

# Ring Strain and Effective Molarities in Ring-Closing Metathesis

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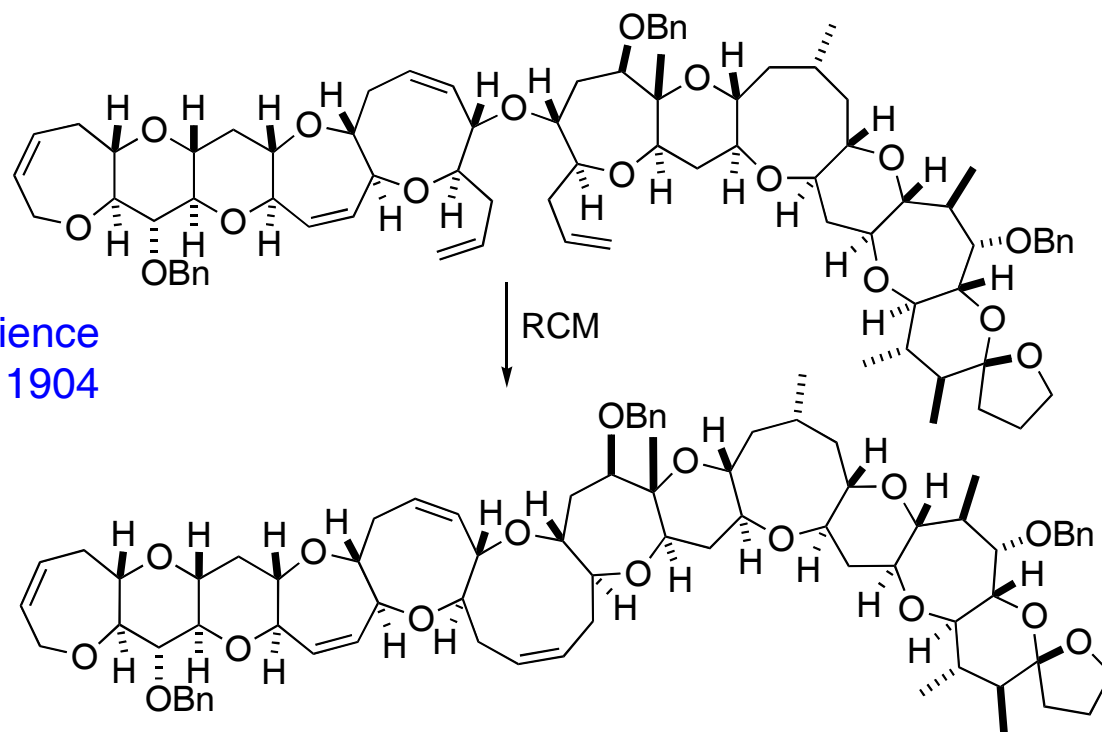
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# Ring-Closing Metathesis in Organic Synthesis

- three main strategies for assembling cyclic molecules:  
ring expansion, ring contraction, intramolecular ring closure

RCM in natural products synthesis: Nicolaou *Angew. Chem. Int. Ed.* 2005, 4490

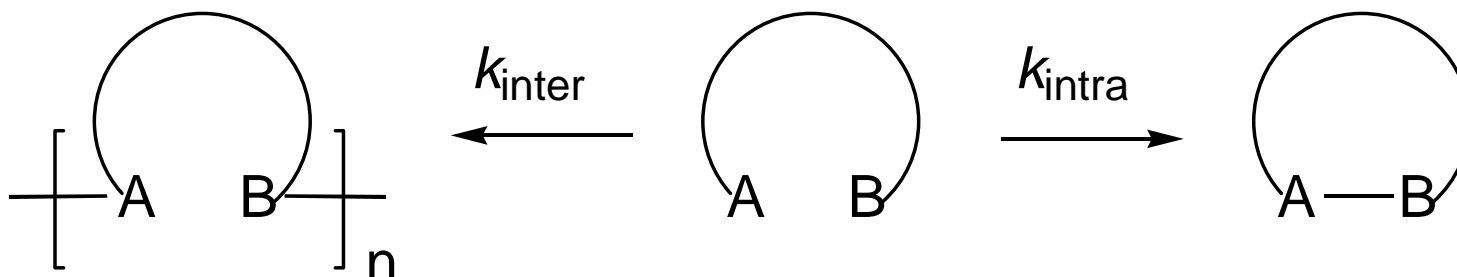
Hirama et al. *Science*  
2001, 294, 1904



- structure–cyclization efficiency relationship poorly understood
- optimization by trial and error

# Cyclization Reactions: Ring-closing vs. oligomerization

- early (macro)cyclizations: Ruzicka, Kerschbaum, Ziegler
- fundamental challenge: selectivity for intra- vs intermolecular rx



- Ziegler "infinite dilution" conditions designed to favour ring-closing
- influxion procedure: constant, low  $[S]$  (added at rate that cyclized product forms). More typically, just dropwise addition

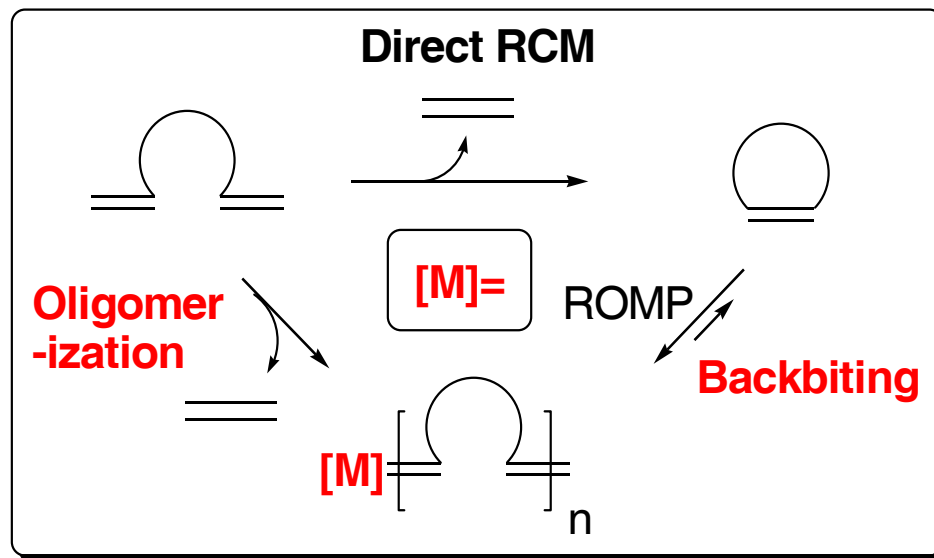
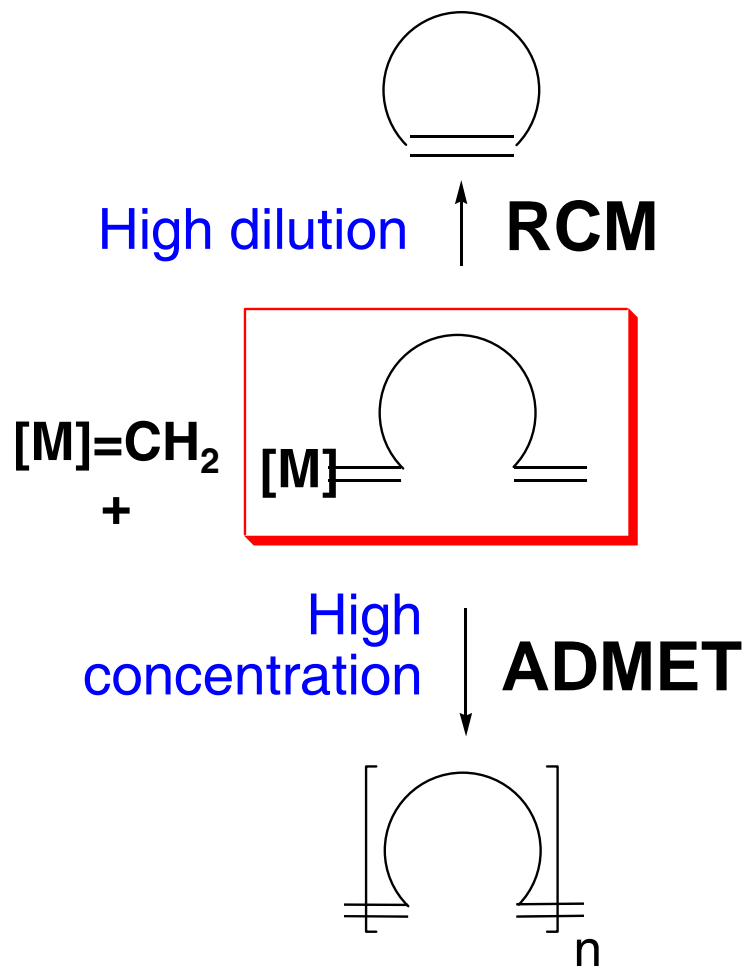
**Effective Molarity:** quantifies ease of cyclization, vs. oligomerization

**EM value** = substrate concentration at which  $\frac{k_{intra}}{k_{inter}} = 1$

**higher EM values: greater tendency toward ring-closing**

- cyclization dominates if  $[S]_0 \ll EM$
- Low-EM substrates: higher dilutions needed to favour cyclization

## Using dilution to promote RCM

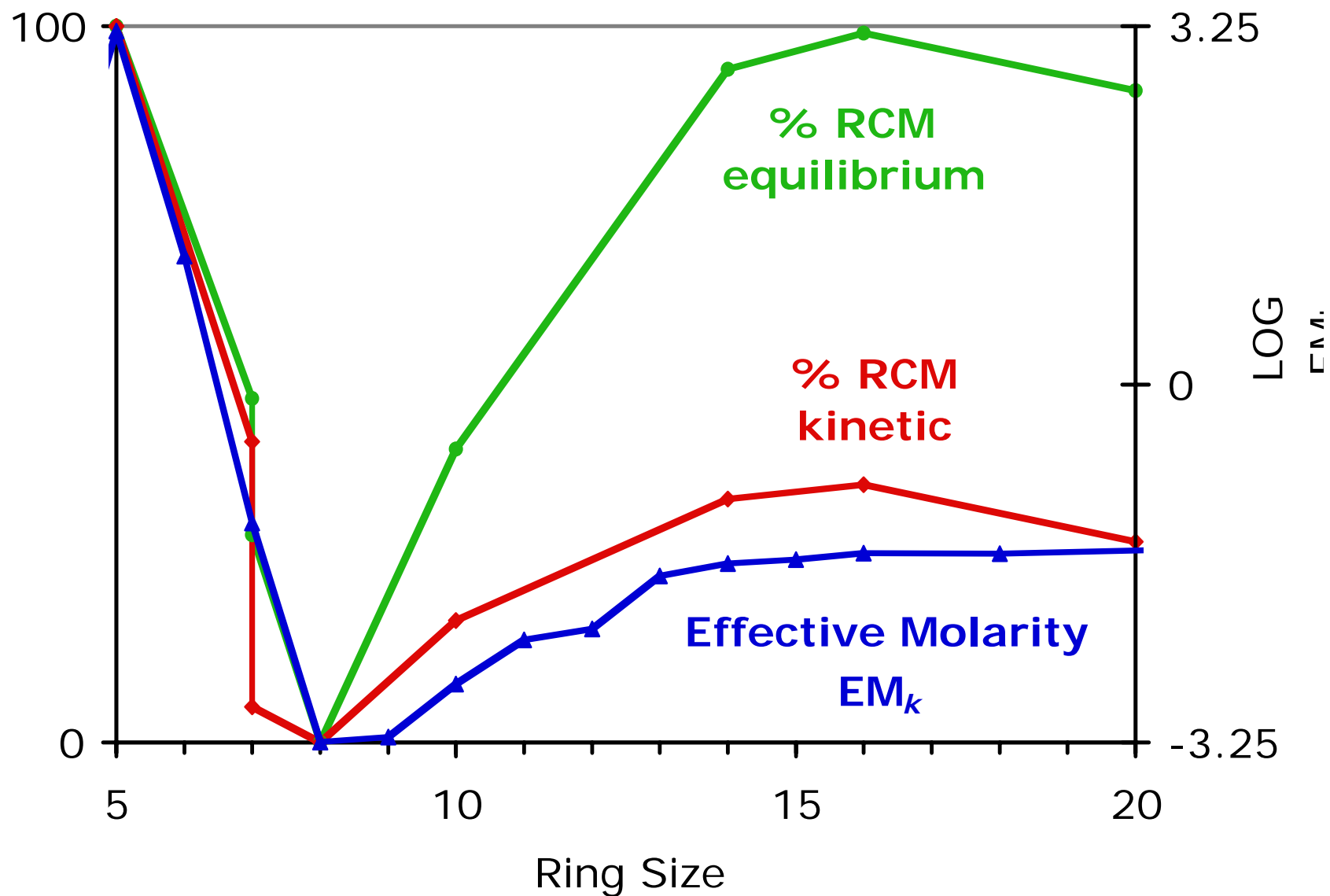
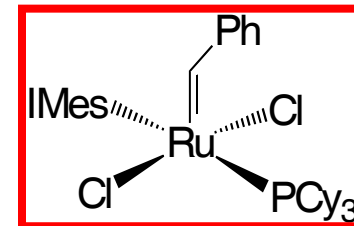


Conrad, J.C.; Eelman, M.D.; Duarte Silva, J.A.; Monfette, S.; Parnas, H.H.; Snelgrove, J.L.; Fogg, D.E. *J. Am. Chem. Soc.* **2007**, *129*, 1024-1025.

- elevated temp. or long reaction needed to overcome low [S]
- added risk: competing catalyst decomposition (add [M] dropwise)

# Correlation Between Ring Size, $EM_k$ and % RCM

Lactone, catechol, malonate rings



## Implications for organic synthesis

1. direct RCM dominates for 5, 6-membered rings, or other strong bias toward cyclization (high EM)
2. oligomerization must otherwise be considered
  - for many catalysts, oligomerization is not terminal
  - concentration thus determines equilibrium RCM yields

False negatives:

- ....post-oligomerization reaction time is important: must be able to monitor
  - must allow Ru-oligomer to reach equilibrium
  - catalyst lifetime is an issue
  - selectivity, rate of back-biting determined by substrate **and catalyst**

**"it's not working"**... but diene is completely consumed.

**Determine if rx has plateaued.** **Yes:** Dilute. **No:** Add more catalyst; re-iterate.