Frontier Orbital Interactions: Stereoselectivity

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Frontier Orbital Interactions and Applications

Pericyclic Reaction

Addition Reactions

Substitution Reactions

Limitation & Conclusion

Leading Reference:


"Frontier Orbital Interactions and What We Can Do with Them?"

**HOMO**: Highest Occupied Molecular Orbital

**LUMO**: Lowest Unoccupied Molecular Orbital

"... majority of chemical reactions should take place at the position and in the direction of maximum overlapping of the HOMO (or high-lying occupied MO’s) and the LUMO (or low-lying unoccupied MO’s) of the reacting species; in reacting species possessing a singly occupied (SO) MO, this plays the part of the HOMO or of the LUMO, or of both"

Frontier Orbital Interactions and What We Can Do with Them?

Study on the Frontier Orbital Interactions Help to Answer Questions of Structure and Reactivity
Frontier Orbital Interactions and What We Can Do with Them?

Study on the Frontier Orbital Interactions Help to Answer Questions of Structure and Reactivity

Standard FO Treatments of Structure

Stable Conformations

Q: Which is the most stable conformation?

Reactive Conformation

Q: Which is the most reactive conformation?

Structural Anomalies

Q: When might structural anomalies occur?
Frontier Orbital Interactions and What We Can Do with Them?

Study on the Frontier Orbital Interactions Help to Answer Questions of Structure and Reactivity

Standard FO Treatments of Structure

Stable Conformations

Q: Which is the most stable conformation?
A: Formally divide the molecule into two fragments, the most stable conformation will be the one having the smallest HOMO-HOMO interaction.

Reactive Conformation

Q: Which is the most reactive conformation?
A: It is the one having highest lying HOMO and lowest lying LUMO in the transition state.

Structural Anomalies

Q: When might structural anomalies occur?
A: A bond will shorten (or lengthen) if bonding electron density increases (or decreases) and/or antibonding electron density decreases (or increases) between the extremities.
Frontier Orbital Interactions and *What We Can Do with Them?*

Study on the Frontier Orbital Interactions Help to Answer Questions of **Structure** and **Reactivity**

Standard FO Treatments of **Structure**

The *cis* isomer is 3 kcal/mol favored at 25 °C
Frontier Orbital Interactions and *What We Can Do with Them?*

Study on the Frontier Orbital Interactions Help to Answer Questions of *Structure* and *Reactivity*

Standard FO Treatments of Reactivity

*Absolute Reactivity*

Q: Will A react with B?

*Relative Reactivity*

Q: Will A react preferentially with B₁ or B₂?

*Regioselectivity*

Q: Which reactive site of B will A react preferentially with?

*Stereoselectivity*

Q: Which is the best approach for A to attach a given site of B?
Frontier Orbital Interactions and What We Can Do with Them?

Study on the Frontier Orbital Interactions Help to Answer Questions of Structure and Reactivity

Standard FO Treatments of Reactivity

**Absolute Reactivity**

Q: Will A react with B?
A: Reaction is forbidden if their FO overlap is zero.

**Relative Reactivity**

Q: Will A react preferentially with B₁ or B₂?
A: A reacts preferentially with the molecule whose frontier orbitals are closer in energy to its own.

**Regioselectivity**

Q: Which reactive site of B will A react preferentially with?
A: A reacts preferentially with the site whose frontier orbital has the largest coefficient.

**Stereoselectivity**

Q: Which is the best approach for A to attach a given site of B?
A: The preferred trajectory will have the best FO overlap.
**Frontier Orbital Interactions and What We Can Do with Them?**

Study on the Frontier Orbital Interactions Help to Answer Questions of **Structure** and **Reactivity**

**Standard FO Treatments of Reactivity**

**Absolute Reactivity**

Q: Will A react with B?
A: Reaction is forbidden if their FO overlap is zero

**Relative Reactivity**

Q: Will A react preferentially with B<sub>1</sub> or B<sub>2</sub>?
A: A reacts preferentially with the molecule whose frontier orbitals are closer in energy to its own.

**Regioselectivity**

Q: Which reactive site of B will A react preferentially with?
A: A reacts preferentially with the site whose frontier orbital has the largest coefficient.

**Stereoselectivity**

Q: Which is the best approach for A to attach a given site of B?
A: The preferred trajectory will have the best FO overlap.
Frontier Orbital Interactions: Stereoselectivity

pericyclic reactions

Electrocyclic reactions

Torquoselectivity, basic Rondan-Houk treatment
**Frontier Orbital Interactions: Stereoselectivity**

*pericyclic reactions*

**Electrocyclic reactions**

Torquoselectivity, basic Rondan-Houk treatment

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![Chemical structures and reactions](attachment:image.png)
Frontier Orbital Interactions: Stereoselectivity

pericyclic reactions

Electrocyclic reactions

Torquoselectivity, basic Rondan-Houk treatment

Preferred when $R$ is ED group

Preferred when $R$ is EW group
Frontier Orbital Interactions: Stereoselectivity

Electrocyclic reactions

Torquoselectivity, quantitative analysis

\[ \text{LUMO (R)} \quad \text{HOMO (cyclobutadiene)} \]

\[ \text{LUMO (cyclobutadiene)} \quad \text{HOMO (R)} \]

1 \rightarrow \text{con-out} \rightarrow \text{Me} \quad \text{con-in} \rightarrow \text{Me} \quad \text{con-out} \rightarrow >10 

\[ \text{CO}_2^- \quad \text{Me} \quad \text{Me} \quad \text{CO}_2^- \]
Frontier Orbital Interactions: Stereoselectivity

pericyclic reactions

Electrocyclic reactions

Torquoselectivity, quantitative analysis

Frontier Orbital Interactions: Stereoselectivity

cycloaddition reactions

*Endo-Exo* orientation, secondary orbital interactions are important

[4 + 2] and [8 + 2] prefers *Endo* orientation

[6 + 4] prefers *Exo* orientation
Frontier Orbital Interactions: Stereoselectivity

cycloaddition reactions

Endo-Exo orientation, secondary orbital interactions are important

[4 + 2] and [8 + 2] prefers Endo orientation

[6 + 4] prefers Exo orientation

What do you think about the mechanism of this reaction?
Frontier Orbital Interactions: **Stereoselectivity**

cycloaddition reactions

*Syn-Anti* orientation, steric effect vs. secondary orbital interactions

![Chemical Structures](image)

- **Syn**
  - Steric control
- **Anti**
  - Secondary orbital overlap control
**Frontier Orbital Interactions: Stereoselectivity**

Cycloaddition reactions

*Syn-Anti* orientation, steric effect vs. secondary orbital interactions


Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

The non-perpendicular Dunitz-Burgi attack

Traditional model  \rightarrow  Dunitz-Burgi study  \rightarrow  

Burgi H.B. *et al*, *JACS* 1973, 95, 5065
Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

The non-perpendicular Dunitz-Burgi attack

Houk and co-workers showed on their calculation that the angles of nucleophilic attacks on alkenes and alkynes lie in the range 115–130 ° (larger than the angle of attack on carbonyls.) Can you rationalize the result? (JACS 1982, 104, 7162)
Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

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Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

1,2 Asymmetric inductions

The Cram model

\[
\begin{array}{c}
\text{R}_1 \text{R}_2 \text{R}_3 \quad \text{M} \quad \text{L} \quad \text{O} \\
\Rightarrow \quad \text{S} \\
\end{array}
\]

(\text{I})

L: the bulkiest group
X: electronegative group
**Frontier Orbital Interactions: Stereoselectivity**

*addition reactions - Nucleophilic additions*

1,2 Asymmetric inductions

The Cram model

\[ R_1 \rightarrow R_2 \rightarrow R_3 \]

\[ \overset{\text{O}}{\text{M}} \rightarrow \overset{\text{S}}{\text{L}} (\text{or } X) \rightarrow \overset{\text{S}}{\text{R}} \rightarrow \overset{\text{L}}{\text{M}} \]

L: the bulkiest group  
X: electronegative group

Increase the size of R make II become more competitive with I

Cram model cannot explain the outcome of the reduction of 4–*tert*butylcyclohexanone by LiAlH\(_4\)
Frontier Orbital Interactions: **Stereoselectivity**

*addition reactions - Nucleophilic additions*

1,2 Asymmetric inductions

The Felkin model

![Chemical structures showing stereoselectivity in addition reactions](image-url)
Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

1,2 Asymmetric inductions

The Felkin model

Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

1,2 Asymmetric inductions

The Felkin model
Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

1,2 Asymmetric inductions

The Felkin model

- The energy of $\sigma^*_{CX}$ falls as the electronegativity of $X$ increases. (Except $X = F$ and strong dipolar stabilization cases)
- The energy of $\sigma^*_{CL}$ falls as the $CL$ bond weakens
- The HOMO-LUMO gap falls as the number of atoms in $S$, $M$ or $L$ rises
Frontier Orbital Interactions: Stereoselectivity

(addition reactions - Nucleophilic additions)

1,2 Asymmetric inductions

The Felkin model

\[
\begin{align*}
&\text{RCO}^* & \text{LMSC}^* \\
&\pi^* (\text{CO}) & \sigma^* (\text{CL}) \\
&\pi (\text{CO}) & \\
\end{align*}
\]

\[
\begin{align*}
\text{Nu major attack} & \\
\text{Nu minor attack} & \\
\end{align*}
\]

\[
\begin{align*}
\text{anti addition TS} & \\
\text{syn addition TS} & \\
\end{align*}
\]

\text{anti addition transition state has better orbital overlap than syn addition transition state.}


What is the major product of the following reaction?

\[ \text{anti adduct} \quad + \quad \text{syn adduct} \]

![Chemical diagram](image)

1) $\text{H}_3\text{Sn} + \text{alkene}$
2) TESCl

$\text{anti adduct}$ $\text{syn adduct}$

$\text{96}$ $\text{4}$
Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

Dealing with the cyclic system- the "flattening rule"

\[ \begin{align*}
\text{axial attack} & \\
C_3 & \quad \text{He} \\
45^\circ & \\
12^\circ & \\
21^\circ & \quad \text{H}_a
\end{align*} \]

\[ \begin{align*}
\text{equatorial attack} & \\
\end{align*} \]

TS in the nucleophilic addition will be strongly stabilized when the C\textsubscript{2}–X and C---Nu bonds are antiperiplanar.
**Frontier Orbital Interactions: Stereoselectivity**

*addition reactions - Nucleophilic additions*

Dealing with the cyclic system- the "flattening rule"

*axial* attack

*equatorial* attack

better for electronic transfer and minimizes the torsional repulsions.
Frontier Orbital Interactions: Stereoselectivity

addition reactions - Nucleophilic additions

Dealing with the cyclic system - the "flattening rule"

"Axial attack is favored by flattened or flexible rings"

Arrange the following compounds in order of increasing preference for axial nucleophilic attack (LiAlH₄ for example)?

1)  
1. \[\text{1) \quad \begin{array}{c}
\text{1)} \\
\text{1}
\end{array}\]
2. \[\text{2)} \\
\text{2}
\end{array}\]
3. \[\text{3)} \\
\text{3}
\end{array}\]

2)  
4. \[\text{4)} \\
\text{4}
\end{array}\]
5. \[\text{5)} \\
\text{5}
\end{array}\]
6. \[\text{6)} \\
\text{6}
\end{array}\]
7. \[\text{7)} \\
\text{7}
\end{array}\]
Arrange the following compounds in order of increasing preference for *axial* nucleophilic attack (LiAlH₄ for example)?

1) 

```
  1)  1   <  2   <  3
      \  /    \    \
      (  )    (  )
      O       O
```

2) 

```
  2)  4   <  5   <  6   <  7
      \  /    \    \    
      (  )    (  )  (  )
      O       O       O
```

The experimentally observed percentagegs for *axial* attack

<table>
<thead>
<tr>
<th></th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiAlH₄</td>
<td>80</td>
<td>85</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>78</td>
<td>88</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>MeMgl</td>
<td>12</td>
<td>34</td>
<td>42</td>
<td>56</td>
</tr>
</tbody>
</table>

Casadevall E. *et al.*, *Tet. Let.* 1976, 17, 2841
Frontier Orbital Interactions: Stereoselectivity

addition reactions - electrophilic additions

Houk model for electrophilic addition to alkenes

Houk K.N. et al, JACS 1982, 104, 7162
**Frontier Orbital Interactions: Stereoselectivity**

*addition reactions - electrophilic additions*

Houk model for electrophilic addition to alkenes

- ED and bulky groups prefer *anti* position
- Small groups prefer *inside* position

\[
\begin{align*}
\text{Ph} & \quad \text{OLi} \\
\text{Me} & \quad \text{MeI} \\
\text{Ph} & \quad \text{H} \\
iPr & \quad \text{OLi}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{Ph} & \quad \text{O} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

87% 13%

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Addition reactions - applied to the aldol addition

Aldol reaction can be considered as the combination of nucleophilic and electrophilic addition.

The Nu–C–O angle is obtuse

The El–C–C angle is acute
Frontier Orbital Interactions: Stereoselectivity

Addition reactions - applied to the aldol addition

Aldol reaction can be considered as the combination of nucleophilic and electrophilic addition.

The Nu–C–O angle is obtuse

The El–C–C angle is acute

obtuse angle

acute angle

syn
Frontier Orbital Interactions: Stereoselectivity

Addition reactions - applied to the aldol addition

Aldol reaction can be considered as the combination of nucleophilic and electrophilic addition.
Frontier Orbital Interactions: Stereoselectivity

addition reactions - applied to the aldol addition

Aldol reaction – Anh's treatment

**Step 1.** Generate diastereomeric transition state models.

Z–enolate

![Z1](image1)

E–enolate

![E1](image2)
Frontier Orbital Interactions: Stereoselectivity

addition reactions - applied to the aldol addition

Aldol reaction – Anh's treatment

**Step 1.** Generate diastereomeric transition state models.

\[
\begin{align*}
Z\text{-enolate} & : Z_1 \quad & Z_2 \\
E\text{-enolate} & : E_1 \quad & E_2
\end{align*}
\]

**Step 2.** The calculation modeling addition reaction to aldehyde showed that the bulk of R group forces the incoming nucleophile to approach the aldehyde from the side bearing hydrogen. Thus, rotate (move) the aldehyde in the models to this direction.

\[
\begin{align*}
20 - 30^\circ & \quad \text{Nu}
\end{align*}
\]
Frontier Orbital Interactions: Stereoselectivity

addition reactions - applied to the aldol addition

Aldol reaction – Anh's treatment

Step 1. Generate diastereomeric transition state models.

Step 2. The calculation modeling addition reaction to aldehyde showed that the bulk of R group forces the incoming nucleophile to approach the aldehyde from the side bearing hydrogen. Thus, rotate (move) the aldehyde in the models to this direction.

Step 3. Base on the relative bulk of $R_1$, $R_2$ and the change of the interreaction after the movement, decide the best transition state.

With Z-enolate: If $R_2 < R_1$, $Z_1$ is favored over $Z_2$; If $R_2 \geq R_1$, $Z_2$ is favored over $Z_1$

With $E$-enolate: If $R_2 < R_1$, $E_1$ is favored over $E_2$; If $R_2 > R_1$, $E_2$ is favored over $E_1$

Anh's treatment is quite good for Z-enolate aldol addition, but still not clear for the $E$-enolate
Frontier Orbital Interactions: *Stereoselectivity*

_addition reactions - applied to the aldol addition_

Aldol reaction – Anh's treatment

**Z-enolate**

$$\begin{array}{c}
\text{R}_2 \text{OMgBr} \\
\text{H} \quad \text{tBu}
\end{array} + \begin{array}{c}
\text{Me} \\
\text{H}
\end{array} \rightarrow \begin{array}{c}
\text{Me} \\
\text{H} \quad \text{tBu}
\end{array} + \begin{array}{c}
\text{Me} \\
\text{H} \quad \text{tBu}
\end{array}$$

<table>
<thead>
<tr>
<th>R₂</th>
<th>Z₁</th>
<th>Z₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>100</td>
<td>:</td>
</tr>
<tr>
<td>tPr</td>
<td>48</td>
<td>:</td>
</tr>
<tr>
<td>tBu</td>
<td>20</td>
<td>:</td>
</tr>
</tbody>
</table>

**E-enolate**

$$\begin{array}{c}
\text{R}_2 \text{OMgBr} \\
\text{H} \quad \text{tBu}
\end{array} + \begin{array}{c}
\text{R} \\
\text{H}
\end{array} \rightarrow \begin{array}{c}
\text{Me} \\
\text{H} \quad \text{tBu}
\end{array} + \begin{array}{c}
\text{Me} \\
\text{H} \quad \text{tBu}
\end{array}$$

<table>
<thead>
<tr>
<th>R</th>
<th>E₁</th>
<th>E₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>48</td>
<td>:</td>
</tr>
<tr>
<td>tBu</td>
<td>29</td>
<td>:</td>
</tr>
</tbody>
</table>

_Felman T., Dubois J.E., *Tet.* 1978, 34, 1343_
**Frontier Orbital Interactions: Stereoselectivity**

*substitution reactions–retention of configuration*

FO interaction illustrations of bimolecular substitution reaction at saturated centers

For the best FO overlap, normally, $S_E2$ reactions happen with the retention of configuration while the $S_N2$ happens with the inversion.
Frontier Orbital Interactions: Stereoselectivity

substitution reactions–retention of configuration

FO interaction illustrations of bimolecular substitution reaction at saturated centers

For the best FO overlap, normally, $S_{E2}$ reactions happen with the retention of configuration while the $S_{N2}$ happens with the inversion. The question is if it is possible to obtain $S_{N2}$ reactions with the retention of configuration.
**Frontier Orbital Interactions: Stereoselectivity**

Substitution reactions—retention of configuration

FO interaction illustrations of bimolecular substitution reaction at saturated centers

For the best FO overlap, normally, **S\(_E\)2** reactions happen with the retention of configuration while the **S\(_N\)2** happens with the inversion. The question is if it is possible to obtain **S\(_N\)2 reactions with the retention of configuration**.

\[
\alpha_{CY}^* = N \left( \varphi_C + \frac{\langle \varphi_C | P | \varphi_Y \rangle}{E_C - E_Y} \right)
\]

To reduce the contribution of \(\varphi_Y\), we can rise \(E_C\), lower \(E_Y\), or do both.

- \(E_C\) rise when the electronegativity of the reaction center lowered (Carbon to Silicon for example)
- \(E_Y\) lowered when replacing the leaving group by a more electronegative homolog.

Increasing s character of the hybrid orbitals of the center.

Harder nucleophile induce greater retention of configuration.
Frontier Orbital Interactions: Stereoselectivity

substitution reactions—retention of configuration

Examples for the retention at the center in $S_N2$ reactions

Nucleophilic substitution FO interaction

<table>
<thead>
<tr>
<th>Nu</th>
<th>$X^-$</th>
<th>H</th>
<th>OMe</th>
<th>SMe</th>
<th>F</th>
<th>Br or Cl</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLi (alkyl or aryl)</td>
<td>Re</td>
<td>Re</td>
<td>Re</td>
<td>Re</td>
<td>Re</td>
<td>In</td>
</tr>
<tr>
<td>Allyllithium</td>
<td>Re</td>
<td>Re</td>
<td>In</td>
<td>In</td>
<td>In</td>
<td>In</td>
</tr>
<tr>
<td>KOH</td>
<td>Re</td>
<td>Re</td>
<td></td>
<td>Re</td>
<td>In</td>
<td>In</td>
</tr>
</tbody>
</table>

Moreau J.J. et al, Top. Stereochem. 1984, 15, 87
**Frontier Orbital Interactions: Stereoselectivity**

*substitution reactions–retention of configuration*

Examples for the retention at the center in $S_N^2$ reactions

![HOMO-LUMO diagram](image)

Nucleophilic substitution FO interaction

<table>
<thead>
<tr>
<th>Nu</th>
<th>Re (%)</th>
<th>In (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtLi</td>
<td>63</td>
<td>100</td>
</tr>
<tr>
<td>BuLi</td>
<td>82</td>
<td>59</td>
</tr>
<tr>
<td>Allyllithium</td>
<td>86</td>
<td>100</td>
</tr>
<tr>
<td>PhCH$_2$Li</td>
<td>99</td>
<td>100</td>
</tr>
</tbody>
</table>

Moreau J.J. *et al*, *Top. Stereochem.* 1984, 15, 87
Frontier Orbital Interactions: Stereoselectivity

factors control asymmetric induction

"The preferred trajectory will have the best FO overlap"

- Chelation, when existing, has the strongest influence

- Torisional effects and non-perpendicular attacks are second in importance

- Dipolar and antiperiplanar effects are the next critical factors

- Charge control becomes dominant mostly in compounds containing fluorine of in rigid systems

- Conformational control come to the fore in the absence og highly polar substituents of in the reactions with very early or very late TS

- Steric control are included in all systems
Frontier Orbital Interactions: Stereoselectivity

limitations

"The preferred trajectory will have the best FO overlap"

- Easy to use qualitatively and generally gives predictions agreeing with experiment results (80% as the author stated)

- The FO method just considers the HOMO-LUMO interactions; Thus, the relations between lower orbitals should be taken into account when studying the outcomes of reactions

- "Best FO overlap" means statically. The imperfect trajectories may happen if they have enough energy and vaguely resemble ideal geometry

- The HOMO-LUMO interactions just provide information concerning the transition state potential energy, so the kinetic parameter should be considered when examining the reaction