Conformational and Stereochemical Control of Medium to Large Rings

Lecture Overview

Can a macrocycle be conformationally defined and can their conformations be accurately predicted?

Helpful References


Amphidinolide X

Can a macrocycle be used as a stereocontrol element in stereoselective synthesis?

12,13-Desoxyepothilone B

Miyakolide macrocyclic precursor

Epothilone B (anticancer)
Consider the following kinetic scheme:

\[
\begin{align*}
A_1 & \overset{k_{21}}{\rightleftharpoons} A_2 & \overset{k_{32}}{\rightarrow} A_3 & \overset{k_{34}}{\rightarrow} A_4 \\
\text{Slow} & & \text{Fast} & \text{Slow}
\end{align*}
\]

The above equation describes two quickly interconverting species (conformations of a single molecule for instance) which react at different rates to form product.

- So why can we apply conformational analysis (a ground state phenomenon) to study reactivity?

The above reaction (which we will return to) involves a selective, exothermic process.

- The reaction with the lower absolute barrier, will lead to the major product under this scheme (thus A4 is preferred).

We must make an assumption that the relative position of ground state conformers also translates to the transition state.
"Erythromycin, with all of our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers."

- The discovery of pikromycin, the first macrolide antibiotic, introduced additional complexity to synthetic organic chemists

- Related natural products erythromycin and aglycons known as the erythronolides became ambitious targets for synthesis

- How did chemists tackle these challenges for synthesis?
  • Concavity/convexity was the dominant form of stereocontrol
  • Often bicyclic systems were used in this capacity, even if they were not present in the final target

- This approach is exemplified by Woodward and coworkers synthesis of erythronolide A

- Here, a single dithioacetal is used to direct a reduction and oxidation step to secure the desired stereochemistry
Still helped deconvolute the seemingly intractable problems associated with medium and large ring stereocontrol. Consider the following examples:

- Peripheral attack: reagents prefer to attack medium-sized rings from the exterior rather than the interior.

(±)-Periplanone-B. Total Synthesis and Structure of the Sex Excitant Pheromone of the American Cockroach

“This principle of peripheral attack appears to be general as a strategy for stereochemical control in the synthesis and modification of germacranes and related medium-ring compounds. It does, however, require knowledge of the conformation of the starting olefin.”


Career highlights: Flash chromatography (>7400 citations), Macromodel (>2700 citations), Solvation in molecular mechanics (>1500 citations), Monte Carlo searching (>650 citations), Still-Gennari modification of HWE (>650 citations).
“Cyclooctane is unquestionably the conformationally most complex cycloalkane owing to the existence of so many forms of comparable energy…”

- Still argues that torsional effects contribute to the relatively small 0.5 kcal/mol difference between conformers

*Computationally determined energies and conformations:

- **Chair-boat**:
  - $\Delta G_{\text{rel}} = 0$ kcal/mol
  - Destabilizing transannular nonbonded interactions!

- **Chair-chair**:
  - $\Delta G_{\text{rel}} = 0.52$ kcal/mol

- **Boat-boat**:
  - $E_{\text{rel}} = 3.4$ kcal/mol
With our newfound understanding of the dominant cyclooctane conformations, let us revisit a reaction that was presented earlier.

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

\[
\text{LDA, Mel} \quad \text{Me} \quad \text{Me}
\]

\[
\begin{align*}
\text{LDA} & \quad \text{Me} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{OLi} & \quad \text{OLi}
\end{align*}
\]

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

| Enolate 1 | \(\Delta G_{\text{rel}} = 0.50 \text{ kcal/mol}\) |

- Placing the enolate within the boat *relieves* transannular nonbonded interactions
- For this reason, \(sp^2\) hybridized carbon atoms should generally be placed at position 3

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

| Enolate 2 | \(\Delta G_{\text{rel}} = 0 \text{ kcal/mol}\) |

- Both enolates are very similar in energy, and they both lead to the same *anti* product
- Which conformer is most likely to proceed through the lowest energy transition state?

A “thought experiment”: provide a rational for the depicted stereochemical outcome

\[
\begin{align*}
\text{Hg(OAc)}_2, \text{H}_2\text{O} & \quad \text{Me} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} \quad \text{Hg-OAc}
\end{align*}
\]

- Step 1: consider the conformation of the substrate
- Both *cis* double bonds are placed in a position that relieves transannular strain

\[
\begin{align*}
\text{Hg(OAc)}_2 & \quad \text{Me} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{OAc}^{-}
\end{align*}
\]

Computed energies and conformations: B3LYP/6-31G*
Cyclooctenone differs in conformation from what one might predict based upon the previous examples.

Consider the following reaction:

\[ \text{Me}_2\text{CuLi} \rightarrow 99\% \text{ anti} \]

Placing unsaturation in the 2-3 positions relieves transannular nonbonded interactions. Is there a problem with this conformation?

Placing enone at the 4-5-6 positions affords proper overlap.

Now consider the hydrogenation of an exocyclic enone:

\[ \text{"Rh", H}_2 \rightarrow 91\% \text{ anti} \]

Consider the relevant conformations:

Why does the relative stereochemistry of the product predominate?

Computed conformations: B3LYP/6-31G*
Macrocycles tend to minimize transannular non-bonded interactions and high-energy torsional arrangements.

While many conformations for cyclodecane exist, two commonly depicted ones are drawn above.

\[ \text{boat-chair-boat} \]
\[ \Delta G_{\text{rel}} = 0 \text{ kcal/mol} \]

\[ \text{chair-chair-boat} \]
\[ \Delta G_{\text{rel}} = 1.4 \text{ kcal/mol} \]

Consider this dimethylcuprate addition:

\[ \text{Me}_2\text{CuLi} + \text{Me} \]
\[ \Delta G_{\text{rel}} = 0.38 \text{ kcal/mol} \]
To this point, we have discussed the conformational control of 8 and 10-membered rings and the possibility of achieving high selectivity within the context of a given reaction.

What about larger rings?

At this point, the synthesis needed to be reconsidered.

How might they obtain the desired stereochemistry?

General conformational control elements are listed above.

Empirically it can be shown that, in large rings especially, acyclic conformational analysis concepts generally hold.
- Analysis of amphidinolide X and analogues also reveals that stereochemical components may stabilize a given conformation.

- Two lowest energy conformations (result of semi-empirical PM3 Monte Carlo conformational search and further DFT optimization).

- Indeed, larger rings may be conformationally defined if requisite controlling elements are present.

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Type</th>
<th>( \text{IC}_{50} ) (µg/mL)</th>
<th>( \Delta G_{rel} ) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HT29</td>
<td>colorectal</td>
<td>5.15</td>
<td>10</td>
</tr>
<tr>
<td>LXFA 629L</td>
<td>lung</td>
<td>7.89</td>
<td>&gt;10</td>
</tr>
<tr>
<td>MAXF 401NL</td>
<td>breast</td>
<td>7.33</td>
<td>&gt;10</td>
</tr>
<tr>
<td>MEXF 462NL</td>
<td>melanoma</td>
<td>5.95</td>
<td>&gt;10</td>
</tr>
</tbody>
</table>


Computed energies and conformations: B3LYP/6-31G*

- How could we go about predicting the stereoselectivity of this reaction? (especially in the synthesis planning stage)
- Compute the lowest energy conformation:

\[
\text{12,13-Desoxynophitholone B} \xrightarrow{\text{DMDO}} \text{Epethilone B (anticancer)}
\]

Now identify the next lowest energy conformer that leads to the opposite diastereomeric outcome.

How close are the two conformations that lead to opposite stereochemical outcomes in energy?

---

Computing the lowest energy conformation:

\[
\text{Reagent} \rightarrow \text{B3LYP/6-31g(d), SMD implicit solv}
\]

---

Relative Energy

3.23 kcal/mol

(DFT, solvation)
Chem 106

**A Protocol to Analyze and “Predict” Stereochemical Outcomes**

Peripheral attack leads to major diastereomer

$$\text{peripheral attack leads to minor diastereomer}$$

Output from the Monte Carlo conformational search

- Choose a collection of lowest energy conformers that lead to different diastereomeric outcomes (apply peripheral attack)
- After DFT optimization, an $E_{\text{rel}}$ of 3.23 kcal/mol was established

12,13-Desoxyepothilone B

Epothilone B (anticancer)

- $100\% \text{ dr} = >25:1$
- $+3.23 \text{ kcal/mol}$

Higher energy structures rejected

- Global minimum for molecular mechanics
- 1 starting structure
- 0 061 476 candidate structures generated
- 1 884 397 rejected by ring closure
- 57 080 rejected by van der Waals
- 120 000 candidate structures
- +120 000 candidate structures
- -111 360 duplicates rejected
- 8 640 unique structures found

Done with many software packages (for example, Macromodel)
Over 30 literature examples of intermolecular reactions with chiral macrocycles were studied.
### Results

- **Accuracy of predicting the major product**

<table>
<thead>
<tr>
<th>Method</th>
<th>% correct (all E_{rel})</th>
<th>% correct (IE_{rel} &gt; 1 kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM only (gas phase)</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td>B3LYP (gas phase)</td>
<td>73</td>
<td>71</td>
</tr>
<tr>
<td>B3LYP (SMD solvation)</td>
<td>81</td>
<td>78</td>
</tr>
<tr>
<td>M06-2X (SMD solvation)</td>
<td>70</td>
<td>76</td>
</tr>
</tbody>
</table>

- **Accuracy by reaction type**

<table>
<thead>
<tr>
<th>reaction type</th>
<th># of cases</th>
<th>accuracy a (major product)</th>
<th>accuracy b (high selectivity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>epoxidation</td>
<td>9</td>
<td>8 of 9 (89%)</td>
<td>7 of 8 (88%)</td>
</tr>
<tr>
<td>cuprate add.</td>
<td>6</td>
<td>4 of 6 (67%)</td>
<td>3 of 4 (75%)</td>
</tr>
<tr>
<td>hydrogenation</td>
<td>6</td>
<td>4 of 6 (67%)</td>
<td>1 of 2 (50%)</td>
</tr>
<tr>
<td>1,2-addition</td>
<td>6</td>
<td>4 of 6 (67%)</td>
<td>2 of 4 (50%)</td>
</tr>
</tbody>
</table>

a MM-DFT (B3LYP/6-31g(d), SMD) b |E_{rel}| > 1.0 kcal only

- **Accuracy of predicting the level of selectivity**

<table>
<thead>
<tr>
<th>observed dr</th>
<th>MM only</th>
<th>IE_{rel} (kcal/mol)</th>
<th>ambig.</th>
<th>0.0 – 1.0</th>
<th>&gt; 1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 8 : 1</td>
<td>0</td>
<td>6</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 : 8</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 : 1 – 1 : 8</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td>2</td>
<td>8</td>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a the number of compounds with the correct sense of selectivity divided by the total in the specified range.

- **Conclusions**
  - The peripheral attack model is moderately successful
  - This is not surprising because it relies upon the translation of ground-state conformational preferences to the transition state
  - Epoxidation reactions are most likely to be accurately predicted, in the absence of a directing group effect

- **Major product prediction**

<table>
<thead>
<tr>
<th>E_{rel} (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

- **Selectivity prediction**

<table>
<thead>
<tr>
<th>E_{rel} (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>1</td>
</tr>
</tbody>
</table>

- The take away message: perform the conformational analysis, and be wary of a modest E_{rel} (or better yet, compute the TS!)
To this point, we have discussed intermolecular reactions involving medium and large rings. Now, let us transition to the study of intramolecular reactions.

"[Macrocycles have] a high degree of conformational restriction and as a result, proximity effects become operative and very often, these effects will increase the rate of one reaction and slow down others which are normally competing."  

How should we approach this problem?

Second, orient the diene such that A(1,3)-strain is minimized.

Draw the dienophile such that the a pseudo chair conformation still exists (also in this case an *endo* Diels-Alder TS is probably preferred).

An example from Deslongchamps toward hydroxyaphidicolins.
A transannular cascade inspired by the tetracyclines

Tetracycline:

The proposed transformations

C14-macrocycle

The transannular Michael addition

In practice:

What does the following conformer distribution and product ratio suggest about this reaction?

The Michael addition

Curtin-Hammett kinetics!

proceeds to product
The opposite diastereomer is a “matched” case.

**In practice:**

- **A Ce(III)-mediated TA bond-forming reaction**

- **A model for the oxidation:**

- **Remaining obstacles en route to tetracycline**

- **Can TA bond-forming reactions be merged?**