a positive charge migrates

- with aromatic groups, electron donating groups increase migratory aptitude

- migration occurs with retention of configuration in the migrating group

- with aldehydes migration of “H” usually occurs to give carboxylic acids

- transition state is electron deficient (electron withdrawing group on oxygen)

- electron releasing groups stabilise the transition state giving the order of migratory aptitude above

\[
\begin{align*}
\text{Bu}^+ & \xrightarrow{H^+} \text{Bu}^- \\
\text{Bu}^- & \xrightarrow{H^+} \text{Bu}^+ \\
\end{align*}
\]