Geometry-Driven Selectivity in Macrocyclization via Rigid-Body Simulation

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What are Macrocycles?

Definition

- Ring-shaped molecules with ≥12 atoms
- Applications: drug discovery, catalysis, advanced materials

Synthesis Challenge

- Various ring sizes form simultaneously
- Selective formation of specific size is difficult
- Especially challenging under irreversible conditions

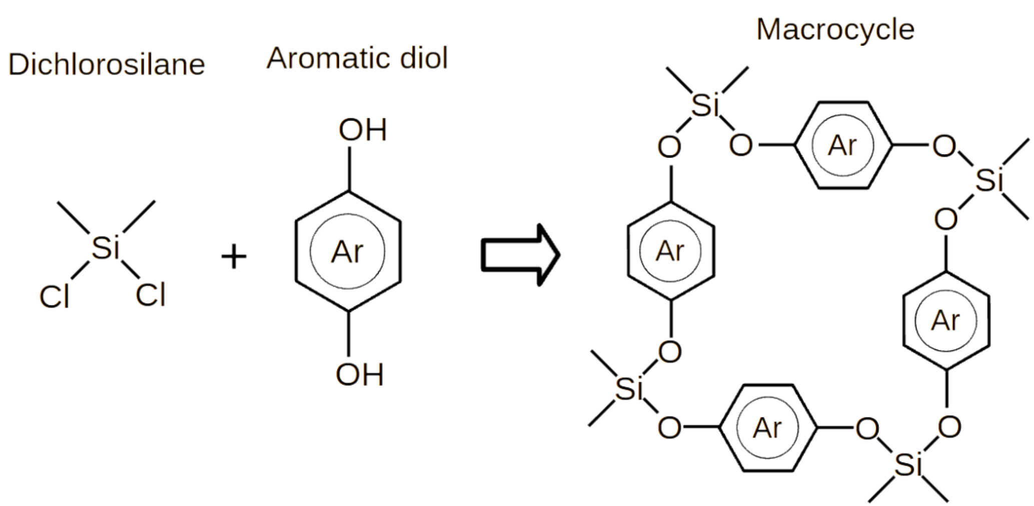
■ Surprising Experimental Discovery

☐ This Experiment(Iwamoto et al. 2025)

Only squares formed at ~100% yield
Completed within minutes
Works even at high concentration

☐The Surprise

Selective formation under irreversible conditions — without any special mechanism



History-dependent assembly, NOT equilibrium

→ **Why does this happen?**

Iwamoto et al. (2025), Chem. Commun. 61, 8180–8183

■ Research Objective

◻ RESEARCH QUESTION

Can geometric constraints alone reproduce the observed selectivity?

◻ KEY IDEA

Build a minimal model with only geometric rules — bond angles and coplanarity

Strip away chemical details to isolate geometry's role

◻ GOAL

Test if geometry alone can drive selective square formation

If yes → geometry is the key mechanism

→ First, let's define a coarse-grained model...

■ Coarse-Grained Rigid-Body Model

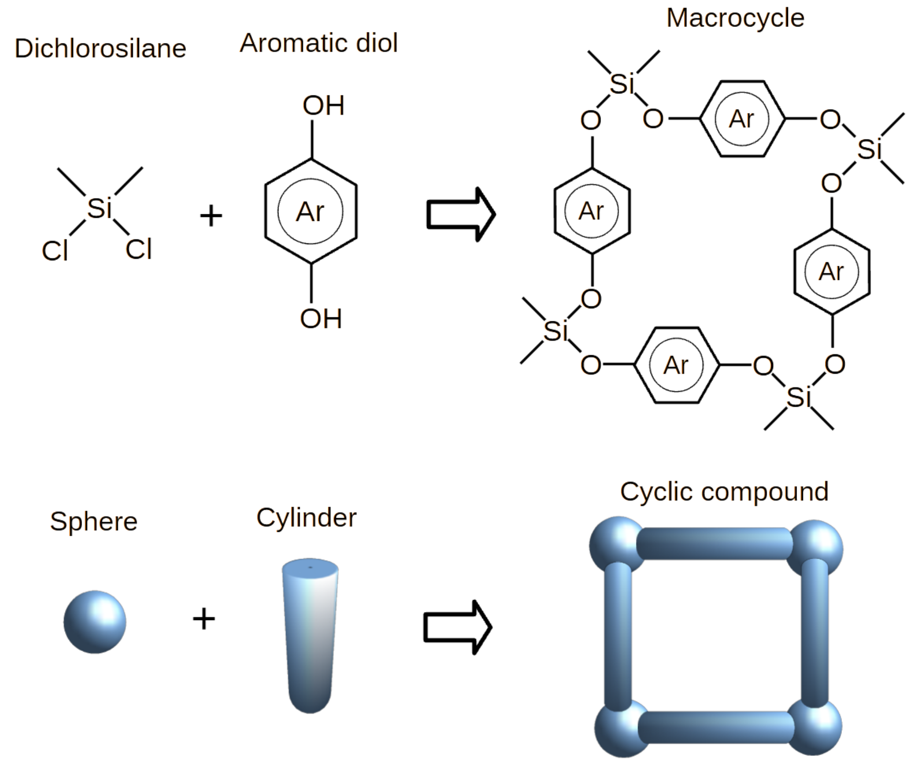
Sphere (S): Organosilicon reagent

- Compact and isotropic
- Valence = 2

Cylinder (L): Aromatic diol

- Short rigid rod
- Each end: Valence = 1

Coarse-grained mapping diagram



■ Implementation

NVIDIA PhysX

- Rigid-body dynamics library
- Collision detection + constraint solving

→ Next, what geometric constraints do we impose?

Geometric Constraints on Bond Formation

1. Capture distance

Bond forms when distance < 0.1

2. Valence

Sphere ≤ 2 bonds, Linker end ≤ 1 bond

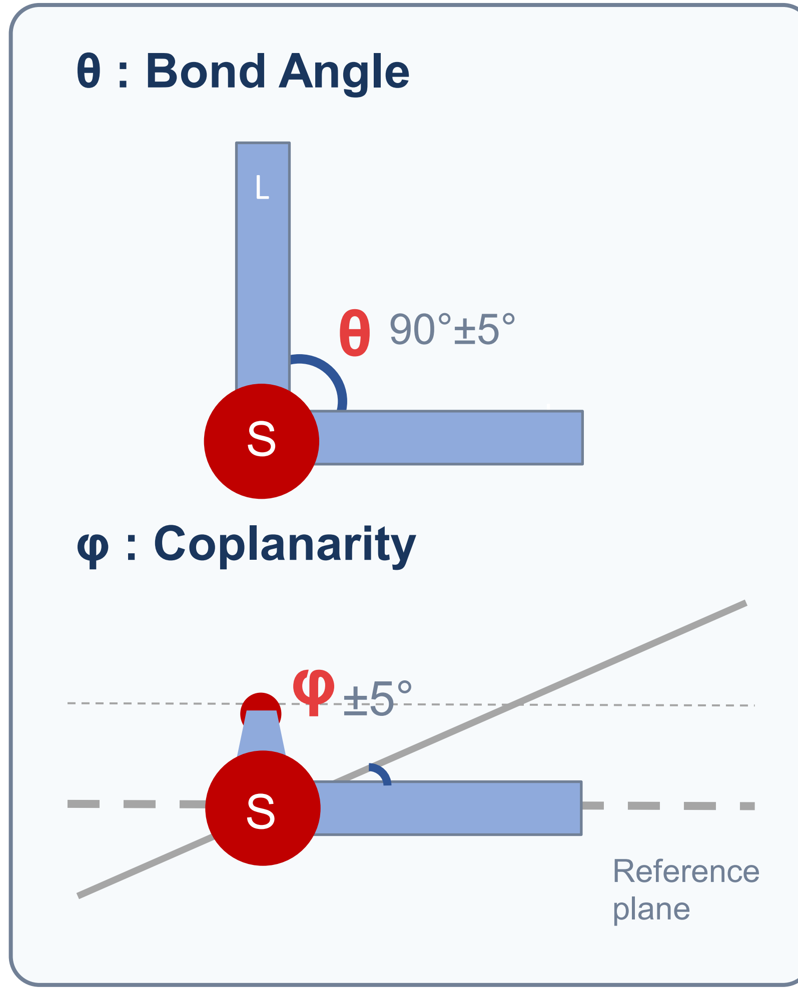
3. Bond angle (θ): 90° ± 5°

DFT calculation: Ar–O–Si–O–Ar ≈ 86°

4. Coplanarity (ϕ): deviation ≤ 5°

Enforces quasi-2D assembly

> **Once formed, bonds are irreversible**



→ How do we set up the simulation?

Simulation Setup

Configuration

- $N = S = 300$
  (Spheres : Linkers = 1:1)
- Box size: 50^3
- Reflective boundary conditions

Statistics

- 1000 independent runs
- MSER for steady-state detection

Identifies when simulation reaches equilibrium

Only uses stable data for analysis

Target

Square macrocycle (tetramer)

4 spheres + 4 linkers in alternating ring

Evaluation Metrics

Target-Object Fraction

→ Φ_target = N_target / N_total

→ How many squares formed?

Square Selectivity

→ $S_4 = N_4$ / N_cycle

→ How pure is the square yield?

Viable-Object Fraction

→ Φ_viable = N_viable / N_total

→ How many clusters can still grow?

τ_target

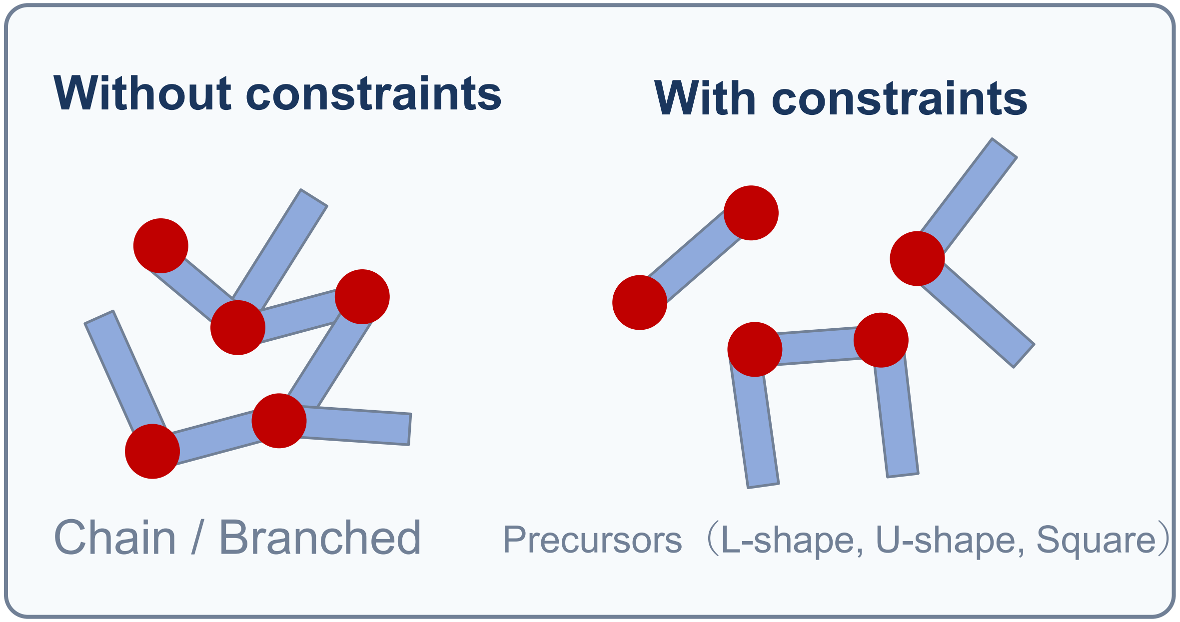
→ simulation time units

→ How fast did the first square form?

■ Passive Geometric Filters: Necessary but Insufficient

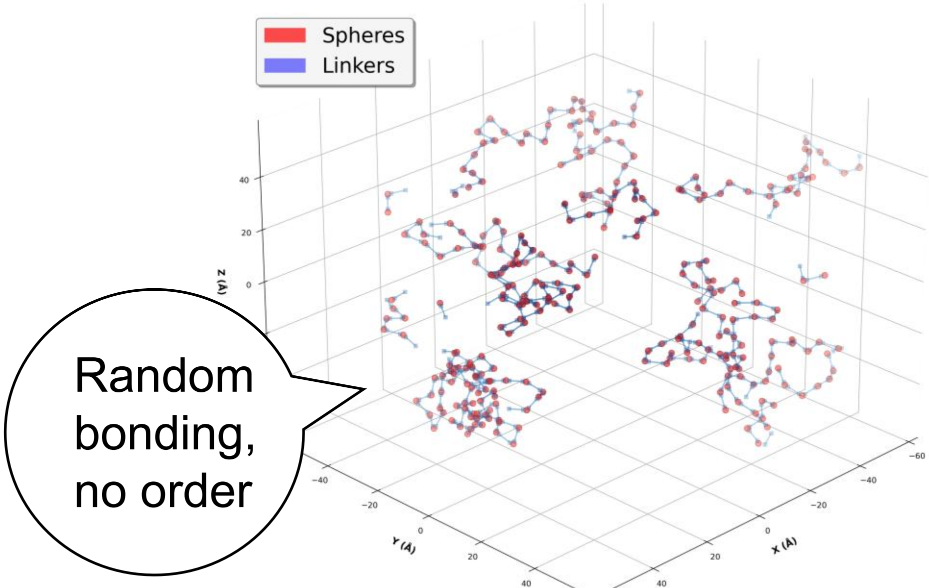
Scenario	Constraints	Φ_viable	S_4	Φ_target
1	Valence only	26%	24%	6%
2	+ Bond angle	48%	47%	6%
3	+ Coplanarity	94%	57%	<1%
4	Both	**97%**	**80%**	**<1%**

High S_4 achieved, but Φ_target remains very low

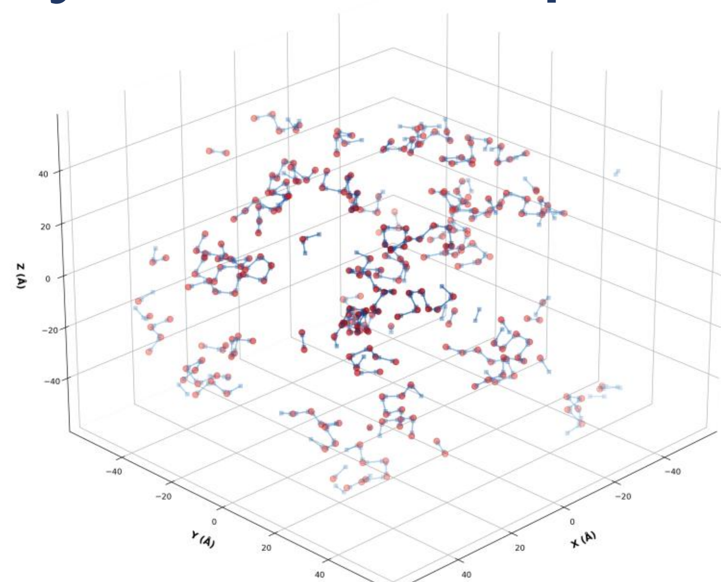


Can post-bond stabilization improve yield?

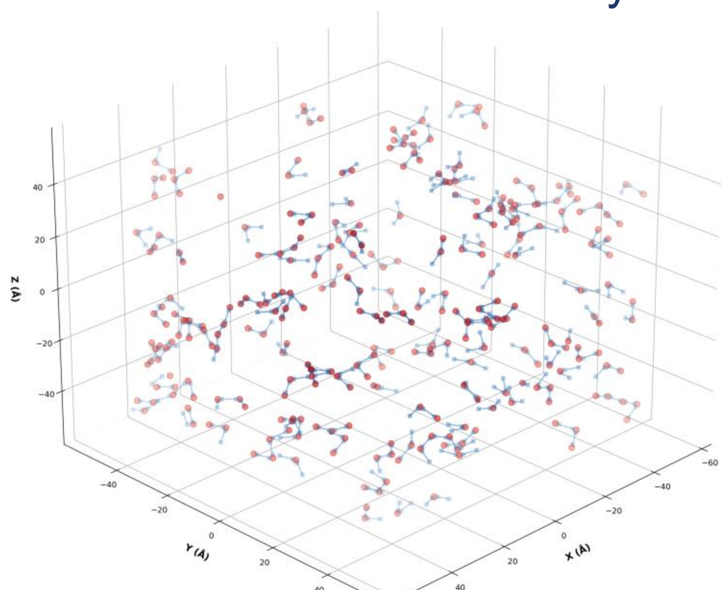
■Scenario1-4: Steady State Snapshots



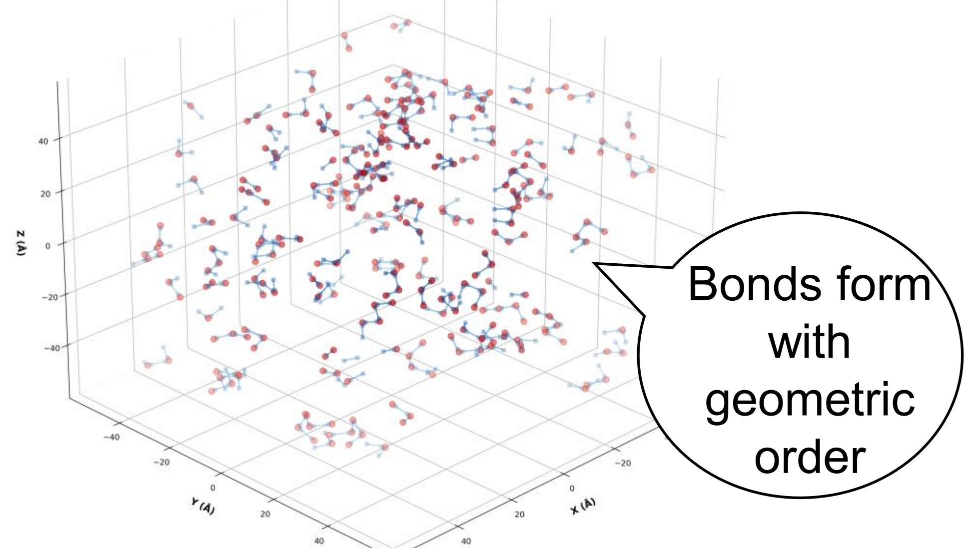
Scenario1: Valence only



Scenario2: +Bond Angle



Scenario3: +Coplanarity



Scenario3: Both

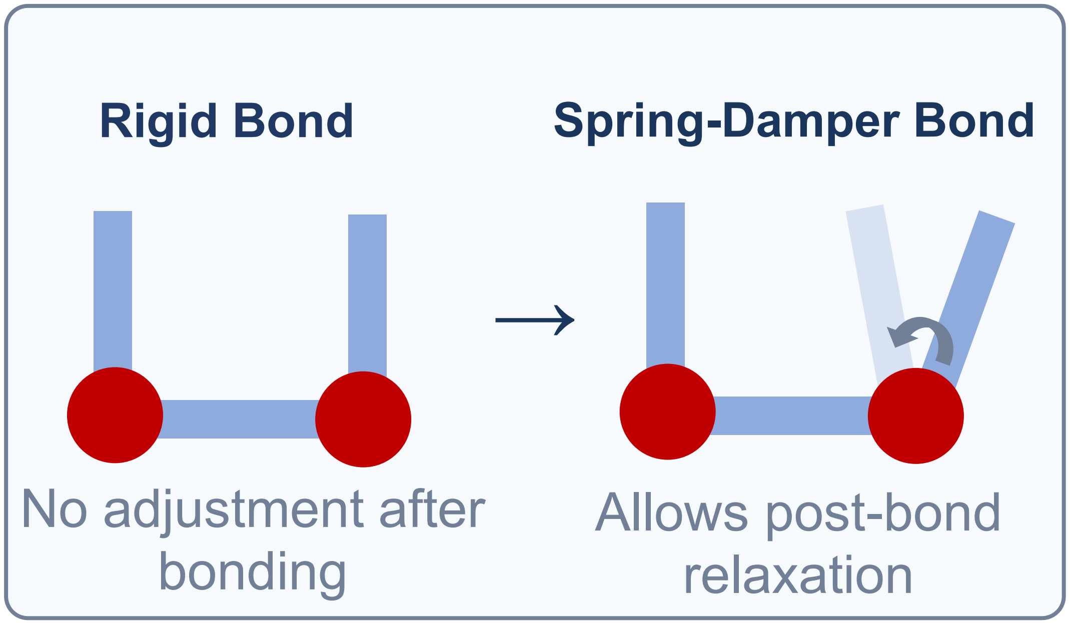
■ Compliant Bonds: 19× Target Yield Improvement

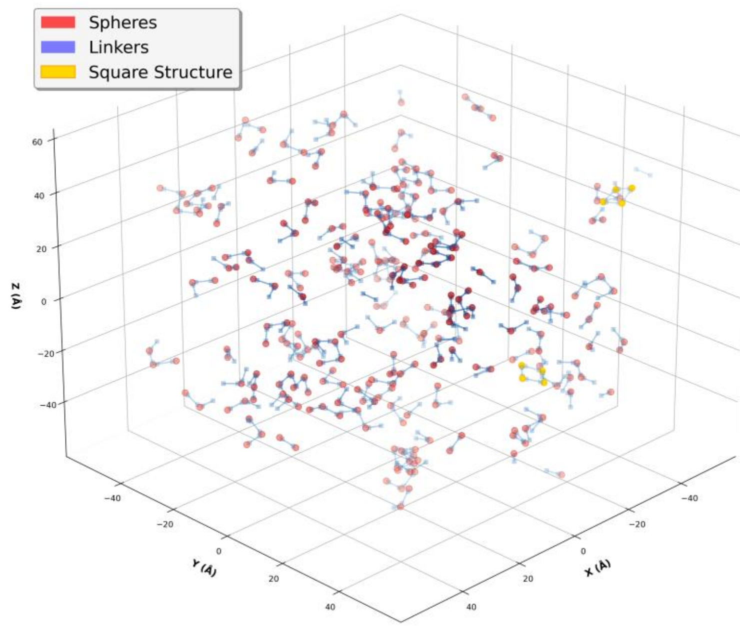
☐ Scenario 5: Spring-Damper Bonds

Bonds can flex and relax into stable configurations

Scenario	Description	Φ_viable	S_4	Φ_target
4	Rigid constraints	97%	80%	0.37%
5	+ Spring-damper	92%	85%	**6.97%**

19× increase in Φ_target (0.37% → 6.97%)





→ What about collision frequency (density)?

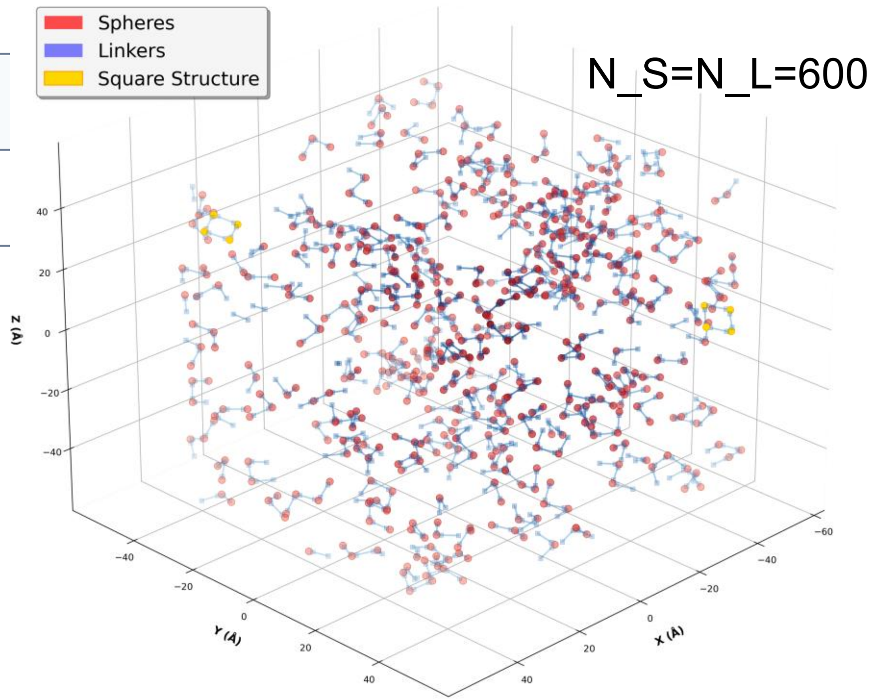
■ High Density: Accelerated While Maintaining Selectivity

□ Scenario 6: Density Sweep

Same as Scenario 4 (rigid bonds + θ, φ constraints)
Box size fixed at 50^3
Increase N_S and N_L → higher density

N_S = N_L	τ_target	S_4	Φ_viable
150	3280	84%	100%
300	2340	80%	97%
600	**2040**	83%	95%

Higher density → faster τ (target formation)
S_4 stable at 80–84%
Viable fraction remains high



→ These results suggest synergy of three elements...

Three Elements for Selective Macrocyclization

1
Strict Local Geometry

Bond angle + Coplanarity

Φ_viable: 26% → 97%

S_4: 80%

2
Post-Bond Stabilization

Spring-Damper mechanism

Φ_target: 0.4% → 7%

τ reduced 4×

3
Appropriate Collision Frequency

Density control

Accelerated formation

S_4 maintained: 80–84%

Selectivity emerges from the synergy of all three elements

■ Future Directions

☐ Parameter Mapping to Experiments

Correspondence with angular rigidity, hemilabile lifetime, linker ratios

☐ Extended Architectures

Multi-component systems, templates, alternative ring sizes

☐ Pathway Analysis

Trajectory descriptors: path entropy, kinetic funneling

This minimal model framework can be extended to diverse assembly problems

References

[1] Martí-Centelles, V., Pandey, M.D., Burguete, M.I., Luis, S.V.: Macrocyclization Reactions: The Importance of Conformational, Configurational, and Template-Induced Preorganization. Chemical Reviews 115, 8736–8834 (2015)

[2] Iwamoto, T., Amano, S., Maeda, K., et al.: Exclusive macrocyclization through multiple Si–O bond formations from diol and dichlorosilane. Chemical Communications 61, 8180–8183 (2025)

[3] NVIDIA PhysX. https://github.com/NVIDIA-Omniverse/PhysX/

[4] Chodera, J.D.: A Simple Method for Automated Equilibration Detection in Molecular Simulations. J. Chem. Theory Comput. 12, 1799–1805 (2016)