Carbenes and Nitrenes

1 Introduction

1.1 Review of carbon valencies and hybridization

Rule of thumb: electron deficiency normally goes in \( p \) orbitals, negative charge in \( s \) orbitals.

2 Carbenes

2.1 Definition

"Carbenes are neutral, highly reactive species containing a divalent carbon atom with an electron sextet"

2.2 Possible hybridizations of methyl carbene

<table>
<thead>
<tr>
<th>Structure</th>
<th>Hybridization</th>
<th>Geometry</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(_3)C(=)H</td>
<td>( sp^2 )</td>
<td>Bent</td>
<td>Singlet</td>
</tr>
<tr>
<td>H(_3)C(=)H</td>
<td>( sp^2 )</td>
<td>Bent</td>
<td>Triplet</td>
</tr>
<tr>
<td>H(_2)CO</td>
<td>( sp )</td>
<td>Linear (not observed)</td>
<td>Triplet</td>
</tr>
</tbody>
</table>

2.3 Comparison between triplet and singlet carbenes

2.3.1 Spin state

\[ \begin{array}{c|c}
sp^2 & 1 \\
\hline
\sigma & \parallel \\
\parallel & \parallel \\
\end{array} \]

These two spin systems can be distinguished by EPR.

2.3.2 Geometry

From X-ray structures (see also subchapter 5.6.1) we know that both singlet and triplet states are bent.

<table>
<thead>
<tr>
<th>Bond angle</th>
<th>Triplet carbene</th>
<th>Singlet carbene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>130-150°</td>
<td>100-110°</td>
</tr>
</tbody>
</table>
2.4 Reactivity differences of singlet vs triplet carbenes

Generation of triplet carbenes

\[ \text{H}_2\text{C}==\text{N} \rightarrow \text{H}_2\text{C}::\text{N} \rightarrow \text{H}_2\text{C} \] 

Different reactivities

\[ \text{H}_2\text{CN}_2 + \text{Me} \rightarrow \text{Me} + \text{Me} \]

Generation of singlet carbenes

\[ \text{CHBr}_3 \rightarrow \text{Me} \rightarrow \text{Me} \]

2.5 Generation of Carbenes

3.1 1,1 elimination

\[ \text{R} = \text{R} \rightarrow \text{R} + \text{R} \]

3.2 Diazocompounds

\[ \text{R}_2\text{C}==\text{N} \rightarrow \text{R}_2\text{C}::\text{N} \rightarrow \text{R}_2\text{C} \]

4 Carbenoids (metal stabilized carbenes)

4.1 Generation

Fischer route

\[ \text{M} = \text{Cr}, \text{Mo}, \text{W} \]

From diazocompounds

\[ \text{Rh}_2(\text{OAc})_4 + \text{EtO} \rightarrow \text{EtO} \rightarrow \text{EtO} \]

4.2 Properties

Improved thermodynamic and kinetic stability with respect to the non-stabilized carbenes.

Fischer carbenes

- low oxidation state metals;
- middle and late transition metals Fe(0), Mo(0), Cr(0), W(0);
- \(\pi\)-acceptor metal ligands;
- \(\pi\)-donor substituents on methylene group (-OR or -NR\(_2\)).

Shrock carbenes

- high oxidation state metals;
- early transition metals Ti(IV), Ta(V);
- non \(\pi\)-acceptor ligands non \(\pi\)-donor substituents.
5 Reactions of Carbenes and Carbenoids

5.1 Cyclopropanation

5.1.1 Intermolecular

\[
\text{Me} + \text{CH}_2\text{N}_2 \rightarrow \text{Pd(OAc)}_2 (1 \text{ mol\%}) \rightarrow \text{MeCO}_2\text{Me} 96\%
\]

5.1.2 Intramolecular

\[
\text{Rh}_2(\text{OAc})_4 \rightarrow \text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2 91\%
\]

5.1.3 Simmons-Smith

\[
\text{OTMS} + \text{ZnEt}_2 (1.5 \text{ equiv}) \rightarrow \text{CH}_2\text{I}_2 (1.5 \text{ equiv}) \rightarrow \text{CH}_2\text{I}_2 0^\circ \text{C to reflux, 4 h}
\]

Mechanism

\[
\text{ZnEt}_2 + \text{CH}_2\text{I}_2 \rightarrow \text{IZnCH}_2\text{I (carbenoid)} + \text{R}^1 \text{R}^2 \text{R}^3 \text{R}^4 \rightarrow \text{R}^1 \text{R}^2 \text{R}^3 \text{R}^4 + \text{ZnI}_2
\]

5.2 C–H insertion

\[
\text{N}_2 \rightarrow \text{Rh}_2(\text{OAc})_4 \rightarrow \text{CHCl}_3 \rightarrow \text{CHCl}_3 96\%
\]

Mechanism

\[
\text{R}^1 \text{R}^2 \text{R}^3 \text{H} + \text{M} \rightarrow \text{R}^1 \text{R}^2 \text{R}^3 \text{R}^5 \rightarrow \text{R}^1 \text{R}^2 \text{R}^3 \text{H}
\]
5.3 Dimerization

\[
\text{MeO} \text{Cr(CO)}_5 \xrightarrow{\text{Pd(PPh}_3)_4 (10 \text{ mol\%}) \text{ Et}_3 \text{N (1.1 equiv)}} \text{rl, 1.5 h} \xrightarrow{\text{MeO} \text{Ph}} \text{Ph} \text{OMe} \\
53\% (E/Z = 2/1)
\]

**Mechanism**

5.4 O–H & N-H insertion

**N–H insertion**

\[
\text{Ph} \text{C}=\text{N}_2 + \text{H} \text{N} \xrightarrow{\text{Cu bronze}} \text{EtOH} \text{ 45 °C} \xrightarrow{\text{Ph}} \text{PhN} \xrightarrow{\text{80\%}}
\]

**O–H insertion**

\[
\text{Ph} \text{C}=\text{N}_2 + \text{H} \text{OCH}_3 \xrightarrow{\text{Cu bronze}} \text{EtOH} \text{ 50 °C} \xrightarrow{\text{Ph}} \text{PhOCH}_3 \xrightarrow{\text{55\%}}
\]

5.5 Ylide Formation

\[
\text{MeO}_2\text{C} \text{CO}_2\text{Me} + \text{S} \xrightarrow{\text{Rh}_2(\text{OAc})_4 \text{ rl, 24 h}} \text{MeO}_2\text{C} \text{CO}_2\text{Me} \xrightarrow{\text{reflux, 2 h}} \text{Ylide, 95\%}
\]

**Mechanism**

5.6 Wolff Rearrangement

\[
\text{Ph} \text{C}=\text{N}_2 \xrightarrow{\text{benzene reflux}} \text{Ph} \text{C}=\text{O} \xrightarrow{\text{Nu}^-} \text{R} \text{C}=\text{O} \xrightarrow{\text{Nu}}
\]

**Reminder:**

Nucleophiles: amines, alcohols...
Little is known about the reaction mechanism from the dibromoolefin to the alkyne, one of the accepted mechanisms proceeds via a carbene intermediate.
5.7.2 Seyferth-Gilbert Homologation

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\text{MeO} - \quad \text{MeO} - \quad \text{MeO} - \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{Cl} & \quad \text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

97%

Mechanism

6 N-heterocyclic carbenes

6.1 History

The first applications of thiazolylides in umpolung organocatalysis were reported as early as 1943 (J. Pharm. Soc. Jpn. 1943, 63, 296) and metal complexes of NHCs were already reported in the late 60's. However, it is only in the last two decades (milestone: 1991, Arduengo, first X-ray structure of a carbene) that NHCs have become ubiquitous both as ligands in organometallic chemistry and as organocatalysts.

6.2 NHCs are singlet carbenes

For NHCs the singlet state is lower in energy than the triplet state, the reason being π-donation into the p-orbital of carbon from the heteroatoms adjacent to the carbene.

6.3 Examples of the most frequent NHCs and their nomenclature

- **Imidazolynidene**
- **Imidazolydene**
- **Benzimidazolydene**
- **Tetrahydropyrimidiyldiene**
- **Pyrrolidinyldiene**
- **Triazolydene**
- **Thiazolidene**

R can be modified to fine-tune the chemical behavior of the NHC (R = alkyl or aryl).

6.4 Properties

NHC are electron rich and particularly stable carbenes. The stability arises both from:

- **shielding effect** by sterically demanding substituents (minor effect);
- **Electronic stabilization** (mesomeric interaction of the lone pairs of electrons on the nitrogen atoms with the empty p orbital of the sp² hybridized carbene).

\[
\begin{align*}
\text{azolium salt} & \rightarrow \text{base} \rightarrow \text{ylide} \rightarrow \text{carbene} \\
\end{align*}
\]

Acidic proton: the pKₐ value of the 2-position of imidazolium salts ranges from 16 to 23 (in DMSO).

6.5 Synthesis (generation)

6.6 Use as ligands

NHC-complexes are known for almost every transition metal, but the most important for organic chemist are:

<table>
<thead>
<tr>
<th>Metal</th>
<th>Class</th>
<th>Example</th>
<th>Catalyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ru</td>
<td>Metathesis</td>
<td>EIOOC COOEt</td>
<td>Grubbs II catalyst</td>
</tr>
<tr>
<td></td>
<td>reactions</td>
<td></td>
<td>CH₂Cl₂, 40 °C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EIOOC COOEt</td>
<td>Grubbs II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grubbs II</td>
<td>PhPCy₃</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Buchwald-Hartwig</td>
<td>Grubbs II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>coupling with hindered substrates</td>
<td></td>
</tr>
<tr>
<td>Pd</td>
<td>Cross-coupling</td>
<td>NH₂ Me Cl Me</td>
<td>Pd-PEPPSI</td>
</tr>
<tr>
<td></td>
<td>reactions</td>
<td></td>
<td>KOBu, DME, 24 h, rt</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pd-PEPPSI</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

NHC behave like phosphines when they are coordinated to metals (electron donating properties) but they have more influence on the coordination sphere of the metal (sterics).
Use as catalysts
See redox neutral chapter.

7 Nitrenes

7.1 Structure & hybridization
Nitrenes are nitrogen analogues of carbenes. The nitrogen atom possesses only six valence electrons; in nitrenes the triplet state is lower in energy than the singlet state.

\[
\begin{align*}
\text{R} & \rightarrow \text{N}^* \\
\text{R} & \underset{\text{N}}{\text{C}} \\
\text{O}
\end{align*}
\]

7.2 Generation

7.2.1 From 1,1-elimination

\[
\begin{align*}
\text{R} & \rightarrow \text{N}^* \\
\text{R} & \underset{\text{N}}{\text{C}} \\
\text{O}
\end{align*}
\]

7.2.2 From azides

\[
\begin{align*}
\text{R} & \rightarrow \text{N}^* \\
\text{R} & \underset{\text{N}}{\text{C}} \\
\text{O}
\end{align*}
\]

7.3 Hoffman-type rearrangements

7.3.1 Hoffman rearrangement

\[
\begin{align*}
\text{R} & \rightarrow \text{N}^* \\
\text{R} & \underset{\text{N}}{\text{C}} \\
\text{O}
\end{align*}
\]

7.3.2 Curtius rearrangement

\[
\begin{align*}
\text{R} & \rightarrow \text{N}^* \\
\text{R} & \underset{\text{N}}{\text{C}} \\
\text{O}
\end{align*}
\]
7.3.3 Lossen rearrangement

\[
\text{Mechanism}
\]

7.4 Beckmann rearrangement

\[
\text{Mechanism}
\]

7.4.1 Mechanistic analogy to Baeyer-Villiger reaction

7.4.2 Industrial nylon synthesis

7.4.3 Metal catalyzed C–H insertion

\[
\text{Mechanism}
\]
Carbenes play a central role in a number of biological processes. One of the most important examples is Vitamin B$_1$ (Thiamine pyrophosphate), a coenzyme involved in many metabolic pathways. For instance, the enzyme *pyruvate decarboxylase* is assisted by TPP in catalyzing the transformation of pyruvate into acetaldehyde: a key step in the anaerobic fermentation… Think about it next time you’ll have a drink!