**I. Basic Principles**

IA. Conformational Analysis - Continued


- Explain the formation of the major and minor products.
- What is the reason for the selectivity?
- What are the names of these and related cycloaromatization reactions? Are they biologically relevant, and who discovered this process?

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**Cycloaromatization Reactions**

- **Schreiner**
- **Bergman**
- **Schmittel**
- **Meyers-Saito**
**The Baldwin Rules for Ring Closure**


\[
\begin{align*}
\text{MeO}_2\text{C} & \text{NH}_2 \quad \text{CO}_2\text{Me} & \quad \text{MeO}_2\text{C} & \text{HN} \quad \text{CO}_2\text{Me} \\
\text{5-endo-trig} & \text{0%} & \text{5-endo-trig} & \text{0%} \\
\text{5-exo-trig} & \text{100%} & \end{align*}
\]

Control experiment: Intermolecular reaction favors conjugate addition.

\[
\begin{align*}
\text{Me} & \quad \text{CO}_2\text{Me} & \quad \text{PhCH}_2\text{NH}_2 & \quad \text{Ph} & \quad \text{NH} & \quad \text{Me} & \quad \text{CO}_2\text{Me} \\
\text{100%} & \text{0%} & \end{align*}
\]

**The Baldwin Rules for Ring Closure**


\[
\begin{align*}
\text{MeO}_2\text{C} & \text{NH}_2 \quad \text{CO}_2\text{Me} & \quad \text{MeO}_2\text{C} & \text{HN} \quad \text{CO}_2\text{Me} \\
\text{5-endo-trig} & \text{0%} & \text{5-endo-trig} & \text{0%} \\
\text{5-exo-trig} & \text{100%} & \end{align*}
\]

\[
\begin{align*}
d=3.2 \text{ Å} & \quad \text{angle}=135^\circ \\
\end{align*}
\]

**Problem:** distance too large and Bürgi-Dunitz trajectory not feasible

\[
\begin{align*}
d=3.7 \text{ Å} & \quad \text{angle}=47^\circ \\
\end{align*}
\]

**Observed:** distance and Bürgi-Dunitz trajectory ok
The Baldwin Rules for Ring Closure

In 1976, J. E. Baldwin published a set of rules on the ease of intramolecular ring closure (J. Chem. Soc., Chem. Commun. 1976, 734). While there are substantial exceptions to these rules, they are often used to rationalize (un)favorable trajectories for ring closures.

<table>
<thead>
<tr>
<th>Ring size</th>
<th>Exo-dig</th>
<th>Exo-trig</th>
<th>Exo-tet</th>
<th>Endo-dig</th>
<th>Endo-trig</th>
<th>Endo-tet</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>D</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>D</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>D</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>-</td>
</tr>
</tbody>
</table>

Disfavored Processes
The Baldwin Rules for Ring Closure

Favored Processes

5-exo-dig  6-exo-dig  7-exo-dig  3-exo-trig  4-exo-trig  5-exo-trig  6-exo-trig

7-exo-trig  3-exo-tet  4-exo-tet  5-exo-tet  6-exo-tet  3-endo-dig  4-endo-dig

5-endo-dig  6-endo-dig  7-endo-dig  6-endo-trig  7-endo-trig

The Baldwin Rules for Ring Closure: Caveats

Does the illustrated ketalization process necessarily violate "the rules"?

\[
\begin{align*}
R & \rightarrow \text{(CH}_2\text{OH)}_2 \\
& \quad \overset{\text{H}^+}{\rightarrow} \text{R} \\
& \quad \underset{\text{H}^+}{\overset{\text{H}_2\text{O}}{\rightarrow}} \text{R}
\end{align*}
\]

Johnson, C.D. "Stereoelectronic effects in the formation of 5- and 6-membered rings: the role of Baldwin's rules." 
The Baldwin Rules for Ring Closure: Caveats

Exceptions to these rules are mostly found among 2nd row and higher elements. The longer bond lengths and larger atomic radii of 2nd row and higher elements allow more relaxed geometries and a greater range of attack trajectories.
The Baldwin Rules for Ring Closure: Exocyclic Enolate Alkylation
By definition, this is an exo-tet cyclization, but stereoelectronically it behaves as an endo-trig

Given the failure of the enolate alkylation on the preceding slide, why are the following two cyclizations successful?

The Baldwin Rules for Ring Closure: Endo-Digonal vs Endo-Trigonal Cyclizations

A. NaOMe MeOH
5-endo-dig

B. NaOMe
5-endo-trig

R = H, OMe

however, the acid catalyzed version does cyclize

The Baldwin Rules for Ring Closure: Endo-Digonal vs Endo-Trigonal Cyclizations

5-endo-trig

In-plane approach; nucleophile lone pair is orthogonal to $\pi^*$
Out-of-plane approach: nucleophile lone pair can't achieve Bürgi-Dunitz angle

5-endo-dig

Allowed due to in-plane pi orbitals
The Baldwin Rules for Ring Closure: Applications

**Jung, M. THL 1996, 37, 3.**

![Chemical structure and reaction](image1)

**Nacro, K. TH 1999, 55, 5129**

**The Baldwin Rules for Ring Closure: Applications**

**Retention!**

![Chemical structure and reaction](image2)