Structure and Reactivity

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Summary

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Structure and Reactivity: Summary

1. Conformational Analysis
(Energy Values in Kcal/mol, M = Medium, L = Large)

1.1 Alkanes
Butane

Sägebock

Newman

Gauche Interaction

Relative Energy
0
staggered
antiperiplanar

3.8
eclipsed
anticinal

0.9
staggered
synclinal
gauche conformer

5
eclipsed
synperiplanar

Special Interaction for Pentane:

Double Gauche Pentane or Syn Pentane Interaction

1.2 Alkenes: Allylic Strain

Allylic A\textsuperscript{1,2} Strain

Allylic A\textsuperscript{1,3} Strain

\textbf{A}\textsuperscript{1,3} Minimized:
- R\textsubscript{L} in free room \(\perp\) to DB
- H towards R\textsubscript{2}
Favored for R\textsubscript{2} bigger R\textsubscript{1}

A\textsuperscript{1,2} Minimized:
- R\textsubscript{L} in free room \(\perp\) to DB
- H towards R\textsubscript{1}
Favored for R\textsubscript{1} bigger R\textsubscript{2}

- If R\textsubscript{1} and R\textsubscript{2} are of similar size, A\textsubscript{1,3} is more important.
- R\textsubscript{3} is usually less important for selectivity.
1.3 Cyclohexane

![Diagram of cyclohexane conformations: chair, half chair, twist boat, boat, with relative energies and transition state energy (E_a = 10 kcal/mol)].

### A value

<table>
<thead>
<tr>
<th>R</th>
<th>A value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>1.7</td>
</tr>
<tr>
<td>CH₂CH₃</td>
<td>1.7</td>
</tr>
<tr>
<td>CH(CH₃)₂</td>
<td>2.1</td>
</tr>
<tr>
<td>C(CH₃)₃</td>
<td>4.7</td>
</tr>
<tr>
<td>CH₂OH</td>
<td>1.7</td>
</tr>
<tr>
<td>CO₂Et</td>
<td>1.2</td>
</tr>
<tr>
<td>CN</td>
<td>0.2</td>
</tr>
<tr>
<td>C = C-H</td>
<td>0.4</td>
</tr>
<tr>
<td>CH = CH₂</td>
<td>1.6</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>2.8</td>
</tr>
<tr>
<td>Si(CH₃)₃</td>
<td>2.5</td>
</tr>
<tr>
<td>Sn(CH₃)₃</td>
<td>1.0</td>
</tr>
<tr>
<td>O₂CCH₃</td>
<td>0.7</td>
</tr>
<tr>
<td>OCH₃</td>
<td>0.6</td>
</tr>
<tr>
<td>N₃</td>
<td>0.5</td>
</tr>
<tr>
<td>F</td>
<td>0.3</td>
</tr>
<tr>
<td>Cl</td>
<td>0.6</td>
</tr>
<tr>
<td>Br</td>
<td>0.6</td>
</tr>
<tr>
<td>I</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**2 gauche interactions (also called 1,3-diaxial interactions):**

![Diagram showing gauche interactions with R axial and R equatorial, and A value expression: \(-\Delta G\) (axial-equatorial)].

**A value (R) = -\(\Delta G\) (axial-equatorial)**

!!! A value are exact only for monosubstituted cyclohexanes!!!

**Important Exception: Anomeric Effect**

![Diagram illustrating Anomeric Effect with R axial and R equatorial, showing A value: -0.6! Axial is favored].

**Anomeric Effect:** In the axial position, a better stabilization with the more electronegative \(\sigma^{*}_{C-O}\) is possible.
1.4 Other Important Stereoelectronic Effects

**Gauche Effect**

[Chemical structures and diagrams explaining gauche effect with stereochemical notation.

**Enolate Formation**

[Chemical structures and diagrams explaining enolate formation with stereochemical notation.

Microscopic Reversibility:

Hydrogen is acidic only \( \perp \) to C=O!

Protonation from Enolate is \( \perp \) to C=C!

2. C=C Functionalization

2.1 Hydroboration

Hydroboration with BH\(_3\): Minimize strongest Allylic strain, BH\(_3\) comes opposite from R\(_L\).

**A\(^{1,3}\) Minimized**

**A\(^{1,2}\) Minimized**

Regioselectivity: H goes to more stabilized carbocation, because the mechanism is asynchronous:

Partial positive charge \( \delta^+ \)

tertiary carbocation > secondary carbocation > primary carbocation
Hydroboration with bulky boron reagents: Minimize reagent-substrate interactions

\[ R_1 R_2 R_3 \xrightarrow{BR_2H} R_1 R_2 R_3 \xrightarrow{H_2O_2} R_1 R_2 R_3 \]

\( A^{1,2} \) not minimized

\[ R_1 R_2 R_3 \xrightarrow{H_{OM}} R_1 R_2 R_3 \xrightarrow{A_{1,2} \text{ minimized}} R_1 R_2 R_3 \]

\( A_{1,2} \) minimized but strong steric interaction with reagent!

Reagent control is important!

2.2 Epoxidation

Directed Epoxidation with \( m \)-CPBA

\( m \)-CPBA

OH directs \( m \)-CPBA

\[ R_1 R_2 \xrightarrow{BH_3} R_1 R_2 \xrightarrow{m \text{-CPBA}} R_1 R_2 \]

\( A^{1,3} \) minimized

Prediction easy for cyclic substrates:

Directed reactions often allows for good selectivity in organic chemistry!

Sharpless Asymmetric Epoxidation

Allylic O binds to Ti: directed reaction

Substitution at \( R_4 \) is not tolerated

Important:

- \( t \)-BuOOH does not react until bound to Ti \( \Rightarrow \) Catalysis is possible
- Face of attack of the peroxide is determined by the chiral diester ligand, not the conformation of the substrate \( \Rightarrow \) very good reagent control
2.3. Fürst-Plattner Rule

\[ R \overset{Br_2}{\longrightarrow} R \text{Br}_2 \]

thermodynamically more stable

\[ \text{favored product} \]

twist boat, high energy
directly to chair

\[ \text{The thermodynamically more stable product is not observed, because an unfavorable twist-boat intermediate has to be formed.} \]

3. Addition to Carbonyl Compounds

3.1. Felkin-Ahn Model

\[ \text{Polar Felkin-Ahn Rule} \]

Electron-deficient groups behave as \( R_L \)

\[ \text{Favorable Interaction } n_{Nu} \text{ to } \sigma^*_{C-X} \]

\[ X = \text{OR, F, Cl, Br, I, ...} \]

3.2. Addition to Carbonyl Compounds Not Following the Felkin Ahn Model

3.2.1. Chelate Control

- Metal forces two donors in plane through chelation
- Nu comes towards smallest substituent (H)
Factors favoring chelation

- **R group sterically not hindered:**
  - good: \( R = \text{Me, Bn, MeOCH}_2 \) (MOM), BnOCH\(_2\) (BOM)
  - bad: \( R = \text{Bu, SiMe}_3, \text{SiPr}_3 \) (TIPS)

- **non-coordinating solvents:**
  - Toluene, CH\(_2\)Cl\(_2\) >> Et\(_2\)O > THF >> DMF, EtOH, H\(_2\)O

- **Strong Lewis Acid, with more than one coordination site available**
  - Bad: Na\(^+\), K\(^+\) (too weak Lewis Acid), BF\(_3\) (only 1 coordination site), LiX
  - Good: MgX\(_2\), ZnX\(_2\), LiX, TiCl\(_4\), SnCl\(_4\), SnCl\(_2\), LnX\(_3\), AlCl\(_3\), ...

**Importance of anion X:** If X is not too tightly bond to the metal, it can dissociate generating a new free coordination site. F\(^-\), R\(^-\) generally don't dissociate, Cl\(^-\) and OAc\(^-\) can dissociate and Br\(^-\), I\(^-\), OTf\(^-\) often dissociate easily. For example BF\(_3\) is not a chelating agent, but BBu\(_2\)OTf is a chelating agent.

### 3.2.2. Directed Reduction

Sodium trisacetoxy borohydride is a very weak reducing reagent ⇒ Only intramolecular reduction is possible

### 3.2.3 Reagents Binding to Carbonyl During Addition

**Borane Reduction**

- \( R_L \) is \( \perp \) to C=O
- \( BR_2 \) bind to O during reduction
- Minimize \( BR_2\)-Substrate interaction ⇒ Smallest Substituent towards \( BR_2 \) (H)

Other important examples where Felkin-Ahn models does not apply:

*Allylation, Aldol Reactions via Chair Transitions States*
4. Allylation

**Allylation**

\[ \text{RCHO} \rightarrow \text{OH} \]

**Crotylation**

\[ \text{MeRCHO} \rightarrow \text{OH} \]

- 6-membered, chair transition state
- Substituent in equatorial position
- Transfer from double bond geometry to stereochemistry (E to anti, Z to cis)

**Chiral Reagents For Allylation Reactions**

Roush Reagent

\[ \text{CO}_2\text{iPr} \text{Me} \rightarrow \text{OH} \]

Brown Reagent

\[ \text{(-)-Ipc}_2\text{B-allyl} \rightarrow \text{OH} \]
5. Aldol Reactions

5.1 Enolate Generation

With LDA

For big X (CR₃, NR₂)

\[
\begin{align*}
\text{X} & \quad \text{R} + \quad \text{HN}^\text{Pr}_2 \\
\text{LDA} & \\
\text{X/R interaction minimized}
\end{align*}
\]

For small X (OR, H)

\[
\begin{align*}
\text{X} & \quad \text{Pr} \\
\text{X/Pr interaction minimized}
\end{align*}
\]

exception for esters: Adding HMPA leads to \textit{Z} (\textit{cis}) Enolate

\[
\text{HMPA: good ligand for lithium} \Rightarrow \text{Cyclic transition state is partially disrupted}
\]

Deprotonation of Imides with Bu₂BOTf and NEt₃ (soft enolization)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{B} \\
\text{Bu}_2\text{BOTf} & \quad \text{NET₃} \\
\text{Cis Enolate only}
\end{align*}
\]

Very strong \textit{A}₁,\textit{β} with Imides!

Deprotonation of Ketones

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{9-BBN-BOTf} & \quad \text{NET₃} \\
\text{NET₃} & \quad \text{NET₃}
\end{align*}
\]

Very strong \textit{A}₁,\textit{β} with Ketones!

\[
\begin{align*}
\text{Cy}_2\text{BCl} & \quad \text{NET₃} \\
\text{Cy}_2\text{BO} & \quad \text{NET₃}
\end{align*}
\]

\*

The complete switch of selectivity is not well understood, some authors proposed an extra Cl-hydrogen interaction
5.2 Zimmermann-Traxler Transition State

- Chair transition state (Zimmerman-Traxler)
- R group of aldehyde equatorial
- Geometry of double bond transferred to stereocenter: cis to syn, trans to anti

5.3 Evans Auxiliary

Evans Syn Aldol:

Important: In order to activate the aldehyde for addition, B has to bind to the aldehyde. As B has only two free binding sites, the oxazolidinone carbonyl is now free and rotates to minimize dipole interactions.

Crimmins Syn Aldol

Important: In order to activate the aldehyde for addition, B has to bind to the aldehyde. As B has only two free binding sites, the oxazolidinone carbonyl is now free and rotates to minimize dipole interactions.
5.4 Ketone (Paterson) Aldol

- Chair transition state
- \( R_1 \) group of aldehyde equatorial
- Position of chiral group: minimize steric interaction with \( BR_2 \) for cis enolate, aldehyde comes towards \( R_M \), not \( R_L \), minimize \( A^{1,3} \) with Me of enolate for trans enolate, \( R_M \) and not \( R_L \) towards \( BR_2 \), aldehyde comes towards H

5.5 Proline Catalyzed Aldol

- Anti aldol with external Lewis Acid
6. Rearrangements

6.1 Cationic Rearrangements

The group which stabilizes the best the cation is migrating

2 electrons - 3 centres transition state

Name Reactions: Wagner Meerwein, Pinacol, semi-Pinacol, Prins-Pinacol.

6.2 Carbene and Nitrene Rearrangements


Name Reactions: Curtius, Hofmann, Lossen, Schmidt

6.3 [3,3] Sigmatropic Rearrangements

- Chair transition state (with rare exceptions)
- R groups at SP³ centers equatorial
- Transfer of double bond geometry to stereocenter and stereocenter to double bond geometry

Name Reactions: Cope (X = C), Oxy-Cope (X = C, R₂ = OH), Anionic Oxy-Cope (X = C, R₂ = O⁻), Claisen (X = O), Johnson-Claisen (X = O, Y = OR), Ireland-Claisen (X = O, Y = OLi, OSiR₃)
7. Umpolung

7.1 Stoichiometric Umpolung Reagents

Acyl anion equivalents:

\[
\begin{align*}
R'O^- &= \text{Dithiane} \\
\text{Cyanide} &\quad \text{Nitronate}
\end{align*}
\]

Electrophile α to carbonyl:

\[
\text{R} = \text{NO}_2
\]

7.2 Catalytic Umpolung

The Benzoin Condensation

\[
\text{RCHO} + \text{RCHO} \xrightarrow{\text{cyanide cat.}} \text{R}^*\text{RCH} = \text{RCHO}
\]

The Stetter Reaction

\[
\text{RCHO} + \text{R'CHX} \xrightarrow{\text{carbene cat.}} \text{R}^*\text{R'CHX}
\]

Mechanism for the carbene-catalyzed benzoin condensation:
8. Reactions Involving N-N and N-O Bonds

8.1 Hydrazones

Wolff-Kishner Reduction

Other reactions with hydrazones derived from hydrazine: Wharton rearrangement, Barton halogenation

Reactions of Tosylhydrazones

Reactions of Tosylhydrazones

8.2 Umpolung with Hydrazones and Oximes

8.3 Polonovski and Pummerer Rearrangements
9. Cross-Coupling and Olefin Metathesis

9.1 General Mechanism for Cross Coupling

\[
\begin{align*}
R-X + R_1-M & \xrightarrow{\text{catalyst}} R-R_1 \\
R-R_1 & \xrightarrow{\text{Reductive Elimination}} \text{PdL}_2 \\
\text{R-Oxidative Addition} & \xrightarrow{\text{Addition}} \text{PdL}_2 \\
\text{R-Transmetallation} & \xrightarrow{\text{Elimination}} \text{R}-M \\
\end{align*}
\]

- Catalyst: most often Pd, but also Ni, Fe
- M = BX₂: Suzuki
- M = SnR₃: Stille
- M = ZnX: Negishi
- M = MgX: Kumada
- Special: R₁-M = R₂

**Scope:**
- R and R₁ groups
  - Easy: R, R₁ = aryl, alkenyl, alkynyl
  - Difficult: R₁ = alkyl
  - Very difficult R = alkyl (topic of current research)
- X groups
  - Easy: I, Br, OTf
  - Difficult but more interesting: Cl, OTos, H

9.2 Heck Coupling

\[
\begin{align*}
\text{Base-Mediated Reduction} & \xrightarrow{\text{base-H⁺X⁻}} \text{PdL}_2 \\
\text{Oxidative Addition} & \xrightarrow{\text{Addition}} \text{PdL}_2 \\
\text{β-H Elimination} & \xrightarrow{\text{Elimination}} \text{Ligand Exchange} \\
\end{align*}
\]

9.3 Olefin Metathesis

\[
\begin{align*}
\text{Grubbs: stable, functional group tolerant} \\
\end{align*}
\]

- Schrock: more reactive, less stable

**Grubbs:**
- 1. Generation
- 2. Generation
- Hoveyda-Grubbs

**Schrock:**
- Mes = mesitylene