Baldwin’s Rules

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Important References –

Jack Baldwin

Events in the life

1964 – received Ph.D. from Imperial College London
1967 – joined faculty at Pennsylvania State University
1970 – moved to Massachusetts Institute of Technology
1976 – published The Rules
1978 – moved to Oxford University, Fellow of Royal Society
1997 – knighted
2005 – retired

Current research interests

biomimetic natural product synthesis
synthetic methods
biosynthesis

Baldwin’s-Rules Nomenclature

3, 4, 5, 6, or 7
The number of atoms in the forming ring

_Endo_ or _Exo_
The orientation of the breaking bond relative to the smallest forming ring

_Tet, Trig, or Dig_
The geometry of the carbon atom participating in ring closure

The Rules

<table>
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<tr>
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<tbody>
<tr>
<td>3 – 7-Exo favored</td>
<td>3 – 7-Exo favored</td>
<td>3 &amp; 4-Exo disfavored</td>
</tr>
<tr>
<td>5 &amp; 6-Endo disfavored</td>
<td>3 – 5-Endo disfavored</td>
<td>5 – 7-Exo favored</td>
</tr>
<tr>
<td></td>
<td>6 &amp; 7-Endo favored</td>
<td>3 – 7-Endo favored</td>
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</tbody>
</table>

The Scope of the Rules

1. Disfavored ring closures are not impossible, just energetically more demanding than favored ring closures
2. Apply not only to anion cyclizations but also to cation and radical cyclizations

\[
\begin{align*}
\text{方形} & \quad \leftrightarrow \quad \text{矩形} \quad \rightarrow \quad \text{三角形} \\
\text{环} & \quad \rightarrow \quad \text{环}^+ \\
\text{环}^+ & \quad \leftrightarrow \quad \text{环}^+
\end{align*}
\]

The Scope of the Rules

3. Do not necessarily apply to concerted electrocyclic reactions

4. Apply only to ring closures where the attacking atom is a second-row element

Rationalization: Rule 1

Rationalization: Rule 2

Rationalization: Rule 3

Experimental Investigation of the Rules

5-Endo-Trig

5-Exo-Trig

Nazarov, I. N. and Elizarova, A. N. Chem. Abstr. 1948, 42, 7737
Experimental Investigation of the Rules

- **5-Endo-Dig**

\[
\begin{align*}
\text{HO} & \quad \text{Ph} \\
\text{NaH, MeOH, reflux, 2 h, 93%} & \quad \Rightarrow & \quad \text{Ph}
\end{align*}
\]

- **6-Endo-Trig**

\[
\begin{align*}
\text{OH} & \quad \text{HO} \\
5\% \text{aq NaOH, 2 h, 65\%} & \quad \Rightarrow & \quad \text{Ph}
\end{align*}
\]

The Fourth Rule

Cyclizations that open 3-membered rings constitute a separate class

Generally, 5-Exo predominates among competing modes

More Rules: Cyclizations of Enolates

enolendo or enolexo

\[ \text{(enolendo)-exo-tet} \]

\[ \text{(enolexo)-exo-tet} \]

<table>
<thead>
<tr>
<th>exo-tet</th>
<th>exo-trig</th>
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<tr>
<td>3 – 5 (enolendo) disfavored</td>
<td>3 – 5 (enolendo) disfavored</td>
</tr>
<tr>
<td>6 &amp; 7 (enolendo) favored</td>
<td>6 &amp; 7 (enolendo) favored</td>
</tr>
<tr>
<td>3 – 7 (enolexo) favored</td>
<td>3 – 7 (enolexo) favored</td>
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Experimental Investigation: Cyclizations of Enolates

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Graded Favorability

- Some favored ring closures are more favored than others
- For example, 5-Exo-Trig is more favored than 6-Endo-Trig

Exceptions to the Rules

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- Relief-of-strain driven disfavored retro 5-Endo-Trig

\[ \text{O} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{O} \]

- 5-Endo-Trig cyclic N,O-ketal formation

Enzymatic Exception

- calculations predict 5-Exo pathway favored by 1.8 kcal/mol
- designed antibody catalyzes 6-Endo pathway with high selectivity

Janda, K. D., Shevlin, C. G., Lerner, R. A. Science 1993, 259, 490
Electrochemical Exception

Electrochemical 5-Endo-Trig in a Microemulsion

Vit B_{12a}, CTAB, 1-pentanol, tetradecane, H_{2}O, -1.5 V (vs SCE), dark, 5 h, 70%

\[
\begin{align*}
&\text{cis} + \text{trans} \\
&\text{L} = \text{alamine}
\end{align*}
\]

Serine β-Lactone

- A method for β-substitution of amino acids
- The elimination side reaction is not observed
- It requires retro 4-Endo-Trig ring opening

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Nu</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc</td>
<td>NH$_3^+$</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>H$_2^+$TsO$^-$</td>
<td>N$_3$</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>Cbz</td>
<td>OAc</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>H$_2^+$CF$_3$CO$_2^-$</td>
<td>L-Cys</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>Cbz</td>
<td>Me</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>Cbz</td>
<td>t-Bu</td>
<td>48</td>
</tr>
<tr>
<td>7</td>
<td>Cbz</td>
<td>Ph</td>
<td>55</td>
</tr>
</tbody>
</table>

Summary

Insights from Baldwin’s rules

- Ease of ring formation depends on more than ring size
- Cyclizations of small rings may be impeded by the inability of the reacting termini to achieve proper orbital alignment
- Baldwin’s rules are rules of thumb meant to aid in synthetic planning

Exceptions to Baldwin’s rules

- Even within the stated limits of the rules, exceptions can be found
- A Baldwin’s-rules disfavored process can be driven forward under special conditions