Stereoelectronic Effects
Recent Advances and New Insights

An Evans Group Afternoon Seminar
Keith Fandrick
October 10, 2003

I. Introduction to Hyperconjugation and NBO Analysis
II. The Role of Hyperconjugation in Cyclohexane
III. σ-Acceptor Abilities and Trends
IV. Recent Examples

Keywords: hyperconjugation, stereoelectronic, cyclohexane, conformational energies, σ-acceptor, equilibrium, Ceiplak, Anh, ring-opening, silyl, Fock, NBO, methylcyclohexane, dioxane, W-effect, Perlin,
Ethane and Methanol, Staggered vs Eclipsed Conformations

Arguments for Hyperconjugation

<table>
<thead>
<tr>
<th>Deleted Hyperconjugative Interaction</th>
<th>Preferred Conformer</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Deletion</td>
<td>Staggered</td>
</tr>
<tr>
<td>No Hyperconjugation</td>
<td>Eclipsed</td>
</tr>
<tr>
<td>No Vicinal Hyperconjugation</td>
<td>Eclipsed</td>
</tr>
<tr>
<td>No Geminal Hyperconjugation</td>
<td>Staggered</td>
</tr>
</tbody>
</table>

The Stereoelectronic Interactions of Ethane

Hyperconjugation not Sterics leads to the Staggered Conformation

Energy Lowering Due to Hyperconjugation

Orbital drawings

Resonance Theory Representation

Evans D. A.; Chem. 206 notes, 2001
NBO Analysis

- Structures optimized at the HF/6-31G**, MP2/6-31G**, and B3LYP/6-31+G* levels using GAUSSIAN 94/98 packages

- NBO 4.0 program was interfaced with the GAUSSIAN 94/98 packages

- NBO program transforms the canonical delocalized Hartee-Fock (HF) MO's into localized hybrid orbitals (natural bonding orbitals, NBO)

- Filled NBO's describe the hypothetical "strictly" localized Lewis structures

- Deviation of the molecule from the optimized structure form the NBO description can be used to measure the energetics of delocalizations/hyperconjugation

- Energetics of the delocalizations were estimated from the second order perturbation approach and calculated by deletion of the corresponding off-diagonal elements of the Fock matrix in the NBO basis

Alabugin, I. V.  J. Org. Chem. 2000, 65, 3910
Weinhold F. Encyclopedia of Computational Chemistry; Schleyer P. 1998, p 1792
NBO Analysis of Cyclohexane
The Four Main Hyperconjugation Interactions

Energies correspond to RHF/6-31G** (B3LYP/6-31+G**)

Alabugin, I. V.; J. Org. Chem. 2000, 65, 3910
NBO Analysis of Cyclohexane

<table>
<thead>
<tr>
<th>Bond</th>
<th>Bond Length, Å</th>
<th>( \Sigma E_{\text{del}}, \text{ Kcal/mol} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RHF/6-31G**</td>
<td>B3LYP/6-13+G**</td>
</tr>
<tr>
<td>C-H_{\text{ax}}</td>
<td>1.0871</td>
<td>1.1001</td>
</tr>
<tr>
<td>C-H_{\text{eq}}</td>
<td>1.0895</td>
<td>1.0971</td>
</tr>
</tbody>
</table>

- Calculated longer bond lengths correspond to lower C-H coupling constants, in accord with a Normal Perlin effect \((J_{\text{CH}_{\text{ax}}} < J_{\text{CH}_{\text{eq}}})\)

- Analysis indicates: **C-H bonds are better donors than C-C bonds**

Alabugin, I. V.; J. Org. Chem. 2000, 65, 3910
1-Methyl-1-cyclohexyl Cation
Two Distinct Chair Conformations, Hyperconjugative effects

-At least two different structures are observed for the methyl-cyclohexyl cation by NMR

1,3-Dioxane, W-Effect?

Summary of Delocalizing Interactions for C-H bonds
In 1,3-Dioxane

<table>
<thead>
<tr>
<th>donor orbital</th>
<th>acceptor orbital</th>
<th>energy, kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \sigma_{C(5)-H(5)_{ax}} )</td>
<td>( \sigma^*<em>{C(6)-H(6)</em>{ax}} )</td>
<td>3.28</td>
</tr>
<tr>
<td>( \sigma_{C(6)-H(6)_{ax}} )</td>
<td>( \sigma^*<em>{C(5)-H(5)</em>{ax}} )</td>
<td>3.29</td>
</tr>
<tr>
<td>( \sigma_{C(5)-H(5)_{eq}} )</td>
<td>( \sigma^*_{C(6)-O(1)} )</td>
<td>4.23</td>
</tr>
<tr>
<td>( \sigma_{C(6)-O(1)} )</td>
<td>( \sigma^*<em>{C(5)-H(5)</em>{eq}} )</td>
<td>1.63</td>
</tr>
<tr>
<td>( \text{LP}(2)O(1) )</td>
<td>( \sigma^*<em>{C(2)-H(2)</em>{ax}} )</td>
<td>2.33</td>
</tr>
<tr>
<td>( \text{LP}(1)O(1) )</td>
<td>( \sigma^*<em>{C(2)-H(2)</em>{eq}} )</td>
<td>5.86</td>
</tr>
<tr>
<td>( \sigma_{C(2)-H(2)_{eq}} )</td>
<td>( \sigma^*_{C(6)-O(1)} )</td>
<td>4.05</td>
</tr>
<tr>
<td>( \sigma_{C(6)-O(1)} )</td>
<td>( \sigma^*<em>{C(2)-H(2)</em>{eq}} )</td>
<td>1.92</td>
</tr>
<tr>
<td>( \text{LP}(1)O(1) )</td>
<td>( \sigma^*<em>{C(2)-H(2)</em>{eq}} )</td>
<td>2.18</td>
</tr>
<tr>
<td>( \text{LP}(1)O(1) )</td>
<td>( \sigma^*<em>{C(6)-H(6)</em>{eq}} )</td>
<td>2.11</td>
</tr>
<tr>
<td>( \sigma_{C(6)-H(6)_{eq}} )</td>
<td>( \sigma^*<em>{C(6)-H(6)</em>{ax}} )</td>
<td>2.04</td>
</tr>
<tr>
<td>( \text{LP}(2)O(1) )</td>
<td>( \sigma^*<em>{C(6)-H(6)</em>{eq}} )</td>
<td>6.27</td>
</tr>
<tr>
<td>( \sigma_{C(5)-H(5)_{ax}} )</td>
<td>( \sigma^*<em>{C(6)-H(6)</em>{ax}} )</td>
<td>3.28</td>
</tr>
<tr>
<td>( \sigma_{C(6)-H(6)_{ax}} )</td>
<td>( \sigma^*<em>{C(5)-H(5)</em>{ax}} )</td>
<td>3.29</td>
</tr>
<tr>
<td>( \sigma_{O(1)-C(2)} )</td>
<td>( \sigma^*<em>{C(6)-H(6)</em>{eq}} )</td>
<td>1.81</td>
</tr>
<tr>
<td>( \sigma_{C(6)-H(5)_{eq}} )</td>
<td>( \sigma^*_{O(1)-C(2)} )</td>
<td>3.39</td>
</tr>
<tr>
<td>( \sigma_{C(5)-C(4)} )</td>
<td>( \sigma^*<em>{C(6)-H(6)</em>{eq}} )</td>
<td>2.41</td>
</tr>
<tr>
<td>( \sigma_{C(6)-H(5)_{eq}} )</td>
<td>( \sigma^*_{C(5)-C(4)} )</td>
<td>3.03</td>
</tr>
</tbody>
</table>

Alabugin, I. V.; J. Org. Chem. 2000, 65, 3910
NBO analysis of 1,3-Dioxane, extra interaction

- Proposed W-effect

\[ \text{Proposed W-effect} \]

\[ n_{eq} \rightarrow \sigma_{CH}^{*} \]

- Proposed New interaction

\[ \text{Proposed New interaction} \]

\[ \rho_{O_{lp}} \rightarrow \sigma_{CH}^{*} \]

-W-effect found to be small, <1 kcal/mol.

-P orbital for a lone pair is a better donor than the corresponding sp\(^3\) lone pair.

-New interaction is favored due to better orbital overlap.

-Interaction is smaller than \( \sigma_{CHeq} \rightarrow \sigma_{CO}^{*} \), but it serves to tip the balance of delocalizing interactions in the favor of "equatorial" delocalization.

Conclusions from NBO analysis
Summary of equatorial interactions for dioxane and dithiane

-NBO analysis, $E(\text{del})$, correlates well with C-H bond lengths in cyclohexane, 1,3-dithiane, and 1,3-dioxane.

-NBO analysis of 1,3-dioxane and 1,3-dithiane suggests the donor ability of $\sigma$-bonds are:

$\text{C-H} > \text{C-S} > \text{C-C} > \text{O-C} \approx \text{C-O} > \text{S-C}$

Alabugin, I. V.; J. Org. Chem. 2000, 65, 3910
σ-Acceptor Abilities: Trends
For Monosubstituted Ethanes, CH₃CH₂X

-E_{del} calculated by deletion of the off-diagonal Fock matrix elements between interacting orbitals, NBO analysis
-σ-Acceptor abilities correlate with electronegativity across a period
-Down a row, σ-acceptor abilities increase

σ-Acceptor Abilities: Trends
The Origin of the σ-Acceptor Trends in Ethane

Correlation of $E_{\text{del}}$ for $\sigma_{\text{C-H}} \rightarrow \sigma^*_{\text{C-X}}$ Interactions and Electronegativity

$E_{\text{del}}$ kcal/mol

Electronegativity

$R^2 = 0.9692$

Correlation energy of $\sigma^*_{\text{C-X}}$ and Electronegativity

$\sigma^*_{\text{C-X}}$ Energy, a.u.

Electronegativity

$R^2 = 0.9683$

-E$_{\text{del}}$ depends on the energy separation of the HOMO and LUMO
Correlation of $E_{\text{del}}$ and $E(2)$

$y = 1.1301x - 0.1262$
$R^2 = 0.9798$

Second-order perturbation analysis of the Fock Matrix in the NBO basis set

$$E(2) = -\eta_{\sigma} \left( \frac{\sigma/F/\sigma^*}{\varepsilon_{\sigma^*} - \varepsilon_{\sigma}} \right)^2 = -\eta_{\sigma} \frac{F_{ij}^2}{\Delta E}$$

- $\Delta E$ is the energy difference between the $\sigma$ and $\sigma^*$ orbitals
- $\eta_{\sigma}$ is the population of the donor $\sigma$ orbital
- $F_{ij}$ is correlated with the orbital overlap matrix element $S_{ij}$ and the acceptor orbital polarization

- $E(2)$ overestimates stabilizing interactions, but shows excellent correlation with $E_{\text{del}}$

- Energetics of delocalizations depends on: $\Delta E$, orbital overlap, and polarization of the acceptor orbital

σ-Acceptor Abilities: Trends

Delocalizing interactions with substituted ethenes:

-Halogen acceptor abilities are F < Cl > Br

-In ethanes, the $\Delta E$ term is more important. In ethenes, the significance of $F_{ij}$ increases

-Rationale for the increase dependence of $F_{ij}$ is the shorter C=C bond relative to C-C

-$F_{ij}$ depends on the overlap of the donor and acceptor orbitals, thus it has an exponential dependence on the distance between the two orbitals

-Anh's warning: one must compare similar systems when using FMO

Testing the Steric Model, Methylcyclohexane

Elongation of the C$_\alpha$-C$_\beta$ bond by 0.3 Å

\[ \Delta E = 32.00 \text{ kcal/mol} \]

\[ \Delta E = 32.46 \text{ kcal/mol} \]

Parameters and Energetics (kcal/mol), Bond Lengths (Å) and Angles (deg.)

<table>
<thead>
<tr>
<th>Conformation</th>
<th>State</th>
<th>( \Delta E )</th>
<th>C$<em>\alpha$-C$</em>\beta$</th>
<th>C$<em>\beta$-C$</em>\gamma$</th>
<th>C$<em>\beta$-C$</em>\alpha$-C$_\text{Me}$</th>
<th>H$<em>a$-C$</em>\gamma$-C$_\beta$</th>
<th>H$_a$-H</th>
<th>C$<em>\text{Me}$-C$</em>\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td>Ground</td>
<td>0</td>
<td>1.545</td>
<td>1.538</td>
<td>112.4</td>
<td>109.9</td>
<td>2.381</td>
<td>3.211</td>
</tr>
<tr>
<td>Axial</td>
<td>Distorted</td>
<td>32.00</td>
<td>1.845</td>
<td>1.521</td>
<td>112.2</td>
<td>109.8</td>
<td>2.507</td>
<td>3.402</td>
</tr>
<tr>
<td>Equatorial</td>
<td>Ground</td>
<td>0</td>
<td>1.540</td>
<td>1.537</td>
<td>111.7</td>
<td>109.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equatorial</td>
<td>Distorted</td>
<td>32.46</td>
<td>1.840</td>
<td>1.522</td>
<td>109.8</td>
<td>109.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-Consistent with Steric Model

Testing the Steric Model, Methylcyclohexane

Compression of the $\text{C}_\alpha-\text{C}_\beta$ and $\text{C}_\beta-\text{C}_\gamma$ bonds by 0.2 Å

$\Delta E = 70.05 \text{ kcal/mol}$

$\Delta E = 70.59 \text{ kcal/mol}$

Parameters and Energetics (kcal/mol), Bond Lengths (Å) and Angles (deg.)

<table>
<thead>
<tr>
<th>Conformation</th>
<th>State</th>
<th>$\Delta E$</th>
<th>$\text{C}<em>\alpha-\text{C}</em>\beta$</th>
<th>$\text{C}<em>\beta-\text{C}</em>\gamma$</th>
<th>$\text{C}<em>\beta-\text{C}</em>\alpha-\text{C}_\text{Me}$</th>
<th>$\text{H}<em>\text{a}-\text{C}</em>\gamma-\text{C}_\beta$</th>
<th>$\text{H}_\text{a}-\text{H}$</th>
<th>$\text{C}<em>\text{Me}-\text{C}</em>\gamma$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td>Ground</td>
<td>0</td>
<td>1.545</td>
<td>1.538</td>
<td>112.4</td>
<td>109.9</td>
<td>2.381</td>
<td>3.211</td>
</tr>
<tr>
<td>Axial</td>
<td>Distorted</td>
<td>70.05</td>
<td>1.345</td>
<td>1.338</td>
<td>112.0</td>
<td>112.3</td>
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<tr>
<td>Equatorial</td>
<td>Ground</td>
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<td>1.537</td>
<td>111.7</td>
<td>109.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equatorial</td>
<td>Distorted</td>
<td>70.59</td>
<td>1.340</td>
<td>1.336</td>
<td>111.8</td>
<td>111.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-Not Consistent with Steric Model

-Note: same argument used to explain higher conformational energies of 2-methyl-1,3-dioxanes

Testing the Steric Model, Methylcyclohexane

Bending the C\textsubscript{\alpha}-C\textsubscript{\beta}-C\textsubscript{Me} bond angle inward by 4\(^\circ\)

\[
\Delta E = 1.18 \text{ kcal/mol}
\]

\[
\Delta E = 1.21 \text{ kcal/mol}
\]

Parameters and Energetics (kcal/mol), Bond Lengths (Å) and Angles (deg.)

<table>
<thead>
<tr>
<th>Conformation</th>
<th>State</th>
<th>(\Delta E)</th>
<th>(\text{C}<em>{\alpha})-(\text{C}</em>{\beta})</th>
<th>(\text{C}<em>{\beta})-(\text{C}</em>{\gamma})</th>
<th>(\text{C}<em>{\beta})-(\text{C}</em>{\alpha})-(\text{C}_{\text{Me}})</th>
<th>(\text{H}<em>{\text{a}})-(\text{C}</em>{\gamma})-(\text{C}_{\beta})</th>
<th>(\text{H}_{\text{a}})-(\text{H})</th>
<th>(\text{C}<em>{\text{Me}})-(\text{C}</em>{\gamma})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td>Ground</td>
<td>0</td>
<td>1.545</td>
<td>1.538</td>
<td>112.4</td>
<td>109.9</td>
<td>2.381</td>
<td>3.211</td>
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<tr>
<td>Axial</td>
<td>Distorted</td>
<td>1.18</td>
<td>1.547</td>
<td>1.538</td>
<td>108.4</td>
<td>110.3</td>
<td>2.266</td>
<td>3.135</td>
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<td>Ground</td>
<td>0</td>
<td>1.540</td>
<td>1.537</td>
<td>111.7</td>
<td>109.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equatorial</td>
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<td>1.21</td>
<td>1.540</td>
<td>1.338</td>
<td>107.7</td>
<td>109.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-Not Consistent with Steric Model

-Note: bending the angle outward is consistent with steric model

Testing the Steric Model: 2-Methyl-1,3-dioxane

\[ \Delta E = 0.37 \text{ kcal/mol} \quad \Delta E = 0.33 \text{ kcal/mol} \quad \Delta E = 0.35 \text{ kcal/mol} \quad \Delta E = 0.37 \text{ kcal/mol} \]

Parameters and Energetics (kcal/mol), Bond Lengths (Å) and Angles (deg.)

<table>
<thead>
<tr>
<th>Conformation</th>
<th>State</th>
<th>( \Delta E )</th>
<th>C( \alpha )-O( \beta )</th>
<th>O( \beta )-C( \gamma )</th>
<th>O( \beta )-C( \alpha )-C( \text{Me} )</th>
<th>H( \text{a} )-C( \gamma )-O( \beta )</th>
<th>H( \text{a} )-H</th>
<th>C( \text{Me} )-C( \gamma )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td>Ground</td>
<td>0</td>
<td>1.395</td>
<td>1.405</td>
<td>112.5</td>
<td>110.7</td>
<td>2.350</td>
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<td>Axial</td>
<td>Distorted</td>
<td>0.37</td>
<td>1.420</td>
<td>1.427</td>
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<td>3.052</td>
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<td>Distorted</td>
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<td>1.420</td>
<td>1.428</td>
<td>114.6</td>
<td>111.0</td>
<td>2.361</td>
<td>3.100</td>
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<tr>
<td>Equatorial</td>
<td>Ground</td>
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<td>1.391</td>
<td>1.404</td>
<td>108.6</td>
<td>109.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equatorial</td>
<td>Distorted</td>
<td>0.33</td>
<td>1.415</td>
<td>1.427</td>
<td>106.3</td>
<td>109.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equatorial</td>
<td>Distorted</td>
<td>0.35</td>
<td>1.415</td>
<td>1.425</td>
<td>110.3</td>
<td>109.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Expect greater steric interactions due to shorter C-O bonds
- Compression of C\( \alpha \)-C\( \beta \) bond by 0.2 Å leads to a smaller energy gap than expected
- Bending O\( \beta \)-C\( \alpha \)-C\( \text{Me} \) bond inward and outward does not show energetics consistent with steric model
Methylcyclohexane, AIM Atomic Energies
The Role of Ring Strain

Structural optimizations were performed with Gaussian 94
AIMPAC was used to calculate AIM atomic energies
AIMPAC/AIM allows one to calculate the energetics of a part or a group of given structure

A-value = 1.8 to 2.2 kcal/mol

Energies (kcal/mol) are the comparison of the equatorial versus axial energy differences of the indicated group or atom

Energies in **Blue** correspond to stabilization (lower energy) relative to the equatorial conformer, energies in **Red** indicate destabilization (higher energy) relative to the equatorial conformer

Cuevas G.; *J. Phys. Chem. A*, 2003, ASAP
Energies (kcal/mol) are the comparison of the equatorial versus axial energy differences of the indicated group or atom.

Energies in Blue correspond to stabilization (lower energy) relative to the equatorial conformer, energies in Red indicate destabilization (higher energy) relative to the equatorial conformer.

A-Value = 5.36 kcal/mol

Alternate Explanation For Equatorial Preference

Following Alabugin's results, $\Sigma E_{\text{del}}^{H\text{ax}} > \Sigma E_{\text{del}}^{H\text{eq}}$, Authors propose that the equatorial preference is a reflection, or partly due, to the axial preference for the methine hydrogen due to greater hyperconjugative interactions.

The proposition offers an alternative explanation for the trend of conformational energies of halocylocohexanes, $E_{CX}$; Br<Cl<F. The trend is due, or partly due to the order of acceptor abilities of the anti-bonding C-X orbitals.

The explanation also provides a rationale for the low conformational energy of methylthianium. It does not have an acceptor orbital to stabilize the equatorial conformation.

Alabugin, I. V.; J. Org. Chem. 2000, 65, 3910
Alternate Explanation For Equatorial Preference

Testing Ribeiro's Hypothesis

Is there a relationship between the acceptor abilities of substituents on substituted cyclohexane and conformational energies?

If there is, then one should see a correlation between A values and the acceptor abilities of C-X bonds.

Result:
No correlation, but not so fast...

Note, acceptor orbital energies are taken from Alabugin ethane calculations.

Alternate Explanation For Equatorial Preference

Testing Ribeiro's Hypothesis

Same analysis, but using the acceptor orbital values from the ethene calculations.

Note: OH and OMe change their acceptor orbital abilities depending on their conformations.

\[ \sigma_{CH} \rightarrow \sigma^*_{CX} \]
\[ \sigma_{CH} \rightarrow \sigma^*_{CH} \]

\[
\begin{align*}
\text{H} & \quad \sigma_{CH} \rightarrow \sigma^*_{CX} \\
\text{H} & \quad \sigma_{CH} \rightarrow \sigma^*_{CH}
\end{align*}
\]

March. S.; Advanced Organic Chemistry, 2001


Plot of A-values vs Hyperconjugative Stabilizing Energy

\[ y = 4.8508x + 7.2372 \]
\[ R^2 = 0.8941 \]

<table>
<thead>
<tr>
<th>A-value; ( \Delta G^o ) (kcal/mol)</th>
<th>Hyperconjugative Stabilizing Energy (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.79</td>
<td>0.2</td>
</tr>
<tr>
<td>8.16</td>
<td>0.3</td>
</tr>
<tr>
<td>9.33</td>
<td>0.4</td>
</tr>
<tr>
<td>8.40</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>0.8</td>
</tr>
</tbody>
</table>
Epimerization Equilibrium of 2-Aryl-1,3-\(N,N\)-Heterocycles

Epimerization 1

\[
\begin{align*}
\text{Epimerization 1} & \\
\text{Epimerization 2} & \\
X = p-\text{NO}_2, p-\text{CF}_3, p-\text{Br}, p-\text{Cl}, H, p-\text{F}, p-\text{Me}, p-\text{OMe}, p-\text{NMe}_2
\end{align*}
\]

Epimerization Equilibrium of 2-Aryl-1,3-N,N-Heterocycles

Epimerization 1

Epimerization 2

Plot of $\Delta G^0$ vs Hammett-Brown $\sigma^+$ values

$y = -0.2723x + 1.6955$

$R^2 = 0.9003$

$y = -0.0499x - 0.3711$

$R^2 = 0.0811$

$p$-NMe$_2$

$p$-NO$_2$
Epimerization Equilibrium of 2-Aryl-1,3-N,N-Heterocycles

Second-order perturbation analysis of the Fock matrix, NBO basis

Stabilization energy from a single donor-acceptor interaction

\[ E(2)_{ij} = -\eta_\sigma \left( \frac{\sigma/F/\sigma^*}{\varepsilon^*_\sigma - \varepsilon_\sigma} \right)^2 = -\eta_\sigma \frac{F_{ij}^2}{\Delta E} \]

Difference in Hyperconjugative Stabilization Energies in the Epimerization Equilibrium

\[ \Delta \sum E_{ij} = \Delta \sum E_{ij}^R - \Delta \sum E_{ij}^L \]

R and L denotes right and left sides of the epimerization equilibrium

Plot of Theoretical Stereoelectronic Stabilization Energies vs \( \Delta G^0 \) for Epimerization 1

\[ \Delta \sum E_{ij} \] (kcal/mol)

\[ \Delta G^0 \] (kcal/mol)

- A similar plot for Epimerization 2 displays an \( R^2 \) value of 0.1202

\[ y = 0.5265x - 2.1583 \\ R^2 = 0.913 \]
Epimerization Equilibrium of 2-Aryl-1,3-\(N,N\)-Heterocycles

The relevant hyperconjugative stabilizing interactions for Epimerization 1

Lewis Structures of the relevant interactions

\[ n_N - \sigma^*_{C3-\text{Aryl}} \]

\[ n_N - \sigma^*_{C3-H} \]

\[ n_N - \sigma^*_{C3-N4} \]
Epimerization Equilibrium of 2-Aryl-1,3-N,N-Heterocycles

Role of donor-acceptor energy difference and Fock matrix element

- Delocalizing interaction energies are more dependent upon the Fock matrix element, due to the higher changes in the Fock matrix energetics relative to the donor acceptor energy difference terms.
Epimerization Equilibrium of 2-Aryl-1,3-\(N,N\)-Heterocycles

Role of bond polarization in hyperconjugative stabilization

Graphical Representation of the Polarization Coefficients on C3

\(p\)-NMe\(_2\)

- \(\sigma^*\)C-Ar

\(p\)-NO\(_2\)

- \(\sigma^*\)C-N

- \(\sigma^*\)C-H

\(- F_{ij}\) is correlated with the overlap matrix element \(S_{ij}\) and acceptor orbital polarization

-Conformational changes of the heterocycles are around 1°

-Bond polarization change of \(\sigma^*\)C3-Aryl and the decrease of the other two interactions accounts for the stabilization energies and the observed epimerization equilibrium
The Cieplak Model: Recent Advances

Recent Literature Example: Reduction of Snoutanones and Adamantanones

\[
\begin{align*}
&\text{O} \\
&\text{R} \\
&\text{NaBH}_4\text{-MeOH} \\
&\text{HO} \\
&\text{H} \\
&\text{R} \\
&\text{NaBH}_4\text{-MeOH} \\
&\text{HO} \\
&\text{H} \\
&\text{R} \\
\end{align*}
\]

\[R = \text{CN, COOCH}_3, \text{CCH, CHCH}_2, \text{CH}_2\text{OCH}_3\]

- Cieplak’s Model
- FMO prohibits such an interaction. The interactions should weaken and elongate the forming bond in the transition state

The Cieplak Model: Alternate Explanation

Carbenes: Experimental Results

\[ \text{N} \equiv \text{N} \xrightarrow{250 \degree C} \text{A} + \text{B} \]

<table>
<thead>
<tr>
<th>R</th>
<th>Ratio A : B</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>90 : 10</td>
</tr>
<tr>
<td>NH(_2)</td>
<td>80 : 20</td>
</tr>
<tr>
<td>Si(CH(_3))(_3)</td>
<td>26 : 74</td>
</tr>
</tbody>
</table>

Note: the exact mechanism of carbene insertion is not known, but above results appear to contradict Cieplak's Model

Knoll, W.; Org. Lett., 2003, 2943
The Cieplak Model: Alternate Explanation
Carbenes: Experimental Results

\[ \text{N-N} \xrightarrow{h\nu, R'-H} \text{NR} \]

<table>
<thead>
<tr>
<th>R</th>
<th>Solvent</th>
<th>Ratio A : B</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH</td>
<td>MeOH</td>
<td>15 : 85</td>
</tr>
<tr>
<td>NH\textsubscript{2}</td>
<td>MeOH</td>
<td>15 : 85</td>
</tr>
<tr>
<td>Si(CH\textsubscript{3})\textsubscript{3}</td>
<td>MeOH</td>
<td>69 : 31</td>
</tr>
<tr>
<td>OH</td>
<td>c-C\textsubscript{6}H\textsubscript{12}</td>
<td>15 : 85</td>
</tr>
<tr>
<td>NH\textsubscript{2}</td>
<td>c-C\textsubscript{6}H\textsubscript{12}</td>
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<td>c-C\textsubscript{6}H\textsubscript{12}</td>
<td>69 : 31</td>
</tr>
</tbody>
</table>

Similiar results with polar and nonpolar solvents discount electrostatic control of substrate's orientation

Knoll, W.; *Org. Lett.*, 2003, 2943
The Cieplak Model: Alternative Explanation
Carbenes: Tomoda's Calculations

Tomoda's Calculated Transition States:

MeOH Insertion

- anti-TS
  - 1.392 Å
- syn-TS
  - 1.374 Å
  - 0.013 Å

Cyclohexane Insertion

- anti-TS
  - 1.392 Å
  - 0.012 Å
- syn-TS
  - 1.383 Å
  - 0.013 Å

- Numbers show the difference in bond length from the indicated bonds and the corresponding bonds on the opposite side of the molecule.

- Longer bond lengths correspond to greater anti-periplanar anomeric effect.

- Support Cieplak's Model??

The Cieplak Model: Alternate Explanation

Carbenes: Tomoda's Calculations

<table>
<thead>
<tr>
<th>Bond Elongation (Å)</th>
<th>Bond Population (e)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>TS</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Methanol</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>NA</td>
</tr>
<tr>
<td>OH</td>
<td>anti</td>
</tr>
<tr>
<td></td>
<td>syn</td>
</tr>
<tr>
<td>TMS</td>
<td>anti</td>
</tr>
<tr>
<td></td>
<td>syn</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>NA</td>
</tr>
<tr>
<td>OH</td>
<td>anti</td>
</tr>
<tr>
<td></td>
<td>syn</td>
</tr>
<tr>
<td>TMS</td>
<td>anti</td>
</tr>
<tr>
<td></td>
<td>syn</td>
</tr>
</tbody>
</table>

-Bond lengths decrease and bond populations increase from going from GS to TS.

-The analysis shows that the AP effect actually decreases in the TS, and the AP effect destabilizes the TS.

-These results are inconsistent with Cieplak's and Anh's models.

The Cieplak Model: Alternative Explanation

Carbenes: Bending of the Carbene carbon

The bending Model

Distal Conformer

Proximal Conformer

The substituent Role
a) induction
b) hyperconjugation
The Cieplak Model: Alternative Explanation

Carbenes: Bending of the Carbene Bridge

\[ \Delta E = E_{pro} - E_{dis} \]

- Calculations performed on Gaussian 98

Plot of Difference in Energy of the Proximal and Distal conformers vs Ln of the observed insertion ratios

\[ r^2 = 0.99 \]
Recent Stereoelectronic Effects
Silyl Effects on Ring-Opening Reactions of Cyclobutenes

\[
\begin{align*}
\text{n-C}_8\text{H}_{17} & \quad \xrightarrow{140 \, ^\circ\text{C}, 1 \, \text{h}} \quad \text{n-C}_8\text{H}_{17} \\
\text{n-C}_8\text{H}_{17} & \xrightarrow{140 \, ^\circ\text{C}, 1 \, \text{h}} \quad \text{PhMe}_2\text{Si} \\
\text{n-C}_8\text{H}_{17} & \xrightarrow{140 \, ^\circ\text{C}, 1 \, \text{h}} \quad \text{PhMe}_2\text{Si} \\
\end{align*}
\]

12 % yield
>96 % yield

Recent Stereoelectronic Effects
Silyl Effects on Ring-Opening Reactions of Cyclobutenes

C'-C-Si angle = 132°

C'-C-Si angle = 92°
C'-C-Si-H dihedral angle = 170°

E (kcal/mol)

Cautions with using FMO
Anh's Warnings

-FMO gives good predictions in ~80 % of the cases studied by Anh

-FMO should only be applied when the following conditions are met:

Only apply FMO to the transition states (in most cases)

Apply FMO only to systems in which the FMO are well separated from other MO

Apply FMO to systems that can be described by a single electronic configuration

Only compare systems that are similar and undergoing the same reaction
(Ethane and ethene acceptor orbital abilities are different)

-Almost all violations of FMO theory occur when these restrictions are not met

Conclusions

- The hyperconjugative interactions due to $\sigma$-bonds are relevant. These interactions have shown importance in bond lengths, NMR coupling constants, appear to be involved in conformational energies, and transition state energies.

- All three terms of the Fock matrix equation need to be considered to account for the hyperconjugation interactions.
  \[ F_{ij} \text{(orbital orientation and proximity and polarizations)} \] and \[ \Delta E \text{(HOMO and LUMO energy levels separation)} \]

- NBO analysis ($E(\text{del})$ or $E(2)$ methods) provides an estimate of the hyperconjugative interactions allowing one to quantitatively unravel their relative importance.

- Hyperconjugative interactions due to $\sigma$-bonds are relatively weak. These interactions should be considered but other interactions can be more important.