Chiral organolithium reagents: configurational stability and dynamic resolution

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Denmark group meeting
March 12, 2013

The Carbon-Lithium bond

R–Li ↔ R⁻Li⁺

CH₃–Li
2.02 Å
80% ionic

Tight ion-pair with little covalent bonding

BUT

the covalent component cannot be neglected!
(¹³C–Li/²Li coupling)

Chiral organolithiums

Central chirality ($\eta^1$)

\[ \text{Li} \quad \Delta G^\circ = 0 \quad \text{enantiomers} \]

\[ \text{Li-}L^* \quad \Delta G^\circ \neq 0 \quad \text{diastereomers} \]

Planar chirality ($\eta^3$)

\[ \text{Li} \quad \Delta G^\circ = 0 \quad \text{enantiomers} \]

\[ \text{Li-L}^* \quad \Delta G^\circ \neq 0 \quad \text{diastereomers} \]

Gawley, R. E. In Stereochemical Aspects of Organolithium Compounds; Verlag Helvetica Chimica Acta: 2010, p 93

First report on a chiral organolithium (Letsinger, 1950)

\[ \begin{align*}
\text{1. sBuLi} & \quad \text{petroleum ether/Et_2O} \\
& \quad -70 \degree C \text{ to } 0 \degree C, \text{ 20 min} \\
\text{2. CO}_2 & \quad \text{COOH}
\end{align*} \]

$\alpha_\text{D} = -45.86^\circ$

\[ \begin{align*}
\text{1. sBuLi} & \quad \text{petroleum ether/Et_2O} \\
& \quad -70 \degree C, \text{ 1 min} \\
\text{2. CO}_2 & \quad \text{COOH}
\end{align*} \]

$\alpha_\text{D} = 0^\circ$

$\alpha_\text{D} = -1.18^\circ$

80% racemization

Demonstrates the ability of the C-Li bond to retain its configuration!

Letsinger, R. L. J. Am. Chem. Soc. 1950, 72, 4842
A configurationally stable organolithium (Still, 1980)

How to assess the configurational stability of a chiral organolithium?

Electrophilic quenching

Dynamic NMR

Hoffmann test (and variants)
Electrophilic quenching

Conceptually simple
Amenable to kinetic studies (→ ΔG\textsuperscript{‡} enantiomerization)
Requires a route to the enantioenriched organolithium precursor

**Dynamic NMR**

In order to distinguish two sites, their **life time** $\tau$ must be longer than

$$\tau = \frac{\sqrt{2}}{2\pi \Delta \nu}$$

$\Delta \nu =$ difference in frequencies of the interconverting sites

For a 400 MHz spectrometer, two signals having a $\Delta \Delta$ of 0.1 ppm ($= 40 \text{ Hz}$) will be resolved if $\tau$ is greater than $5.6 \times 10^{-3} \text{ s}$

$\tau$ is temperature-dependent!

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**Dynamic NMR**

Knowing $\Delta \nu$ and $T_{\text{coalescence}}$, $\Delta G^\ddagger$ can be obtained by combining the equations

$$k = \frac{\pi}{\sqrt{2}} \Delta \nu$$

$$k = \frac{k_B T_{\text{coalescence}}}{h} e^{-\frac{\Delta G^\ddagger}{RT_{\text{coalescence}}}}$$

$T_{\text{coalescence}} = 120 \text{ °C}$

$^1\text{H} \text{ NMR}, 56.4 \text{ MHz}$

$\Delta G^\ddagger = 20.9 \text{ kcal/mol}$

- NMR spectrometers operating at a **higher frequency** will detect coalescence at a **higher temperature**
- Ordinary spectrometers are designed for operation between -150 °C and +150 °C
- Barriers between 5 kcal/mol and 25 kcal/mol can be measured by dynamic NMR
- For organolithiums, the upper limit is ca. 14 kcal/mol (thermal decomposition)

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Öki, M. *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*; Verlag Helvetica Chimica Acta: 1985

Examples

To determine the enantiomerization barrier of chiral organolithiums, the exchange of diastereotopic groups is analyzed by dynamic NMR.


Examples

Allenyllithiums

Mechanisms of enantiomerization:

Electrophilic quenching:

Dynamic NMR:

\[ T_{\text{coalescence}} = -40 \, ^\circ\text{C} \]

\[ ^{13}\text{C NMR, 90.56 MHz} \]

\[ \Delta G^\ddagger = 10.8 \, \text{kcal/mol} \]


The Hoffmann test: a serendipitous discovery

1988 – study of the stereoselective addition of allenylmetal reagents to aldehydes

The allenyltitanium reagent is configurationally stable on the reaction timescale

Hoffmann, R. W.; Lanz, J. W.; Metternich, R. Liebigs Ann. Chem. 1988, 161
The Hoffmann test

1992 – formal report on the test

**Experiment 1:**

\[ \text{R-Li} + \text{electrophile} \rightarrow \text{diastereomer A} + \text{diastereomer B} \]

(±) (±)

**Experiment 2:**

\[ \text{R-Li} + \text{electrophile} \rightarrow \text{diastereomer A} + \text{diastereomer B} \]

(±) enantiopure

**Ratio A/B**

\[ \text{ratio} \frac{A}{B} = \frac{k_{\text{fast}}}{k_{\text{slow}}} \]

**Selectivity factor (s)**

\[ s = \frac{k_{\text{fast}}}{k_{\text{slow}}} \]

**Examples**


Energy diagrams

Experiment 1 (racemic E)  Experiment 2 (enantiopure E)

Configurationally labile

ΔΔG‡ dependent  ΔΔG‡ dependent

Configurationally stable

ΔΔG‡ dependent  ΔG° dependent (1:1)

Curtin-Hammett  non-Curtin-Hammett

s factor and level of conversion

Experiment 2 must go to completion!

✦ Use an excess of the electrophile
✦ Long reaction times are needed when s is high (→ decomposition of SM and products)
✦ s should be < 3

A comparison of the A/B ratios for Experiment 1 and 2 is inconclusive if s < 1.5

If s is not in the optimal range between 1.5 and 3, a different electrophile should be chosen


When $s$ is too small...

\[
\]

\[
\text{Enantiopurity of the electrophile}
\]

A product ratio of 1:1 can be reached in Experiment 2 only if the electrophile is enantiomerically pure

\[
\]
Side reactions

1. Both enantiomers of the organometallic reagent are consumed at the same rate
   + Experiment 1: decreased yield
   + Experiment 2: decreased yield and $\neq 1:1 \text{dr}$

<table>
<thead>
<tr>
<th>Yield (%) in Experiment</th>
<th>Selectivity factor $s$ of the main reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>99</td>
<td>98.9</td>
</tr>
<tr>
<td>97</td>
<td>96.6</td>
</tr>
<tr>
<td>95</td>
<td>94.4</td>
</tr>
<tr>
<td>90</td>
<td>89.0</td>
</tr>
<tr>
<td>80</td>
<td>89.5</td>
</tr>
<tr>
<td>70</td>
<td>68.3</td>
</tr>
</tbody>
</table>

Yield in Exp. 2

The deviation from the ideal 1:1 dr is not significant if the extent of the side reaction and the $s$ factor are small


2. The enantiomers of the organometallic reagent are consumed at different rates ($s^*$)
   + Experiment 1: decreased yield
   + Experiment 2: increased or decreased yield relative to Experiment 1 and $= or \neq 1:1 \text{dr}$

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<tbody>
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<tr>
<td>99</td>
<td>50.4:49.6</td>
</tr>
<tr>
<td>97</td>
<td>50.6:49.4</td>
</tr>
<tr>
<td>95</td>
<td>50.9:49.1</td>
</tr>
<tr>
<td>90</td>
<td>51.8:48.1</td>
</tr>
<tr>
<td>80</td>
<td>63.7:46.3</td>
</tr>
<tr>
<td>80</td>
<td>55.4:44.4</td>
</tr>
</tbody>
</table>

Yield in Exp. 2

Side reactions that occur to an extent of less than 10% will not jeopardize the test

RLi tested with the Hoffmann test

<table>
<thead>
<tr>
<th>R-M</th>
<th>Electrophile</th>
<th>Solvent</th>
<th>Temp.</th>
<th>Conf. stable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph3C-Li</td>
<td>THF</td>
<td>-78 °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph3-P</td>
<td>THF</td>
<td>-78 °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me2C-P</td>
<td>THF</td>
<td>-78 °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me2-P</td>
<td>THF</td>
<td>-78 °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph3Se-P</td>
<td>THF</td>
<td>-78 °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph3P</td>
<td>THF</td>
<td>-78 °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph3PO</td>
<td>THF</td>
<td>-78 °C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hoffmann, R. W. In Stereochemical Aspects of Organolithium Compounds; Verlag Helvetica Chimica Acta: 2010, p 165

Allylmetal reagents

To summarize...

- The substrate is used as a racemate
- The resulting diastereomers only have to be identified as such (NMR, GC, HPLC) – it is not necessary to assign the relative configuration
- When more than 2 diastereomers are generated (e.g., E = aldehyde), their relative configuration must be assigned
- Large s factors, incomplete conversion, insufficient enantiopurity of the electrophile, and side reactions may lead to inconclusive results
- Not suitable to quantify $\Delta G^\ddagger_{\text{enantiomerization}}$
- Variants have been developed

The “poor man’s Hoffmann test” (Beak, 1996)

- Does not require an enantioenriched electrophile – an achiral electrophile is used
- Requires a chiral ligand for RLi

Experiment 1:

\[
\text{R-Li} \quad \text{(z)} \quad \text{chiral} \quad \text{ligand} \quad \text{excess} \quad \text{electrophile} \quad \rightarrow \quad A \quad + \quad \text{ent-A}
\]

The er reflects $\Delta \Delta G^\ddagger$ if RLi is configurationally labile, the population of the diastereomeric complexes if RLi is configurationally stable

Experiment 2:

\[
\text{R-Li} \quad \text{(z)} \quad \text{chiral} \quad \text{ligand} \quad \text{deficiency} \quad \text{electrophile} \quad \rightarrow \quad A \quad + \quad \text{ent-A}
\]

The er reflects $\Delta \Delta G^\ddagger$

\[\text{er Exp1} \neq \text{er Exp2 for stable RLi}\]
\[\text{er Exp1} = \text{er Exp2 for labile RLi (ambiguous)}\]
Energy diagrams

Experiment 1 (excess E)

- **ΔG° dependent:** er reflects the population
- **Configurationally stable**

Experiment 2 (substoichiometric E)

- **ΔΔG‡ dependent:** er reflects s
- **Configurationally labile**

The test cannot establish configurational lability unambiguously: identical er in the two experiments can be the result of equivalence of the activation energies ($s \approx 1$)

Examples

- **Configurationally stable**
  - 2.3 equiv: 56.44 er
  - 0.1 equiv: 91.9 er

- **Could be configurationally labile**
  - 13% conv (1 h): 80.20 er
  - 35% conv (4 h): 80.20 er

References:
Examples


Group exercise: more on allenyllithiums

The configurational stability of an allenyllithium reagent was determined using a different variant of the Hoffmann test:

‖ Experiment 1: deficiency of enantiopure reagent ‖
‖ Experiment 2: excess of enantiopure reagent ‖

How does this test work?
‖ What conclusions can be drawn on the stability of the allenyllithium reagent?
Group exercise: more on allenylithiums

**Experiment 1:** deficiency of enantiopure reagent

At low conversions, 
\[ dr = s \]
when a racemic organolithium reacts with an enantiopure electrophile

**Experiment 2:** excess of enantiopure reagent

Same as Experiment 2 in the Hoffmann test:
\[ dr = 1:1 \] for a stable RLi
\[ dr = s \] for a labile RLi

The allenylithium is configurationally labile over the timescale of addition to camphor

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-configurational stability of organolithiums: timescale

“Configurationally stable” is a term which has a meaning only when it is associated with a temperature and a timescale

- 10 kcal/mol: \( t_{1/2} = 0.03 \) s at \(-78^\circ C\)
- 15 kcal/mol: \( t_{1/2} = 3 \) h at \(-78^\circ C\), 0.01 s at 25 °C
- 20 kcal/mol: \( t_{1/2} = 145 \) years at \(-78^\circ C\), 53 s at 25 °C

Barriers have been determined quantitatively only for a few classes of organolithiums

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Coldham, I.; Sheikh, N. S. In Stereochemical Aspects of Organolithium Compounds; Verlag Helvetica Chimica Acta: 2010, p 253

Clayden, J. Organolithiums: Selectivity for Synthesis; Pergamon: 2002
Configurational stability of organolithiums: summary

- **Benzyl organolithiums**: low barriers (8-10 kcal/mol)

- **α-heteroatom substituted organolithiums**: higher barriers

- **Chelation and bulky groups** increase the barrier

- **Cyclic α-amino, cyclopropyl, oxiranyl, aziridinyl organolithiums**: stable (> 20 kcal/mol)

Coldham, I.; Sheikh, N. S. In Stereochemical Aspects of Organolithium Compounds; Verlag Helvetica Chimica Acta: 2010, p 253
Clayden, J. Organolithiums: Selectivity for Synthesis; Pergamon: 2002

Preparation of chiral organolithiums

**asymmetric deprotonation**

H_a H_b
R' R'

SnBu₃
R' R'

**tin-lithium exchange**

Li
R' R'

dynamic resolution

Li
R' R'
Dynamic resolutions: kinetic vs thermodynamic control

Dynamic Kinetic Resolution (DKR)
$\Delta \Delta G^\ddagger$ dependent

Dynamic Thermodynamic Resolution (DTR)
$\Delta G^\circ$ dependent

Benzylic organolithiums

The organolithium is configurationally labile over the timescale of the experiment, but configurationally stable over the timescale of reaction with TMSCl $\Rightarrow$ DTR

Benzylic organolithiums

\[ \text{IPr}_2\text{N(O)} \quad \text{sBuLi, pentane, } -78^\circ \text{C} \quad \text{E} \quad \text{TMSCI} \quad 79\% \quad 98:4 \]

<table>
<thead>
<tr>
<th>E</th>
<th>yield</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMSCI</td>
<td>79%</td>
<td>98:4</td>
</tr>
<tr>
<td>Bu\textsubscript{3}SnCl</td>
<td>78%</td>
<td>94:6</td>
</tr>
<tr>
<td>allyl-Cl</td>
<td>89%</td>
<td>96:4</td>
</tr>
</tbody>
</table>

DKR or DTR?

- Poor man’s Hoffmann test: **inconclusive**
- Hoffmann test: **labile**
- racemic stannane \(\rightarrow\) enantioenriched product

The organolithium is **configurationally labile** over the timescale of the experiment, and **configurationally labile** over the timescale of reaction with E \(\Rightarrow\) DKR

Diarylmethanes

\[ \text{Me} \quad \text{sBuLi, } -78^\circ \text{C} \quad \text{fBu, fBu} \quad \text{82.5:17.5 er} \]

DKR or DTR?

No experiments were performed to assess the configurational stability of the intermediate organolithium

Lonafarnib

farnesyl protein transferase inhibitor (Phase II/III clinical trials)
α-Oxygen

\[ \text{RCO}N\text{Pr}_2 \xrightarrow{\text{^nBuLi, 2}} \text{pentane, cyclohexane, \(-70^\circ C\)} \]

\[ \begin{align*}
\text{Li}^2 \text{O} & \xrightarrow{\text{crystallization}} \text{Ti(OPr)}_3 \\
\text{(S)} & \xrightarrow{\text{invertive}} \text{(R)}
\end{align*} \]

configurationally labile
one diastereomeric organolithium crystallizes ⇒ Crystallization-Induced Dynamic Resolution

\[ \begin{align*}
\text{RCHO} & \xrightarrow{(\text{PrO})_3\text{Ti}} \text{H}_2\text{O}^+ \xrightarrow{93\%} \text{H} \xrightarrow{92.8 \text{ er}} \text{OCONPr}_2
\end{align*} \]

(+)-quercus lactone A
oak wood flavor
(+)-eldanolide
sugar-cane borer pheromone

Zschage, O.; Hoppe, D. Tetrahedron 1992, 48, 5657

α-Nitrogen

\[ \begin{align*}
\text{Ph} & \xrightarrow{\text{nBuLi, (-)-sparteine, toluene, \(-78^\circ C\)}} \text{Ph} \\
\text{Boc} & \xrightarrow{\text{Ar = pMeO-C}_6\text{H}_4} \text{Boc}
\end{align*} \]

configurationally stable over the timescale of the experiment ⇒ Asymmetric deprotonation

\[ \begin{align*}
\text{Ph} & \xrightarrow{\text{PhBr, -78^\circ C}} \text{Ph} \\
\text{Boc} & \xrightarrow{\text{Ph, -78^\circ C}} \text{Boc}
\end{align*} \]

84%, 98.2 er

configurationally labile at -25 °C
configurationally stable at -78 °C ⇒ DTR

Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. J. Am. Chem. Soc. 1999, 121, 9522

41% overall, 97:3 er
paroxetine (Paxil®)
antidepressant
Chiral organolithium reagents have had a significant impact on stereoselective synthesis.

Assessment of the configurational stability of an organolithium reagent is fundamental for the rational design of stereoselective processes.

NMR spectroscopy and the Hoffmann test have provided information on the configurational stability of several classes of chiral organolithiums.

Several parameters affect the configurational stability: solvent, temperature, substituents, intramolecular coordination – a systematic structure-activity relationship has not been developed.
Bibliography

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