N-HETEROCYCLIC CARBENES:
STRUCTURE AND PROPERTIES
Zachery Matesich 24 February 2015
Roadmap

- Introduction
  - Synthetic Methods
  - History of NHCs

- Properties of NHCs
  - Nature of the carbene
  - Structural properties
  - Electronic properties

- Illustrative Examples

- Conclusion
**N-Heterocyclic Carbene**

**What?**
- Neutral compound
- Divalent carbon atom with 6-electron valence shell
- Usually adjacent to electronegative atom

**Why?**
- Highly nucleophilic
- Stable carbenes due to steric/electron effects
- Structurally versatile

Illustration of syntheses for 4 general NHC cores

**Imidazolium**

\[
\begin{align*}
\text{Ar} - \text{N} &- \text{N} - \text{Ar} \\
\text{Cl} &- \text{THF} \\
\text{Ar} - \text{N} &- \text{N}^+ - \text{Ar} \\
\text{Cl}^{-}
\end{align*}
\]

Smith, *JOC*, 2007, 73, 2784

**Imidazolinium**

\[
\begin{align*}
\text{Cl} &- \text{OEt} \\
1) \text{ArNH}_2, \text{Et}_3\text{N} \\
2) \text{Ar'}\text{NH}_2, \text{Toluene, } \Delta \\
\text{Ar} \text{HN} &- \text{CO} - \text{ArH} \\
\text{Ar} \text{HN} &- \text{CO} - \text{ArH}
\end{align*}
\]

1) BH₃, THF, Δ
2) Conc HCl

Grubbs, *Organometallics*, 2004, 23, 3105

**Triazolium**

\[
\begin{align*}
\text{Ar}^\text{H}_3\text{N} &- \text{NH}_3\text{Ar} \\
\text{Cl}^{-} \\
\text{CH(OEt)}_3, \Delta
\end{align*}
\]

2) Δ

Rovis *JOC*, 2005, 70, 5725

**Benzimidazolium**

\[
\begin{align*}
\text{Br} &- \text{Br} \\
1) \text{Pd(0), RNH}_2 \\
2) \text{Pd(0), R'NH}_2 \\
3) \text{CH(OEt)}_3, \text{HX}
\end{align*}
\]

Diver, *OL*, 2001, 3, 2673
NHCs: Early Beginnings

- **Ofele (1968)**
  - Attempt to generate dihydro-complexes:
    
    \[
    \begin{array}{c}
    \left[ \text{imidazolium salt} \right] \\
    \text{[HCr(CO)\textsubscript{5}]\textsuperscript{\text{\textit{\textminus}}} }
    \end{array}
    \xrightarrow{\Delta} 
    \begin{array}{c}
    \text{imidazolyl Cr(CO)\textsubscript{3} }
    \end{array}
    + 2 \text{ CO}
    \]
  
  - When using imidazolium salts, noted a side reaction:
    
    \[
    \begin{array}{c}
    \left[ \text{imidazolium salt} \right] \\
    \text{[HCr(CO)\textsubscript{5}]\textsuperscript{\text{\textit{\textminus}}} }
    \end{array}
    \xrightarrow{120 \text{ °C}} 
    \begin{array}{c}
    \text{imidazolyl Cr(CO)\textsubscript{5} }
    \end{array}
    + 2 \text{ H}_2
    \]
    
    Light, yellow solid with composition:
    
    C\textsubscript{10}H\textsubscript{8}CrN\textsubscript{2}O\textsubscript{5}

Ofele, K. J. Organomet. Chem. 1968, P42-P43
**NHCs: Early Beginnings**

- **Wanzlick (1968)**
  - Isolation as a mercury dimer:
    
    $\text{2 A} \quad \text{ClO}_4^- \quad + \text{Hg(OAc)}_2 \quad \text{2 ClO}_4^- \quad \text{-2 AcOH}$
    
    
    - $^1\text{H NMR}$ of product reveals downfield shift and lack of coupling

    | DMSO $d_6$ | H(2) (ppm) | H(4), H(5) (ppm) | H(phenyl) (ppm) |
    |------------|------------|------------------|-----------------|
    | A          | -0.29 (t)  | 1.47 (d)         | 1.95 - 2.5      |
    | B          | --         | 1.71 (s)         | 2.2 - 2.7       |

NHCs: Early Beginnings

- **Wanzlick equilibrium**
  - Preferred product of carbene formation is dimer:
    - [Chemical structures] (Diagram)
  - Dimer can revert: @ 170 °C, about 50:50 mix
  - Carbene can react with electrophiles whereas dimer is inactive

NHCs: First “bottle-able” carbene

- Arduengo (1991)
  - Deprotonation of a imidazolium salt

\[
\text{NaH (1 equiv)} \rightarrow \text{DMSO (cat) THF}
\]

- X-ray and \(^1H\) NMR analysis revealed interesting differences in A and B

<table>
<thead>
<tr>
<th></th>
<th>(N_1)-C(_2)-N(_3) angle</th>
<th>Avg C(<em>2) N(</em>{1(3)}) (pm)</th>
<th>(^1H)(_{(4,5)}) (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>(108.5) - (109.7^\circ)</td>
<td>132</td>
<td>7.92</td>
</tr>
<tr>
<td>B</td>
<td>(102.2^\circ)</td>
<td>137</td>
<td>6.91</td>
</tr>
</tbody>
</table>

Synthesis of additional NHCs: 1992

- A, C, D, & E stable as solids
- B stable in solution
- No rationale as to why Wanzlick was unable to isolate the same complexes
- Stability not solely the result of steric parameters or substituents on nitrogen

N-Heterocyclic Carbene

Number of publications per year since 1982 for “NHC”
Nature of the carbene: Overview

- Hybridization of carbon breaks degeneracy of the p orbitals

- Ground state spin multiplicities for carbenes

- Singlet carbenes have filled & vacant orbital \( \rightarrow \) ambiphillic

- If singlet-triplet gap is \( >2 \) eV, singlet state predominant

- Both steric and electronic factors play a large role in influencing the orbital separation

Nature of the carbene: Electronics

- Inductive effects of $\sigma$-withdrawing substituents favor singlet state

- The $\sigma$ nonbonding orbital has increased “s” character

- Smaller gap of $\sigma$-donating substituents favor triplet state

Mesomeric effects involve π-donating/withdrawing substituents

- π-donating (X) include: -F, -Cl, -Br, -I, -NR₂, -PR₂, -SR
- π-withdrawing (Z) include: -COR, -CN, -CF₃, -BR₂, -SiR₃, -SR

The energy of the vacant pπ is increased with the combination of the lone pairs and as the σ orbital is unchanged, the σ- pπ gap increases.

Nature of the carbene: Sterics

- If electronic effects are insignificant, sterics can dictate ground state
- Linear geometries favor triple state
  - One p orbital is left perpendicular to the plane, unaffected, becomes $p_\pi$
  - Other p orbital is stabilized and acquires more “s” character, becomes $\sigma$
- With significant steric bulk, the carbene substituents broaden the bond angle

Nature of the NH carbene: Stability

- Nitrogen heteroatoms are $\sigma$-electron withdrawing and $\pi$-donating
  - Therefore this breaks the degeneracy of the $p_x/p_y$ energy level
- N-C-N bond is bent, forced by the structure of the ring
  - Singlet state is made more favorable
- Steric bulk helps to kinetically stabilize
  - Steric bulk is distal from carbene, which avoids making the bond more linear

Hoffman, R. et al. JACS 1968, 90, 5457-5460.
Nature of the NH carbene: Stability

- Frenking (1996): Effect of aromaticity on NHC stability via NBO

- The $p_{\pi}$ occupancy for 1 is 55.8% delocalized, for 2 is only 39.8%

- Heats of hydrogenation: 1 is -20.8 kcal/mol and 2 is -39.7 kcal/mol

- Shorter C-N bonds in 2 can be accounted for by steric factors of the backbone giving the bond more “s” character

Nature of the NHC-Metal bond

- Tulloch (2001): Extent of \( \pi \)-bonding using Cu complexes

![X-ray structure of Cu-NHC bond length: 1.88 Å, < Cu-C \( \sigma \) bond (1.90 Å)]

- Frenking (2004): Revealed that \( \pi \)-back bonding accounts for about 20% of a Ag-NHC product

Nature of the NHC-Metal bond


- Nolan (2007): Through $^{195}$Pt NMR chemical shifts and $^{195}$Pt-$^{13}$C coupling, the influence of the carbene on the metal center was observed.

- Larger coupling constants indicate more electron density in the σ-bond and upfield chemical shifts indicate more electron rich bonds.

Properties of NHCs: Sterics of Ligand

- Due to shape of NHC (wedge-like), the buried volume ($% V_{bur}$) is used.
- Defined as: percent of the total volume of a sphere occupied by a ligand.
- Reveals that values are highly dependent on orientation of NHC-TM complex.
- Furthermore, values are derived from X-ray structure, so not accurate representation in solution.

Glorius, F. et al. ACIEE 2010, 49, 6940-6952.
Properties of NHCs: Sterics of Ligand

- Cavallo (2010): Attempt for a dynamic model of the metal environment

- The % \(V_{\text{bur}}\) values obtained from geometry optimization are peak of a broad distribution

- Reveal that normal vibrations are not captured by static methods

- Unsaturated are slightly less bulky with shift to smaller values

Properties of NHCs: pK\textsubscript{a}’s

- Compiled pK\textsubscript{a} valued (DMSO)

\[
\begin{align*}
\text{Ph} & : 19.7 \\
\text{OMe} & : 20.5 \\
\text{Bz} & : 21.6 \\
\text{R} & : 22.0 - 22.1 \\
\text{Me} & : 18.6 \\
\text{Me} & : 22.3^{**} \\
\text{Me} & : 27.1^{**} \\
\text{Et} & : ~13 \text{ (R = Me, Et, } n\text{Bu, } n\text{Oct)}
\end{align*}
\]

- Significant rate difference between salts cores:

\[
\begin{align*}
k_{DO} & = 10^7 \text{ to } 10^8 \\
& = 10^0 \text{ to } 10^5 \\
& = 10^3 \text{ to } 10^4 \\
& = 10^{-3}
\end{align*}
\]

Properties of NHCs: $^{13}$C NMR

- Diagnostic $^{13}$C NMR shift for carbene (200 – 330 ppm)

- Saturation causes downfield shift due to a lower population of the carbene $p_\pi$–orbital population

- Correlation between N-C-N bond angle and $^{13}$C shift

Properties of NHCs: Electronic Character

- Tolman’s Electronic Parameter
  - Originally developed to describe phosphines
  - Electron donating into metal caused CO ligand to weaken and can be examined by IR
  - The lower the TEP, the more electron donating the NHC

\[
\text{Ar}^1 \text{-N} \overset{\text{N}}{\text{N}} \text{-Ar}^1 \\
\text{Ar}^2 \text{-N} \overset{\text{N}}{\text{N}} \text{-Ar}^2 \\
\text{Ar}^1 \text{-N} \overset{\text{N}}{\text{N}} \text{-Ar}^1 \\
\text{Ad} \text{-N} \overset{\text{N}}{\text{N}} \text{-Ad}
\]

\[\text{TEP} = \begin{array}{c}
2051.5 \text{ cm}^{-1} \\
2051.5 \text{ cm}^{-1} \\
2050.7 \text{ cm}^{-1} \\
2048.3 \text{ cm}^{-1}
\end{array}\]

\[\text{Ar}^1 = 2,4,6\text{-trimethylphenyl} \\
\text{Ar}^2 = 2,6\text{-diisopropylphenyl}\]

- One caveat: As NHC-metal complexes involve multiple interactions with the NHCs, the values can be influenced

Properties of NHCs: \textit{in silico} TEP

- Use of DFT calculations to generate IR spectra of Ni(CO)$_3$NHC complexes

\[
\begin{array}{cccc}
\text{Ar}^1\cdots\text{N} & \text{Ar}^1 \\
\text{N} & \text{Ar}^2 \\
\text{Ar}^2 & \text{N} & \text{Ar}^1 \\
\text{Ad} & \text{N} & \text{Ad} \\
\end{array}
\]

\[
\text{TEP} = \begin{array}{cccc}
2051.5 \text{ cm}^{-1} & 2051.5 \text{ cm}^{-1} & 2050.7 \text{ cm}^{-1} & 2048.3 \text{ cm}^{-1} \\
2051.2 \text{ cm}^{-1} & 2050.5 \text{ cm}^{-1} & 2050.5 \text{ cm}^{-1} & 2048.9 \text{ cm}^{-1} \\
\end{array}
\]

\textit{in silico} TEP

- Values are in near agreement
- Solvent / source of IR data no longer a dissimilarity
- Can be used to predict structures not yet experimentally determined

Properties of NHCs: NMR Measurements

- Generation of carbene-phosphinidine adducts to measure the $\pi$-accepting properties of carbenes

\[
\begin{align*}
\text{A} & \quad \text{Ph} \\
\text{B} & \quad \text{Ph}
\end{align*}
\]

- In resonance form B, free rotation should be observed in NMR
- Higher $\pi$-accepting NHC will involve more of A and the further $^{31}\text{P}$ shift will be downfield
- Complexes formed through:

\[
\begin{align*}
\text{\text{PhPCl}_2} & \quad \xrightarrow{\text{Hexanes}} \quad \text{P}^+\text{Cl}^- \\
\text{P}^+\text{Cl}^- & \quad \xrightarrow{2 \text{ equiv KC}_8 \text{ or 2 equiv Mg}} \quad \text{Cl}^- \quad \xrightarrow{\text{THF}} \quad \text{P}^\text{Ph}
\end{align*}
\]

Bertrand, G. et al ACIEE. 2013, 52, 2939-2943.
Properties of NHCs: NMR Measurements

- Compounds with similar TEP values, but differing 31P shifts indicate differences in the \( \pi \)-accepting properties of the NHC.

- 1 and 2 have the same TEP, but 1 has more \( \pi \)-accepting character, therefore, 1 is more \( \sigma \)-donating.

- Effect of annelation in 2 and 3.

- Comparison of 4/5 and 6/7 reveal more \( \pi \)-accepting in saturated, as there is less electron delocalization.

Bertrand, G. et al. ACIEE. 2013, 52, 2939-2943.
Stability of NHCs: Dimerization

- As previously observed by Wanzlick, NHCs have propensity to dimerize

\[
E_{\text{dim}} = (A \times \text{NHC}_{\%Buir}) + (B \times \text{NHC}_{ES-T}) + C
\]

- Both steric and electronic factors involved

- Cavallo developed an equation to evaluate:
  \[ E_{\text{dim}} \leq -20 \text{ kcal mol}^{-1} \text{ tend to be dimer} \]

- \( E_{\text{dim}} \geq 0 \text{ kcal mol}^{-1} \text{ tend to be monomeric} \)

Group Problem: Cyclopentane Synthesis

- Stereodivergence based upon use of HNC
- Each NHC essentially structurally identical with regards to sterics

Group Problem: Cyclopentane Synthesis

1) Determine the mechanism for formation of each product

2) Rationalize the divergence in product formation based upon the NHC used

Note: The counterion has no influence on the reaction outcome

- Divergence is result of ability for NHC to act as a leaving group
- More electron rich imidazolium HNC is less likely to leave
- Imiazolium prefers formation of more stable γ-lactone

NHC Applications: Switching reactive pairs

- **Yang (2011): Acyloin Condensation**

![Chemical structures and reactions](image)

- **Sterics guide the formation of the first intermediate**

- **More potential overlap when using triazolium catalyst with aryl aldehyde**

Modifying the basic NHC structure

- Bertrand (2012): Generating an electrophilic AND nucleophilic NHC

- Second nitrogen only acts as inductive electron withdrawing substituent
- C1-N2 bond is 1.341 Å vs 1.310 Å for C1-N1 – revealing pyramidal N2
- TEP value of 2047 cm\(^{-1}\) which puts it less electron donating than normal 6-membered NHC ligands (~2045.5 cm\(^{-1}\))

NHCs versus Phosphines

- Monodentate, 2-electron ligands
- Synthesis for NHCs highly varied, with precursors being air-stable
- NHCs are typically irreversible binding ligands
- Steric/electronic properties in NHCs are typically separately alterable
- Larger trans-effect for NHCs (exploited in a later slide)

**TEP Values**
- Phosphine typically 2056.1 cm\(^{-1}\) \([P(tBu)_3]\) to 2110.8 cm\(^{-1}\) \([PF_3]\)
- NHCs typically 2048.3 [lAd] to 2058.1 cm\(^{-1}\) [slide 31] – stronger electron donor

- NHC more thermally and oxidatively stable
- Different modes of steric influence (NHC – wedge, phosphine – cone)

NHCs versus Phosphines: Case-study

- Grubbs II Ruthenium Olefin Metathesis

Large rate difference reveals that binding to the alkene is $10^4\times$ more favorable than binding the phosphine ligand, leading to higher activity.

Grubbs, R. H. et al. JACS **2001**, 123, 6543-6554.
NHC Applications: Further catalyst improvements

- Grubbs Z-selective Ruthenium Olefin Metathesis

\[ \text{Grubbs, R. H. et al. JACS 2013, 135, 10183-10185.} \]

- Inclusion of second bond between the metal and NHC ligand
- Steric clash of N-mesityl and alkylidene influences selectivity
NHC Applications: Transition metals

- Palladium cross-coupling reactions can be improved
- Aside from increased thermal stability of the catalyst, NHC can influence catalytic cycle
- More electron-rich Pd for OA
- Increased steric properties, as compared to phosphines aid reductive elimination
- Avoidance of Pd black through Pd(0) stabilization

R¹, R² = aryl, heteroaryl, alkyl
X = halide, pseudohalide
M = B(OR)₂ (Suzuki–Miyaura), SnR₃ (Stille), ZnR (Negishi) and also heteroatom coupling partners such as HNR₂ (Buchwald–Hartwig)

NHC Applications: Palladium catalysis

- Palladium catalyzed Heck reaction

\[
\begin{align*}
\text{Cl} & \quad \text{O}_2\text{N} \\
\text{O}_2\text{N} & \quad \text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{A} & \quad \text{O}_2\text{N} \\
\text{O}_2\text{N} & \quad \text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{O}_2\text{N} \\
\text{O}_2\text{N} & \quad \text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{O}_2\text{N} \\
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\]

\[
\begin{align*}
\text{Cl} & \quad \text{O}_2\text{N} \\
\text{O}_2\text{N} & \quad \text{Cl}
\end{align*}
\]

- Pd-C bonds (1.990 Å) similar to other carbene complexes
- High thermal stability – several days in boiling THF with O₂
- No Pd decomposition observed during course of reaction

Conclusion

- Stabilization a combination of steric and electronics properties
- Methods for quantifying NHC properties are improving
- Some predictive models are being developed
- High versatility as ligands through synthesis
- Can be an improvement over use of phosphines
- High thermal and oxidative stability in NHC-metal complexes
References