

# **Steric Repulsion and London Dispersion**

Literature Seminar  
2022. 04. 30

Kyohei Takaoka

## 1. Introduction

- Parameters for Steric Effect
- Computational chemistry

## 2. Quantum Chemical Computation to Separate London Dispersion Effect



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Article

### London Dispersion Helps Refine Steric A-Values: Dispersion Energy Donor Scales

Ephrath Solel, Marcel Ruth, and Peter R. Schreiner\*

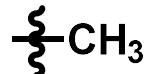
## **1. Introduction**

- **Parameters for Steric Effect**
- Computational chemistry

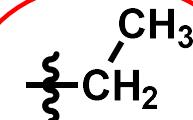
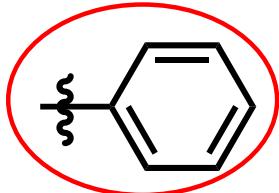
## **2. Quantum Chemical Computation to Separate London Dispersion Effect**

# Size of the Group

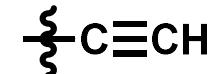
- Which group is larger?



or



or

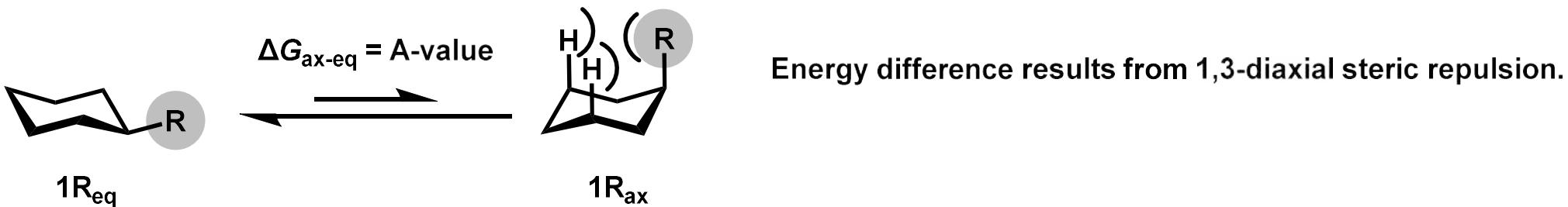


- Parameters to express the size of the group

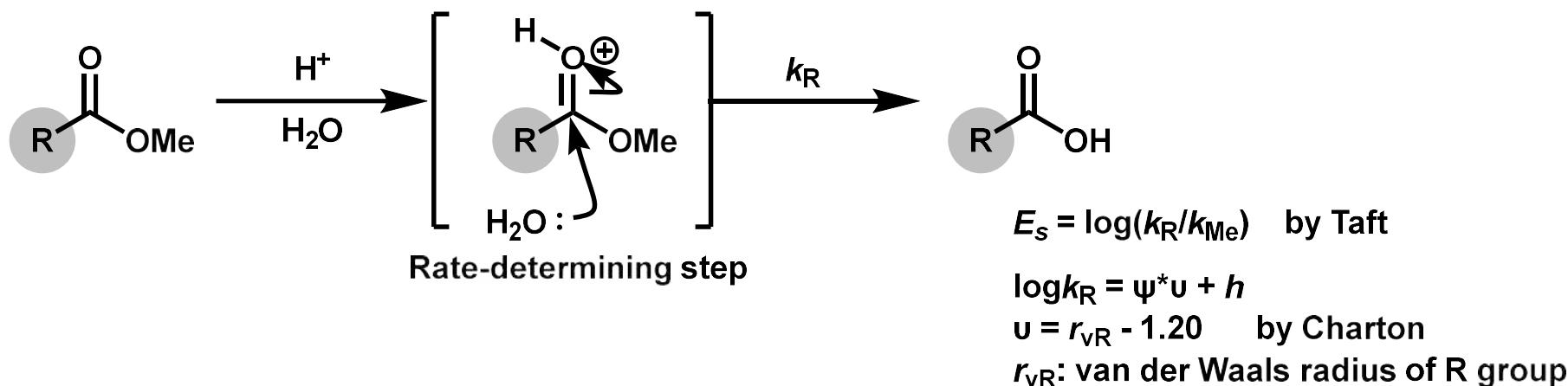
- A-value** Most widely used in organic chemistry
- Taft-Charton parameters**
- Tolman cone angles**
- Interference values**
- Sterimol parameters** Introduced in the main paper

# Size Parameters (1)

- A-value (experimental parameter by Winstein and Holness, 1955)



- Taft-Charton parameters (experimental (by Taft, 1952) to computational (by Charton, 1975))

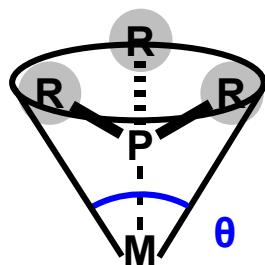


Widely used in quantitative structure-activity relationship (QSAR) study.

1. Harper, K. C.; Bess, E. N.; Sigman, M. S. *Nat. Chem.* **2012**, 4, 366.
2. B. S. Winstein, N. J. Holness, *J. Am. Chem. Soc.*, **1955**, 77, 5562.
3. Charton, M. *J. Am. Chem. Soc.* **1975**, 97, 1552.

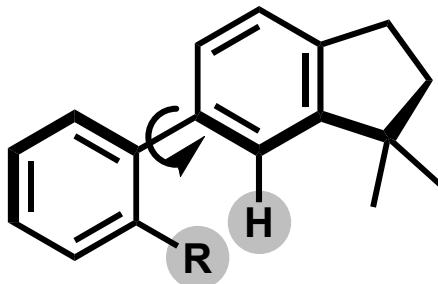
# Size Parameters (2)

- Tolman cone angles (experimental/computational parameters by Tolman, 2010)

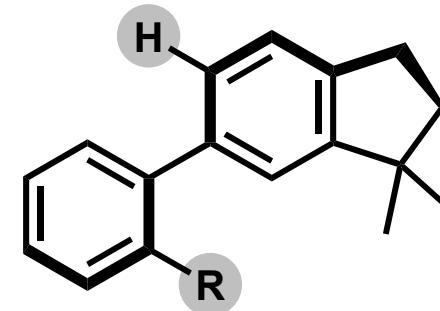


Applied to the phosphine ligands.

- Interference values (experimental parameters by Bott, 1980)



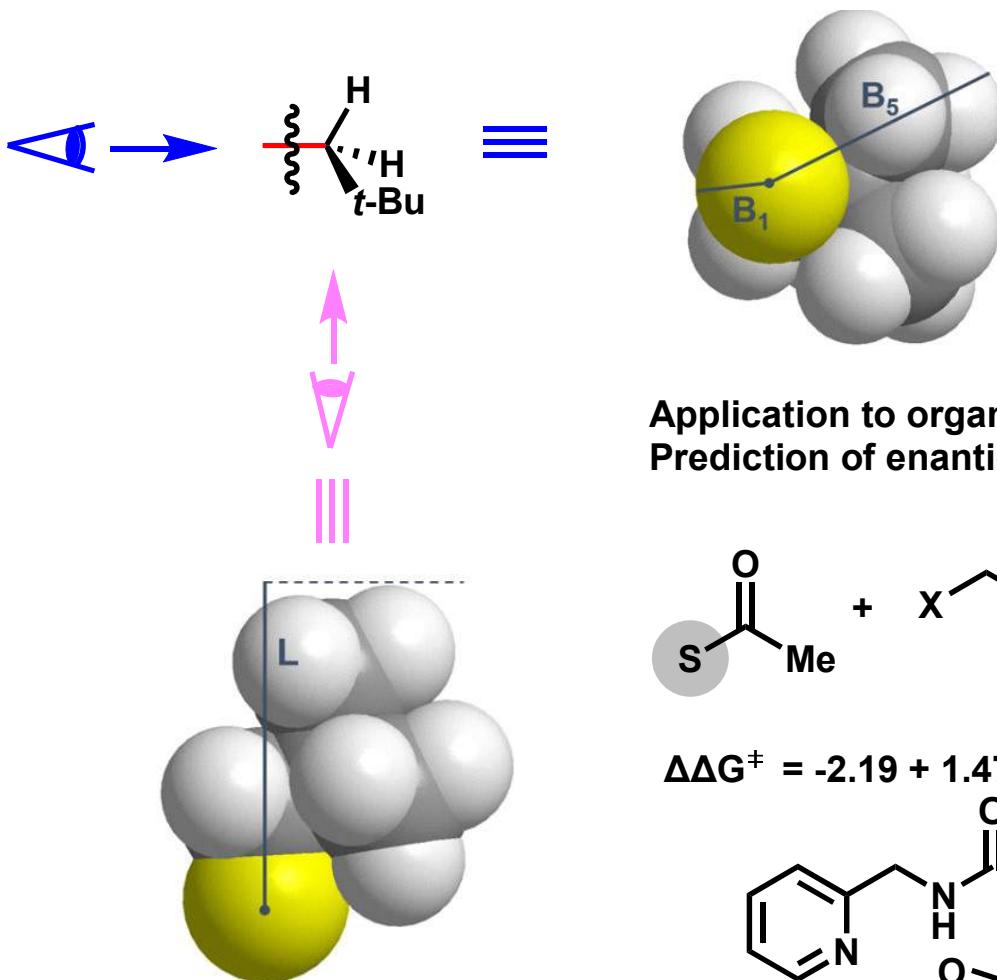
*rotation barrier  $\Delta H$  (kJ/mol)  
= interference value*



1. Harper, K. C.; Bess, E. N.; Sigman, M. S. *Nat. Chem.* **2012**, *4*, 366.
2. Niksch, T.; Gorls, H.; Wiegand, W. *Eur. J. Inorg. Chem.* **2010**, *95*.
3. Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618.

# Size Parameters (3)

- Sterimol parameters (computational parameters by Verloop, 1976)

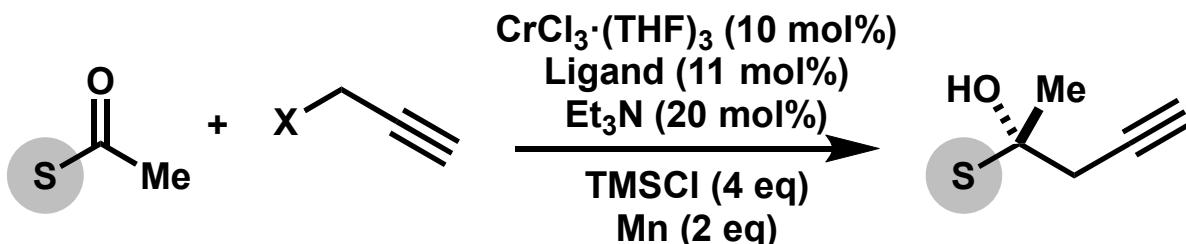


**L: Length of the group  
along the red bond  
In  $\text{CH}_2t\text{-Bu}$ ,  $L = 4.89$**

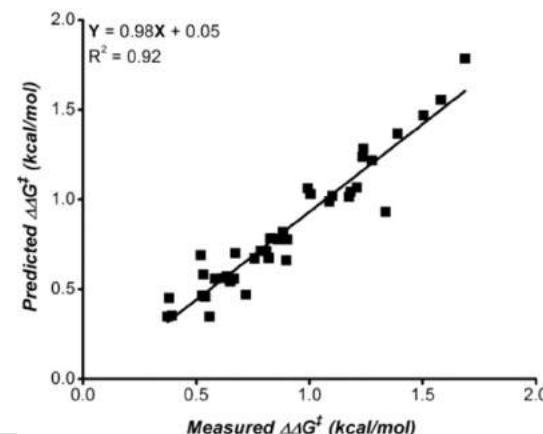
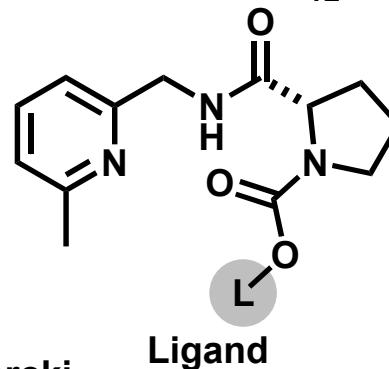
In details, see 140719\_LS\_Hidenori\_Todoroki.

Looking from the red bond,  
 $B_1$ : Minimum width of the group  
 $B_5$ : Maximum width of the group  
In  $\text{CH}_2t\text{-Bu}$ ,  $B_1 = 1.52$ ,  $B_5 = 4.18$

Application to organic chemistry:  
Prediction of enantioselectivity of the catalyst

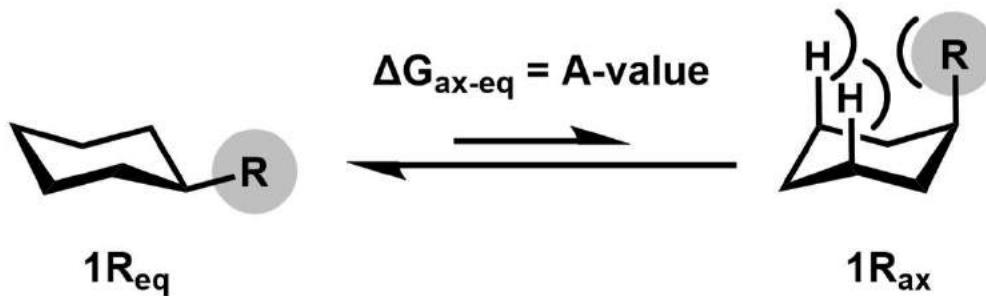


$$\Delta\Delta G^\ddagger = -2.19 + 1.47B_{1L} + 0.94B_{1S} - 0.27B_{1L}B_{1S} - 0.09B_{1L}B_{5S}$$



- Verloop, A. in *Drug Design* Vol. III (ed. Ariens, E. J.) 133 (Academic Press, 1976).
- Harper, K. C.; Vilardi, S.C.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, 135, 2482.
- Bess, E. N.; DeLuka, R. J.; Tindall, D. J.; Oderinde, M. S.; Roizen, J. L.; Du Bois, J.; Sigman, M. S. *J. Am. Chem. Soc.* **2014**, 136, 5783.

# Feature of A-value



- Different value in different conditions (such as temperature, solvent and methods)
- A-value doesn't affect the size of the group simply. (Sometimes **conformation** affect the result, and other times **bond length** affect the result)

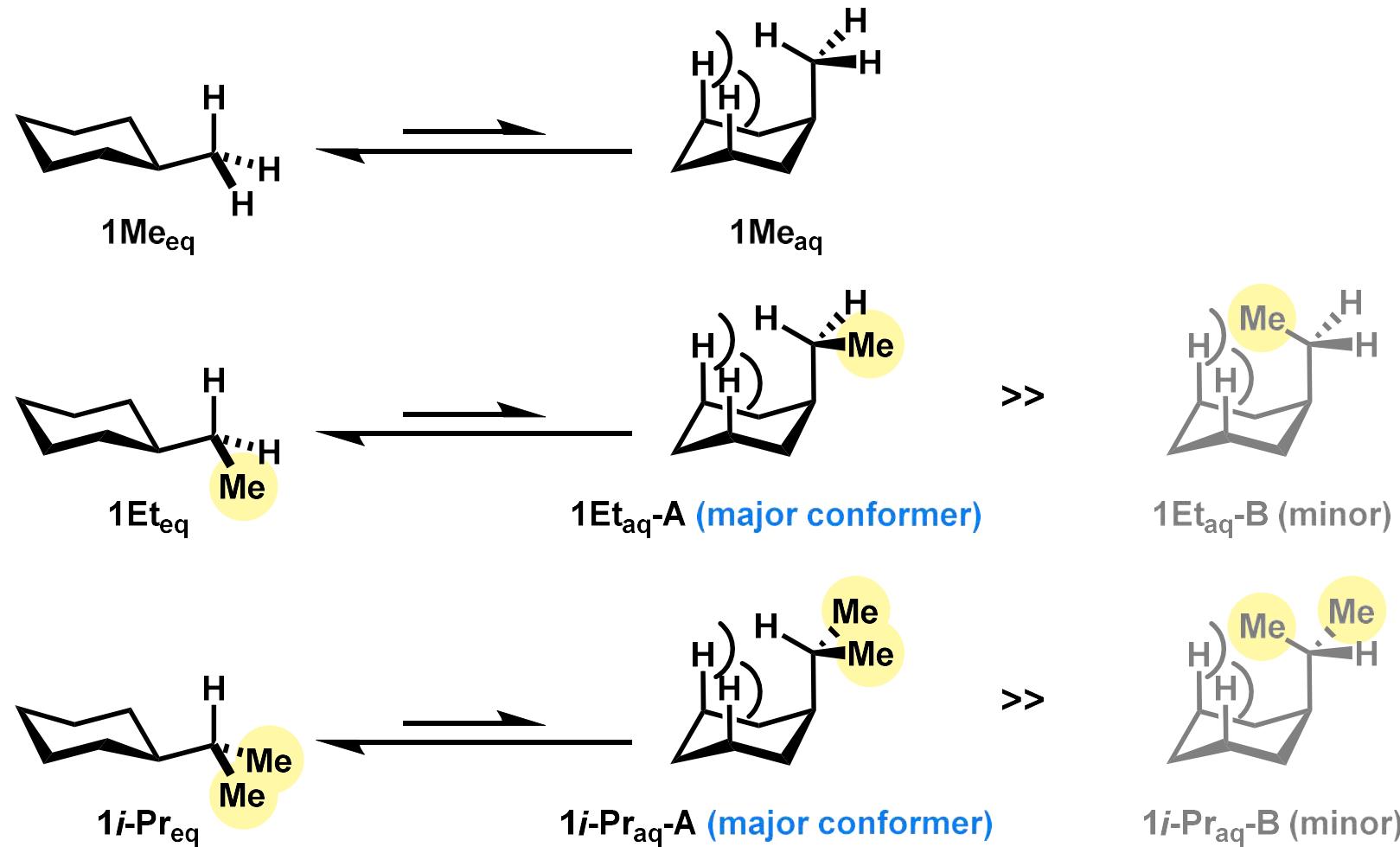
Table 1. Experimental A-Values (in kcal mol<sup>-1</sup>)

| R   | A-value <sup>48</sup> | A-value <sup>49</sup> | Length of C—X bond:   |
|-----|-----------------------|-----------------------|---|
| F   | 0.15                  | 0.25–0.42             | C—C: ~150 pm  |
| Cl  | 0.43                  | 0.53–0.64             | C—F: ~134 pm  |
| Br  | 0.38                  | 0.48–0.67             | C—Cl: ~176 pm   |
| I   | 0.43                  | 0.47–0.61             | C—Br: ~193 pm   |
| CN  | 0.17                  | 0.20                  | C—I: ~213 pm  |
| CCH | 0.41                  | 0.41–0.51             | A-value cannot affect the size of the group especially the bond length is long.<br>(A-value of SiMe <sub>3</sub> is about 2.5.) |
| Me  | 1.70                  | 1.74                  |   |
| Et  | 1.75                  | 1.79                  |   |
| iPr | 2.15                  | 2.21                  |   |
| tBu | >4                    | 4.7, 4.9              |   |
| Ph  | 3.00                  | 2.80                  |   |

- Solel, E.; Ruth, M.; Schreiner, P. R. *J. Am. Chem. Soc.* **2021**, 143, 20837.
- Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; John Wiley & Sons Inc: New York, **1975**; p 114.
- Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons Inc: New York, **1994**; pp 696–697.

# Conformation Affects A-value

- The Size of group: Me < Et < *i*-Pr < *t*-Bu, while A-value: Me (1.70) ~ Et (1.75) < *i*-Pr (2.15) << *t*-Bu (>4)



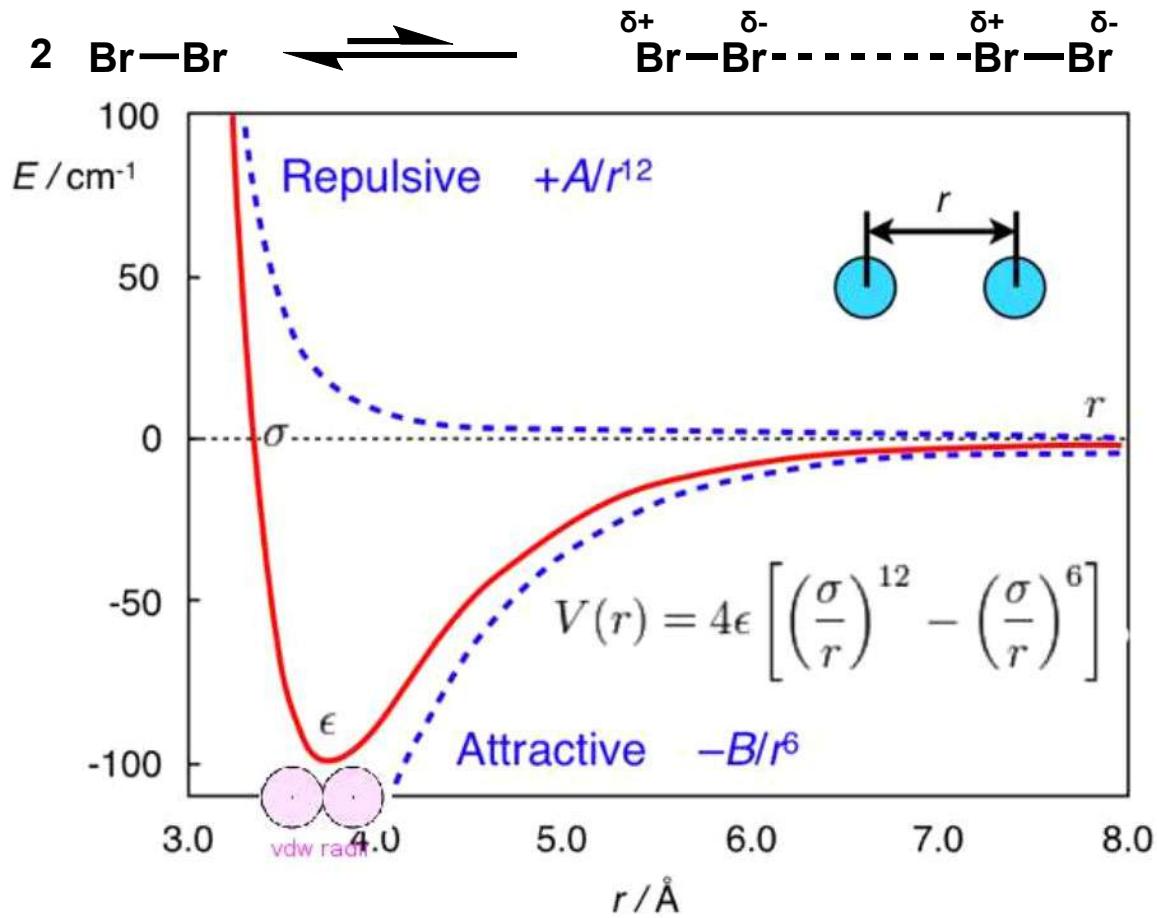
Since Et and *i*-Pr can rotate to minimize the steric repulsion, 1,3 diaxial interaction almost unchanged in axial conformer of Me, Et, *i*-Pr. → Small change in A-value

Same effect was observed in Taft-Charton parameters.

1. Solel, E.; Ruth, M.; Schreiner, P. R. *J. Am. Chem. Soc.* **2021**, 143, 20837.
2. Booth, H. Everett, J. R. *J. Chem. Soc. Perkin Trans. 2*, **1980**, 2, 255.

# Dispersion Stabilization

London dispersion: Attractive interaction between non-polarized compounds

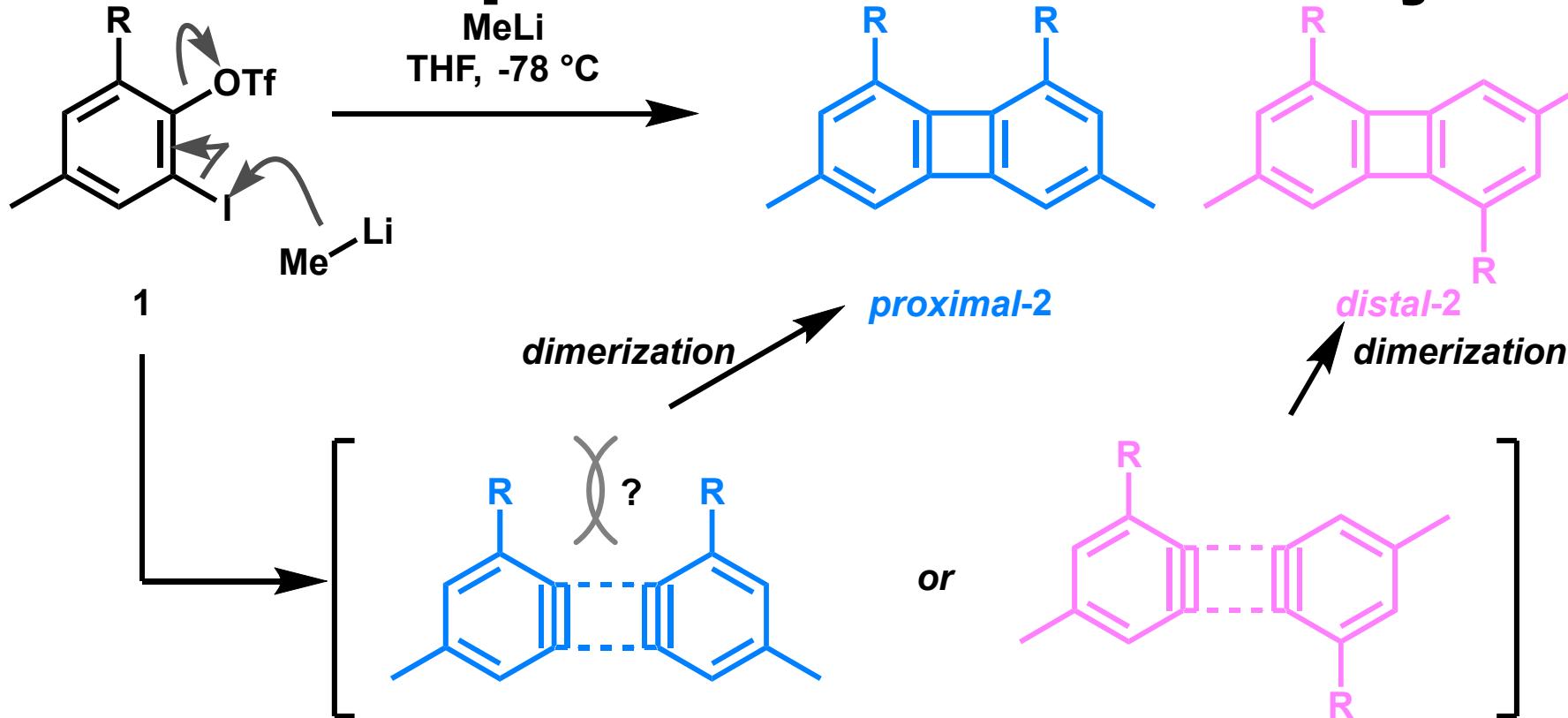


In Lennard-Jones potential, steric repulsion decays as  $r^{-12}$ , while London dispersion decays as  $r^{-6}$ .  
→ In appropriate distance, attractive interaction will be larger.

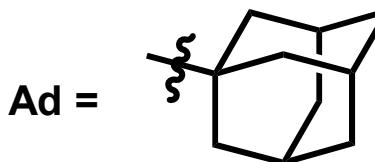
Comparing with other attractive interactions (dipole-dipole forces and dipole-induced dipole forces), London dispersion is weak interaction. → **London dispersion is commonly ignored.**

There is no common parameters for dispersion effect.

# Dispersion Affects Reactivity



| R                | proximal : distal | yield |
|------------------|-------------------|-------|
| R = Me           | 1.1: 1            | 36%   |
| R = <i>t</i> -Bu | 16: 1             | 52%   |
| R = Ad           | >20: 1            | 54%   |
| R = Ad*          | >20: 1            | 74%   |



In larger group, higher reactivity and regioselectivity  
(the regioselectivity is counterintuitive; more repulsive *proximal*-2 was a major product).

→ London dispersion overcomes steric repulsion in this reaction.

\* OTs was used instead of OTf

## **1. Introduction**

- Parameters for Steric Effect
- Computational chemistry (for understanding the main paper)

## **2. Quantum Chemical Computation to Separate London Dispersion Effect**

# Computational Chemistry (1)

· Schrödinger equation

$$H\Psi = E\Psi$$

$$H = T_N + T_e + V_{Ne} + V_{ee} + V_{NN}$$

H: Hamiltonian, E: Energy,  $\Psi$ : Wave function

$T_N$ : Total kinetic energy of atomic nuclei

$T_e$ : Total kinetic energy of electrons

$V_{Ne}$ : Total potential energy between atomic nuclei and electrons

$V_{ee}$ : Total potential energy between two electrons

$V_{NN}$ : Total potential energy between two atom nuclei

To solve the wave function, some approximation is needed.

Examples of approximation:

**Born-Oppenheimer approximation:** Regard  $T_e$  as 0. (Electrons moves very faster than atomic nuclei)

$$H \sim T_e + V_{Ne} + V_{ee} + V_{NN}$$

$$H = -\sum_i^{N_{elec}} \frac{1}{2} \nabla_i^2 - \sum_i^{N_{elec}} \sum_I^{N_{nuc}} \frac{Z_I}{|r_i - R_I|} + \sum_{i>j}^{N_{elec}} \frac{1}{|r_i - r_j|} + \sum_{I>J}^{N_{nuc}} \frac{Z_I Z_J}{|R_I - R_J|}$$

With this approximation, we can solve the wave function of hydrogen-like atoms (H, He<sup>+</sup>, Li<sup>2+</sup>, ...).

**LCAO (Linear Combination of Atomic Orbitals):**

$$\phi_i = \sum_r c_{ri} \chi_r$$

$\phi_i$ : Molecular orbital

$\chi_r$ : Atomic orbital

# Computational Chemistry (2)

In computational chemistry, information of functionals and basis sets is important.

For example...

B3LYP/def2-TZVPP

Functionals

How to solve  
Schrödinger equation?

Basis sets

How many atomic orbitals  
do you use?

Functionals: There are mainly three methods (*ab initio* method, semi-empirical method, density functional theory (DFT) method)

*ab initio* method, semi-empirical method: Solve Schrödinger equation with approximation. Time complexity and the accuracy is in trade-off relationships.

e.g. MP2, HF, CCSD, CCSD(T), CISD, ...

Time complexity: HF ( $O(N^3)$ ) < MP2 ( $O(N^4)$ ) < CCSD ( $O(N^6)$ ) < CCSD(T) ( $O(N^7)$ )

CCSD(T) is used as high precision calculation.

DFT method: Solve Kohn-Sham equation instead of Schrödinger equation. c.f. Hohenberg-Kohn theorem  
e.g. B3LYP, M06, ...

**Time complexity is as same as HF method, but accuracy is as same as MP2.**

In DFT, dispersion effect is neglected, so dispersion correction is sometimes used (such as D3BJ).

# Computational Chemistry (3)

In computational chemistry, information of functionals and basis sets is important.

For example...

B3LYP/def2-TZVPP

Functionals

How to solve  
Schrödinger equation?

Basis sets

How many atomic orbitals  
do you use?

Basis sets: Atomic orbitals that uses in LCAO approximation. There are some variety in this orbital.

STO (Slater type orbital): Accurate atomic orbital

GTO (Gaussian type orbital): Easy to calculate. For example, Pople type (such as 6-311G), Correlation consistent basis sets (such as cc-pVTZ), Karlsruhe type (def2-TZVPP)

Minimum basis set (STO-3G, STO-2G): H (1s), C (1s, 2s, 2p<sub>x</sub>, 2p<sub>y</sub>, 2p<sub>z</sub>)

For further accuracy, Split-valence basis sets, polarization functions and diffuse functions are used.

Split-valence basis sets (6-31G, 6-311G, cc-V<sub>D</sub>Z, cc-pV<sub>T</sub>Z): Use same orbitals. (double zeta means H (1s, 1s), C (1s, 1s, 2s, 2s, ...))

Polarization functionals (6-31G\*, cc-pV<sub>D</sub>Z): Add bigger orbitals (H (1s, 2s, 1p), C (1s, ..., 4s, 3p, 2d))

Diffuse functions (6-31<sub>+</sub>G\*, aug-cc-pV<sub>D</sub>Z)

Single point computation: Methods of conformational optimization and energy calculation are different.  
(B3LYP-D3BJ/def2-TZVPP(energy calculation)//MP2/aug-cc-pV<sub>T</sub>Z(conformational optimization))

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Article

### London Dispersion Helps Refine Steric A-Values: Dispersion Energy Donor Scales

Ephrath Solel, Marcel Ruth, and Peter R. Schreiner\*

# **Prof. Peter R. Schreiner**



**Prof. Peter R. Schreiner**

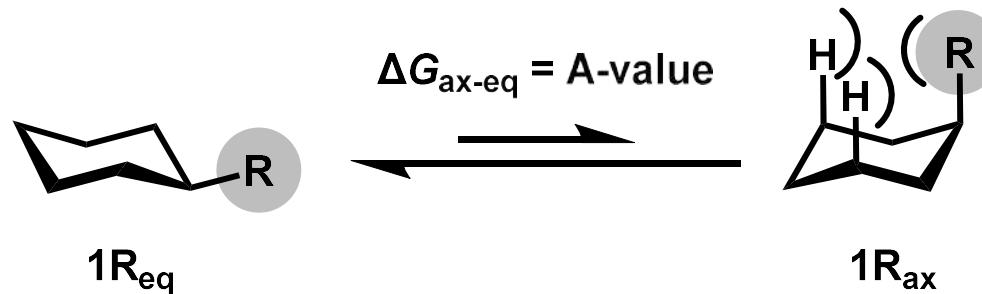
**Career:**

- 1995:** Ph. D. @University of Georgia Athens, USA  
(Prof. Henry F. Schaefer III)
- 1995-1996:** Project coordinator, The Encyclopedia of Computational Chemistry
- 1996-1999:** Habilitand @Gerg-August-Universität Göttingen
- 1999-2002:** Associate Professor  
@University of Georgia, Athens, USA
- 2002-:** Professor @University of Georgia, Athens, USA

**Research Interests:**

**Organocatalysis, Reactive intermediates, Nanodiamonds, Computational chemistry, Tunneling studies, Dispersion**

# Prof. Schreiner's Concept



$$\Delta G_{ax-eq} = (\text{Steric hindrance}) + (\text{Dispersion stabilization})$$

In experimentally  
separation of these two effects is difficult.

Steric hindrance  
(A lot of parameters)

Dispersion stabilization  
(no parameter so far)

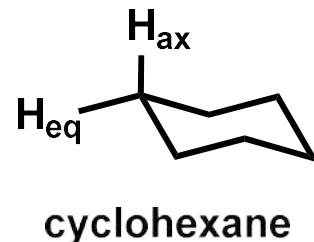
Is it possible to separate these two effects by using computational chemistry?

# Benchmark Study (1)

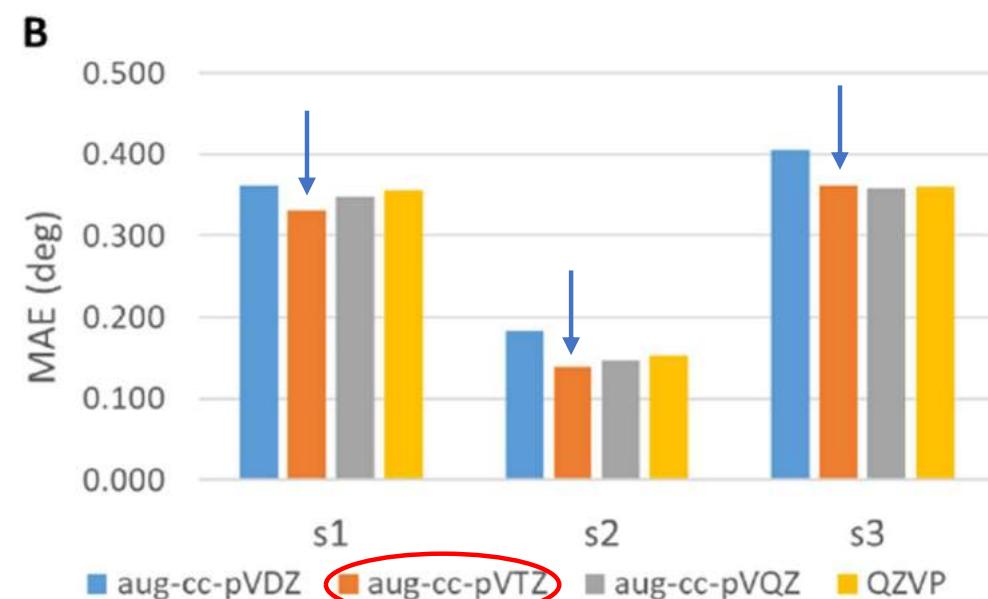
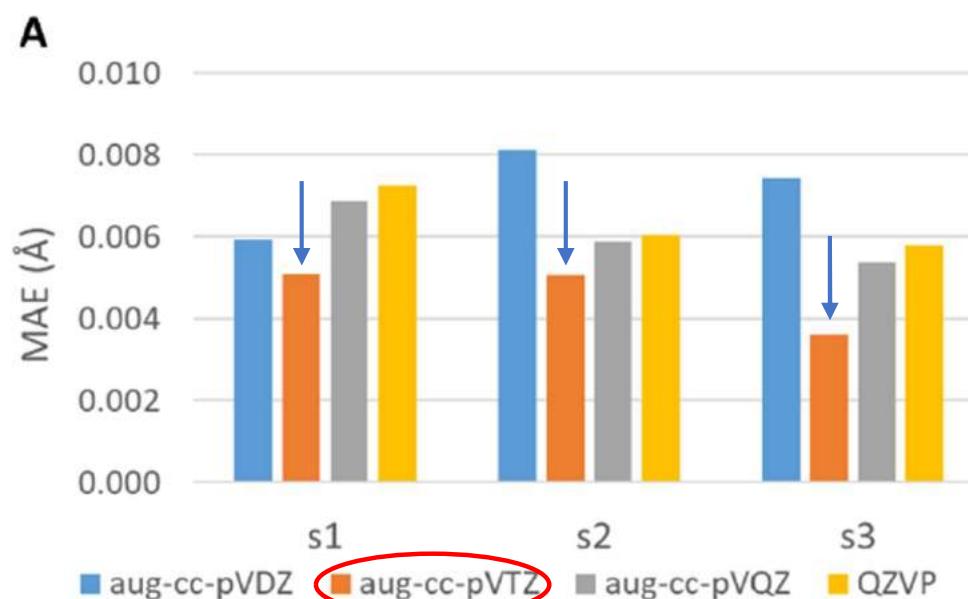
## Basis Set Optimization for Structure

To choose appropriate computational methods for structure optimization, author compared calculated structure with experimental structure of cyclohexane.

Mean absolute error (MAE) of length and angle were compared.



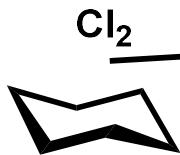
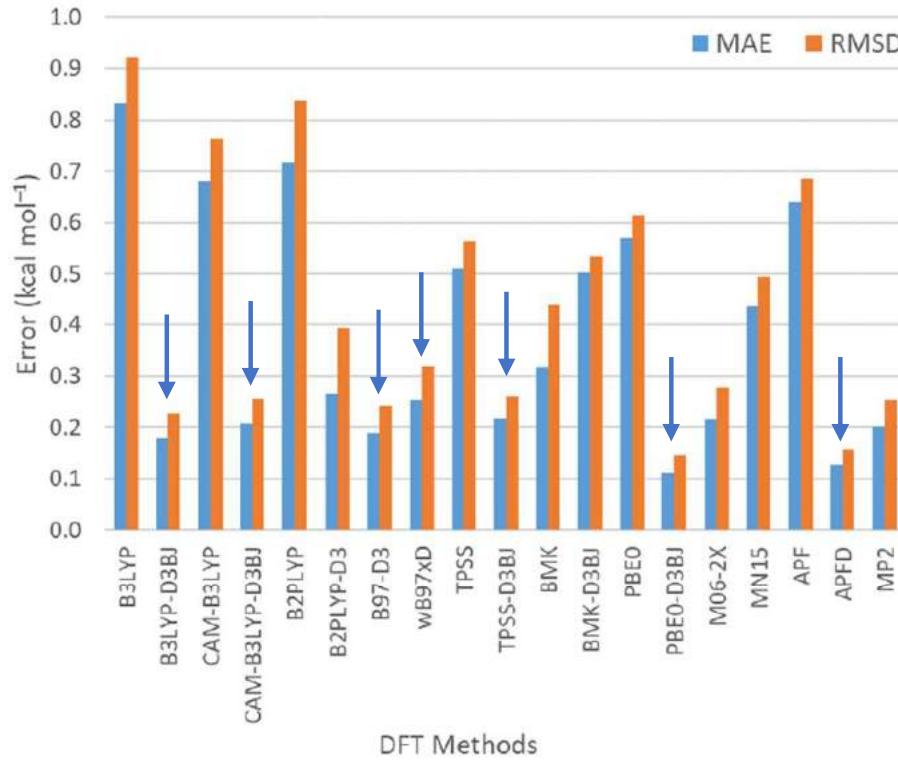
Length: C-C bond, C-H<sub>ax</sub> bond, C-H<sub>eq</sub> bond  
Angle: C-C-C, H-C-H, C-C-H<sub>ax</sub>, C-C-H<sub>eq</sub>



In organic molecules, MP2 *ab initio* method is suitable for getting accurate geometries.  
→ MP2/aug-cc-pVTZ was chosen.

# Benchmark Study (2)

## DFT Functional Optimization for Energy



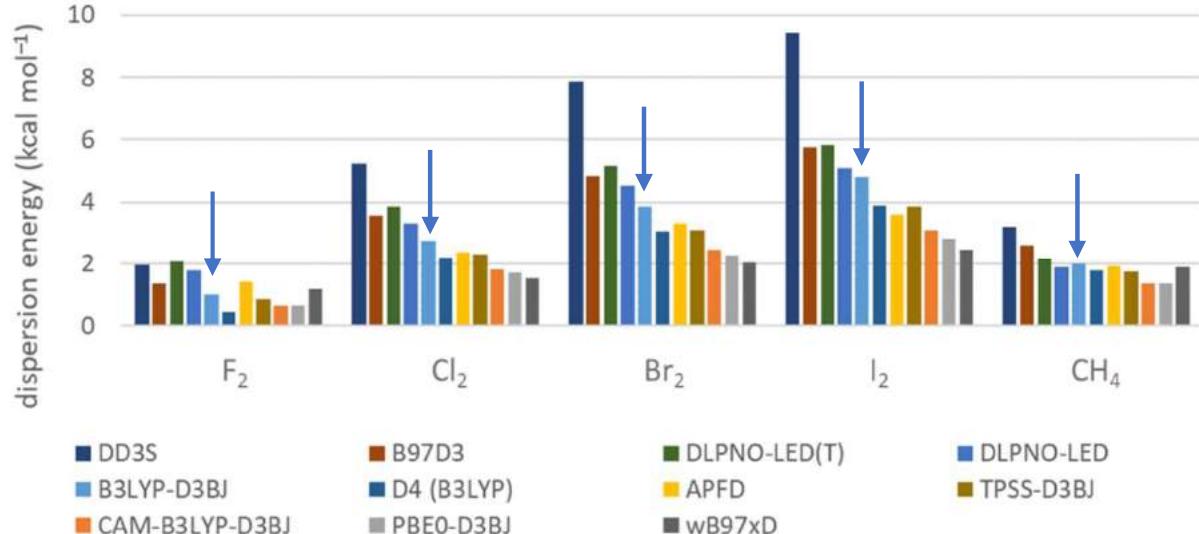
Dispersion energy between cyclohexane and some molecules was calculated. The energies were compared with DLPNO-LED.

→ B3LYP-D3BJ was the best.



Calculated energies of various monosubstituted cyclohexane were compared with DLNPO-CCSD(T)/aug-cc-pVQZ energy.

→ Some of the best performing functionals were selected to next step, quantification of dispersion step.



From here, the single energy computation was conducted at B3LYP/def2-TZVPP//MP2/aug-cc-pVTZ or B3LYP-D3BJ/def2-TZVPP//MP2aug-cc-pVTZ unless otherwise are noted.

# Simple Calculation

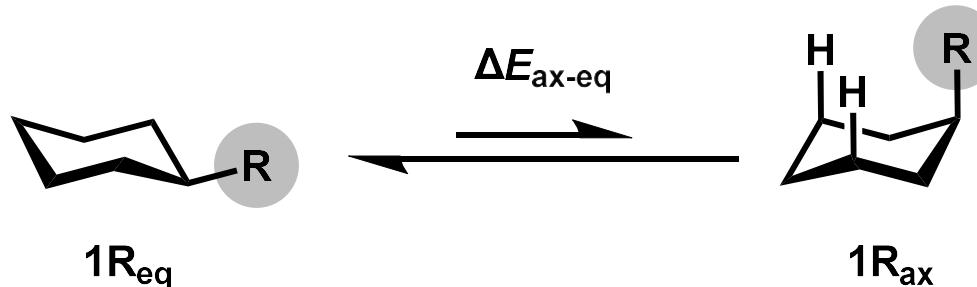


Table 2. Computed Electronic Energy Differences (kcal mol<sup>-1</sup>) between the Axial and Equatorial Conformers with and without LD Corrections<sup>a</sup>

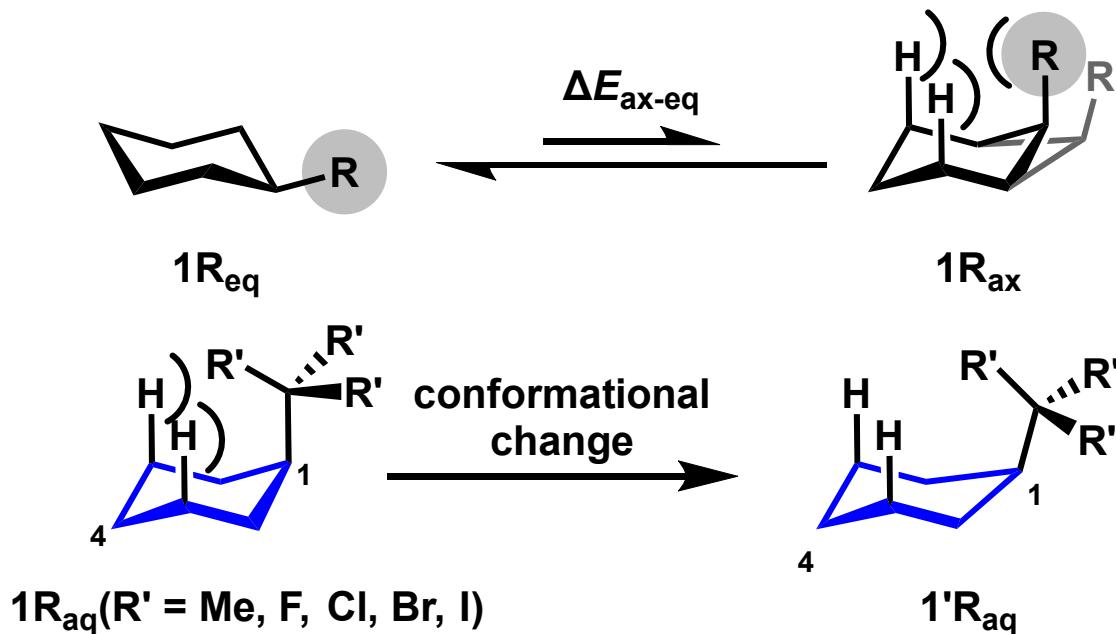
| R                 | $\Delta E_{\text{ax-eq}}$ (B3LYP) <sup>b</sup> | $\Delta E_{\text{ax-eq}}$ (B3LYP-D3BJ) <sup>b</sup> | $\Delta E^{\text{disp}}_{\text{ax-eq}}$ <sup>a</sup> |
|-------------------|--|---|--|
| F                 | 0.29   | 0.23  | 0.06   |
| Cl                | 0.98   | 0.30  | 0.68   |
| Br                | 1.24   | 0.34  | 0.90   |
| I                 | 1.43   | 0.25  | 1.18   |
| CCH               | 1.15   | 0.34  | 0.82   |
| CN                | 0.81   | 0.04  | 0.77   |
| Me                | 2.34   | 1.73  | 0.61   |
| Et                | 2.44   | 1.60  | 0.84   |
| iPr               | 2.46   | 1.37  | 1.09   |
| tBu               | 5.70   | 4.68  | 1.02   |
| Ph                | 4.35   | 2.89  | 1.46   |
| CF <sub>3</sub>   | 2.57   | 2.07  | 0.50   |
| CCl <sub>3</sub>  | 5.15   | 4.26  | 0.89   |
| CBr <sub>3</sub>  | 6.02   | 4.97  | 1.05   |
| CI <sub>3</sub>   | 7.05   | 5.89  | 1.16   |
| SiMe <sub>3</sub> | 3.42   | 1.98  | 1.44   |

To compute the dispersion energy part ( $\Delta E^{\text{disp}}_{\text{ax-eq}}$ ), energy difference between  $\Delta E_{\text{ax-eq}}$  (B3LYP) and  $\Delta E_{\text{ax-eq}}$  (B3LYP-D3BJ) was calculated.

However,  $\Delta E^{\text{disp}}_{\text{ax-eq}}$  of t-Bu is smaller than i-Pr.  
Usually, larger group has larger dispersion energy.  
→ Counterintuitive result!

<sup>a</sup>  $\Delta E^{\text{disp}}_{\text{ax-eq}} = -\{\Delta E_{\text{ax-eq}} \text{ (B3LYP-D3BJ)} - \Delta E_{\text{ax-eq}} \text{ (B3LYP)}\}$  is the difference in energy between the dispersion uncorrected and corrected energies. <sup>b</sup> Single point energy computations with def2-TZVPP on the MP2/aug-cc-pVTZ optimized structures.

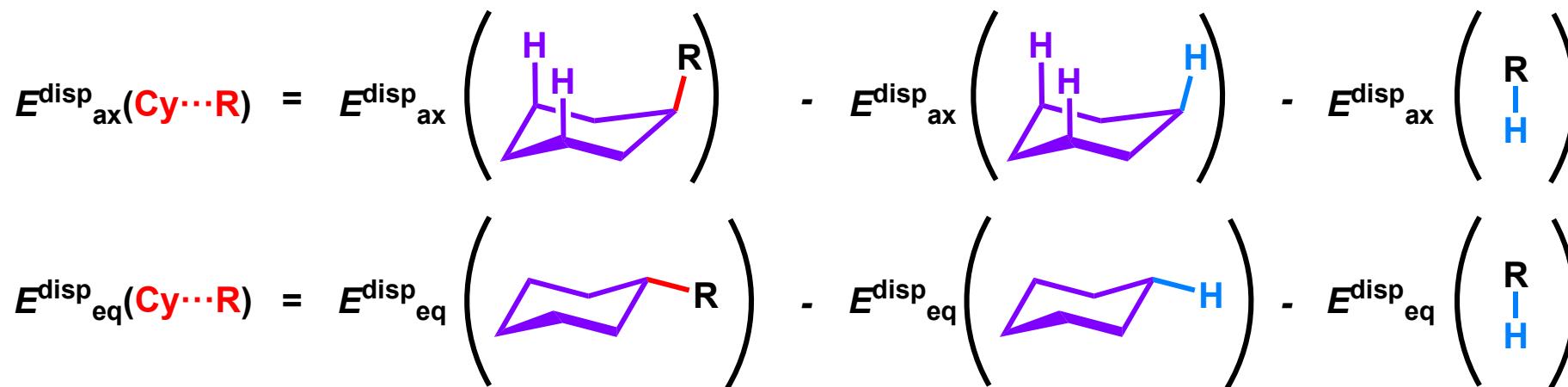
# Rationalization and Correction



Strain relieving deformation changes not only the interaction between R group and cyclohexyl moiety (Cy), but also other intrafragment interactions.  
→ Dispersion energy becomes lower.

At computational calculation,  
 $\angle \text{C4-C1-Me} = 108.6^\circ$   
 $\angle \text{C4-C1-t-Bu} = 120.6^\circ$   
 (MP2/aug-cc-pVTZ geometries)

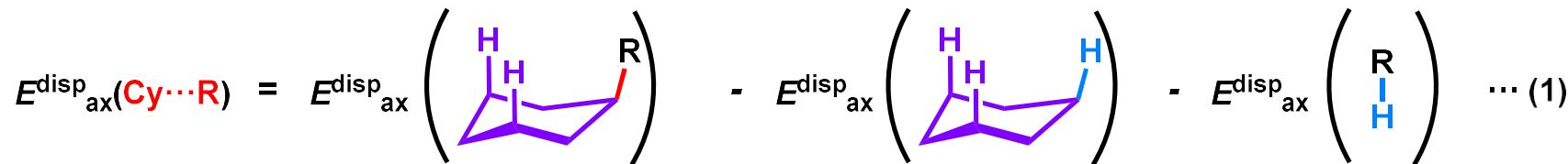
In order to isolate only the LD interaction between R and Cy, calculation was conducted as follows:



$$E^{\text{disp}} = - [E(\text{B3LYP}) - E(\text{B3LYP-D3BJ})]$$

$$\text{Dispersion energy } \Delta E^{\text{disp}}_{\text{ax-eq}} (\text{Cy}\cdots\text{R}) = E^{\text{disp}}_{\text{ax}}(\text{Cy}\cdots\text{R}) - E^{\text{disp}}_{\text{eq}}(\text{Cy}\cdots\text{R})$$

# Correction of Dispersion energy



| R                 | $\Delta E^{\text{disp}_{\text{ax-eq}}}$ | $\Delta E^{\text{disp}_{\text{ax-eq}}}$<br>(Cy) | $\Delta E^{\text{disp}_{\text{ax-eq}}}$<br>(R) | $\Delta E^{\text{disp}_{\text{ax-eq}}}$<br>(Cy $\cdots$ R) |
|-------------------|---|---|--|--|
| F                 | 0.06                                    | -0.04   | -  | 0.10   |
| Cl                | 0.68                                    | -0.06   | -  | 0.74   |
| Br                | 0.90                                    | -0.06   | -  | 0.96   |
| I                 | 1.18                                    | -0.06   | -  | 1.24   |
| CCH               | 0.82                                    | -0.03   | 0.00   | 0.85   |
| CN                | 0.77                                    | -0.03   | 0.00   | 0.80   |
| Me                | 0.61                                    | -0.08   | 0.00   | 0.70   |
| Et                | 0.84                                    | -0.07   | 0.00   | 0.90   |
| iPr               | 1.09                                    | -0.03   | 0.00   | 1.12   |
| tBu               | 1.02                                    | -0.21   | 0.02   | 1.20   |
| Ph                | 1.46                                    | -0.04   | 0.00   | 1.50   |
| CF <sub>3</sub>   | 0.50                                    | -0.16   | 0.00   | 0.66   |
| CCl <sub>3</sub>  | 0.89                                    | -0.25   | 0.01   | 1.13   |
| CBr <sub>3</sub>  | 1.05                                    | -0.26   | 0.01   | 1.30   |
| Cl <sub>3</sub>   | 1.16                                    | -0.28   | 0.02   | 1.42   |
| SiMe <sub>3</sub> | 1.44                                    | -0.10   | 0.04   | 1.49   |

$$E^{\text{disp}} = -[E(\text{B3LYP}) - E(\text{B3LYP-D3BJ})]$$

Dispersion energy  $\Delta E^{\text{disp}_{\text{ax-eq}}}(\text{Cy}\cdots\text{R}) = E^{\text{disp}_{\text{ax}}}(\text{Cy}\cdots\text{R}) - E^{\text{disp}_{\text{eq}}}(\text{Cy}\cdots\text{R})$

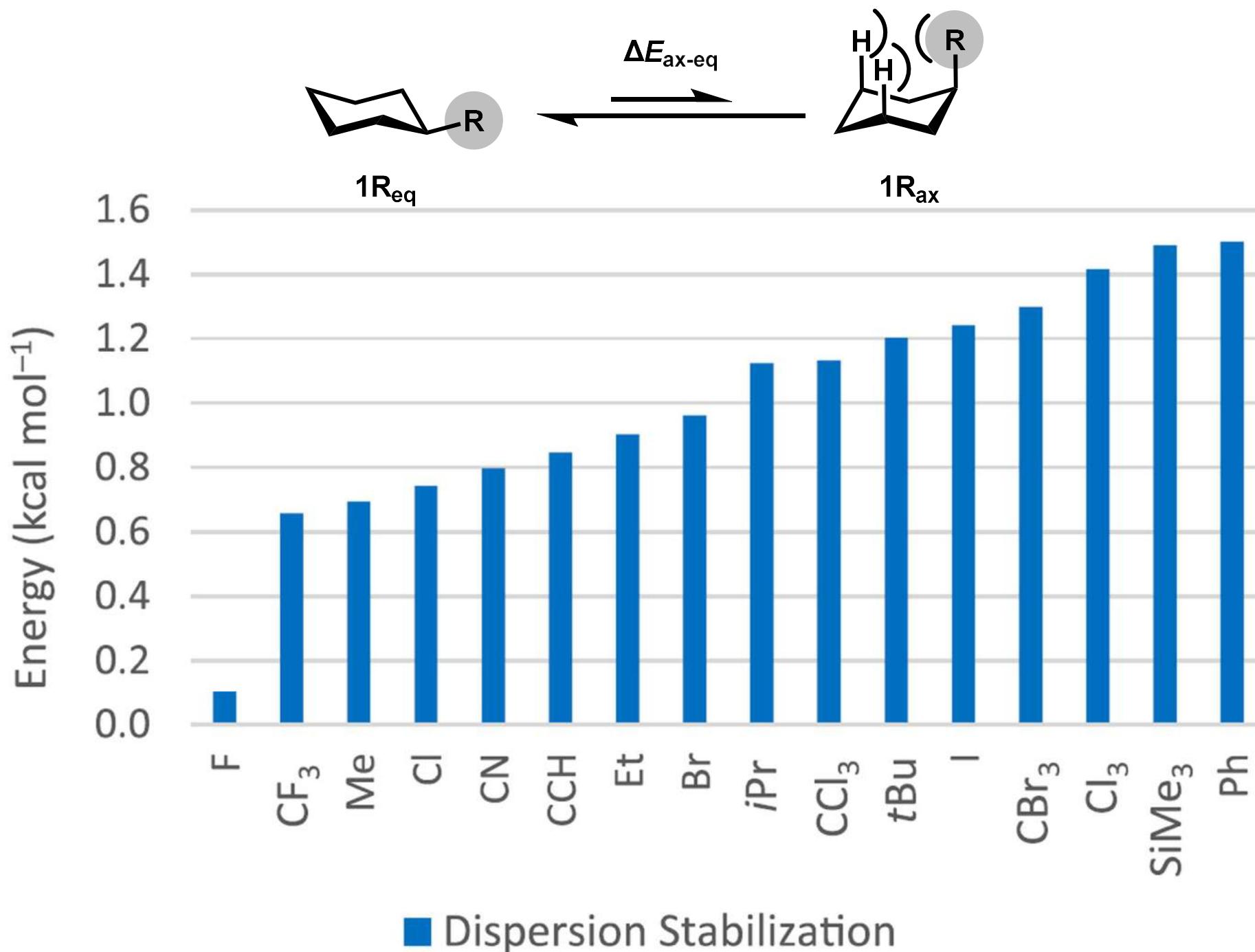
(1) - (2):

$$\Delta E^{\text{disp}_{\text{ax-eq}}}(\text{Cy}\cdots\text{R}) = \Delta E^{\text{disp}_{\text{ax-eq}}} - \Delta E^{\text{disp}_{\text{ax-eq}}}(\text{Cy}) - \Delta E^{\text{disp}_{\text{ax-eq}}}(\text{R})$$

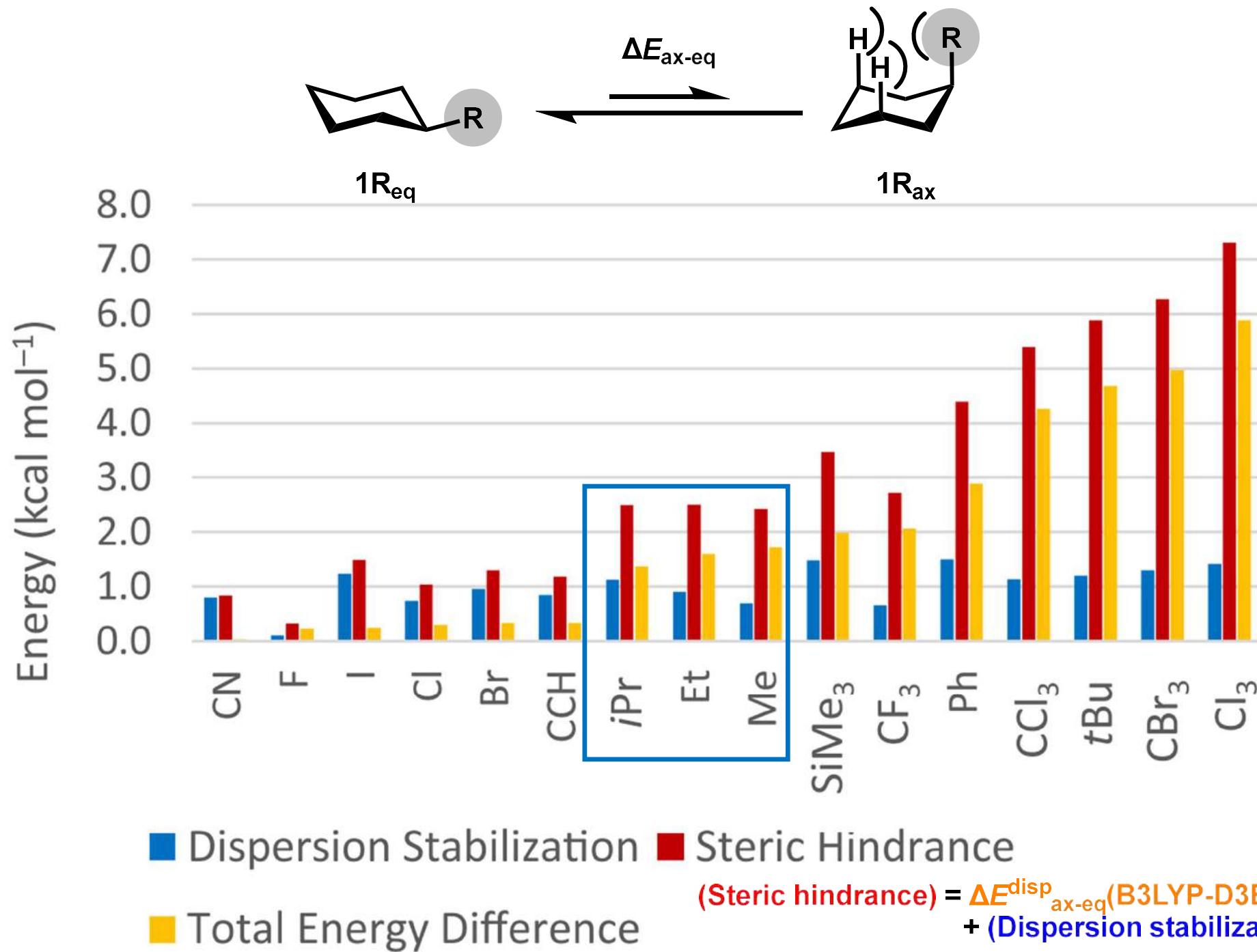
This correlation gave better result.

( $\Delta E^{\text{disp}_{\text{ax-eq}}}(\text{Cy}\cdots\text{R})$  of t-Bu is larger than that of i-Pr)

# Dispersion Effect of Monosubstituted Cyclohexane



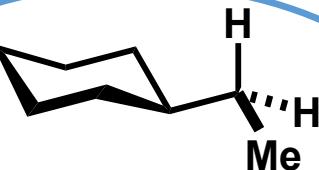
# Steric Effect in Monosubstituted Cyclohexane



# Why Me > Et > *i*-Pr?

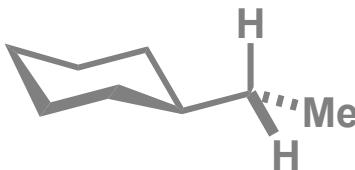
In Ethyl group, there can be 3 equatorial conformers.

Only the most stable  $1\text{Et}_{\text{eq}}\text{-A}$  is considered in the calculation.



$1\text{Et}_{\text{eq}}\text{-A}$

(one gauche interaction)



$1\text{Et}_{\text{eq}}\text{-A}_{\text{mirror}}$

(one gauche interaction)

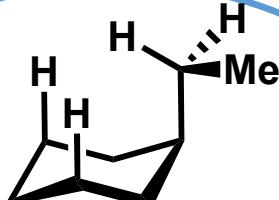


$1\text{Et}_{\text{eq}}\text{-B}$

(two gauche interaction)

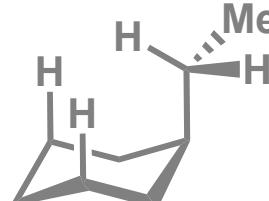
There can be 3 axial conformers.

Only the most stable  $1\text{Et}_{\text{ax}}\text{-A}$  is considered in the calculation.



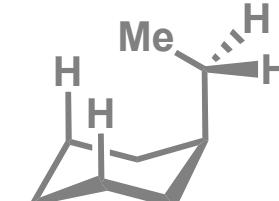
$1\text{Et}_{\text{ax}}\text{-A}$

(one gauche interaction)



$1\text{Et}_{\text{ax}}\text{-A}_{\text{mirror}}$

(one gauche interaction)



$1\text{Et}_{\text{ax}}\text{-B}$

(much higher in energy)

Like this, only the most stable conformer is considered in isopropyl group.

→ Very similar steric hindrance for Me, Et, *i*-Pr.

Dispersion energy is larger in large group.

→  $\Delta E_{\text{ax-eq}}$  gives counterintuitive order; Me > Et > *i*-Pr

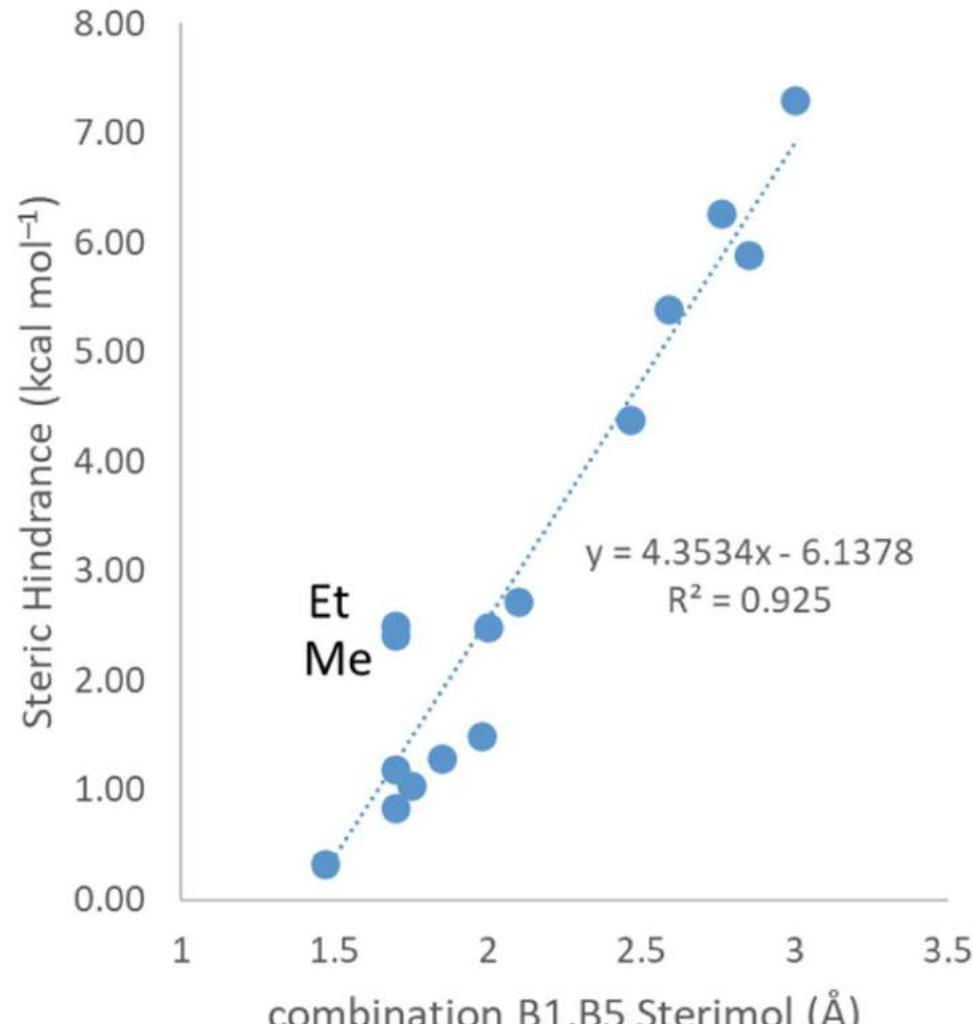
\* On the other hand, all the conformers are considered in A-value, thus steric hindrance is larger in large group.

# Correlation between Sterimol Parameters

|                   | DED  | Steric |
|-------------------|------|--------|
| F                 | 0.10 | 0.33   |
| Cl                | 0.74 | 1.04   |
| Br                | 0.96 | 1.30   |
| I                 | 1.24 | 1.49   |
| CCH               | 0.85 | 1.18   |
| CN                | 0.80 | 0.84   |
| Me                | 0.70 | 2.42   |
| Et                | 0.90 | 2.51   |
| iPr               | 1.12 | 2.50   |
| tBu               | 1.20 | 5.89   |
| Ph                | 1.50 | 4.39   |
| CF <sub>3</sub>   | 0.66 | 2.73   |
| CCl <sub>3</sub>  | 1.13 | 5.39   |
| CBr <sub>3</sub>  | 1.30 | 6.27   |
| CI <sub>3</sub>   | 1.42 | 7.30   |
| SiMe <sub>3</sub> | 1.49 | 3.47   |

Here, dispersion energy donor (DED) scale and the purely steric part were distinguished.

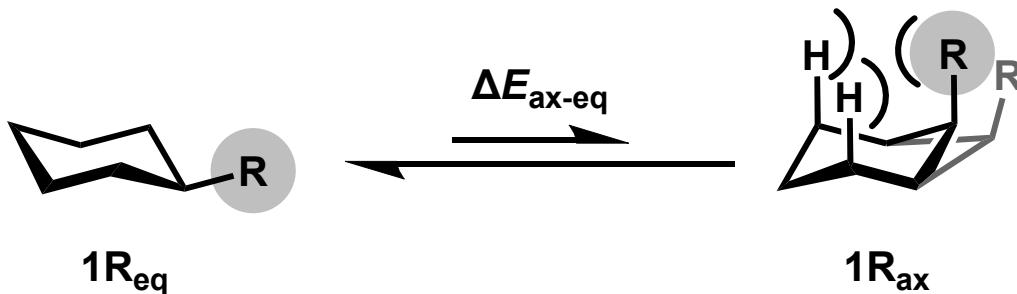
→ Steric part is compared with Sterimol parameters to see the relationships.



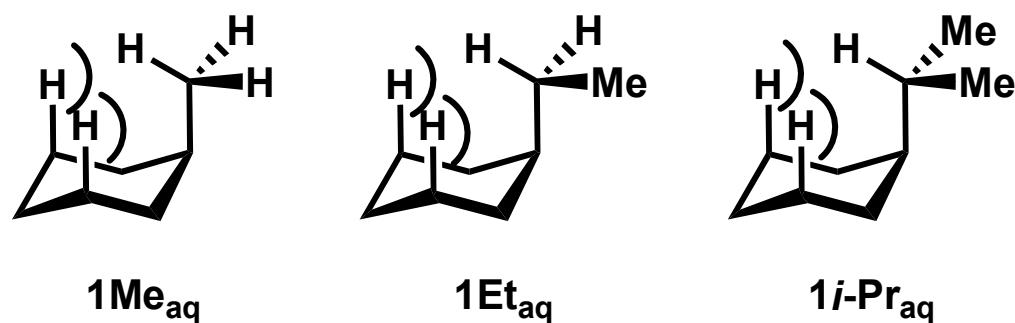
Linear correlation was observed.  
(except for Ph and SiMe<sub>3</sub>.)

# New Idea Instead of A-value

- Some Factors that Cyclohexyl-Ring-System doesn't Reflect the Total Size of the Group



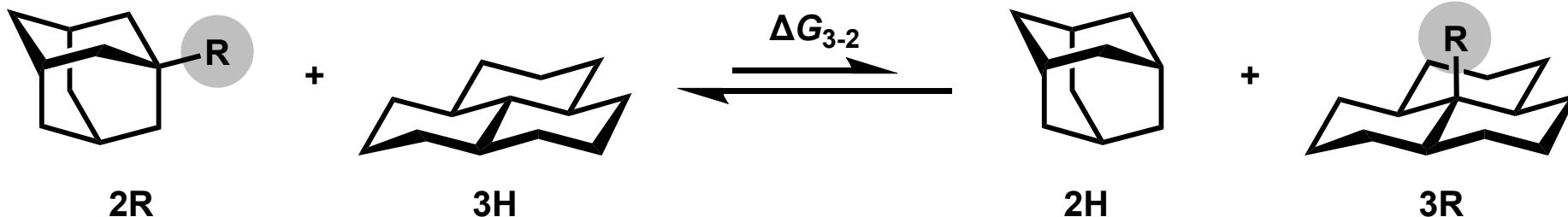
For large group (*t*-Bu, CX<sub>3</sub>, ...), conformation of cyclo hexyl ring slightly changes due to large steric repulsion.



R group rotates to minimize 1,3-diaxial steric repulsion.

→Similar steric hindrance of Me, Et, *i*-Pr

- Another System for Measuring Steric Hindrance for R group



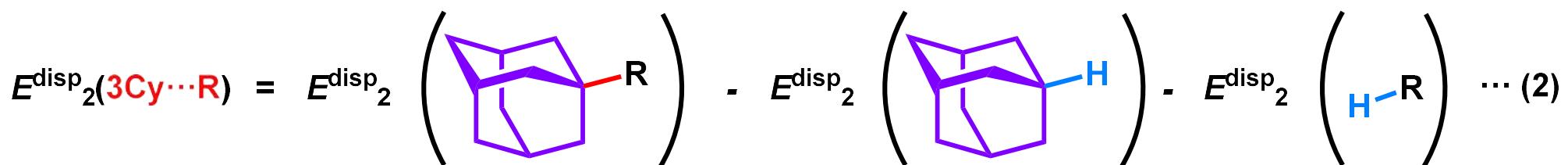
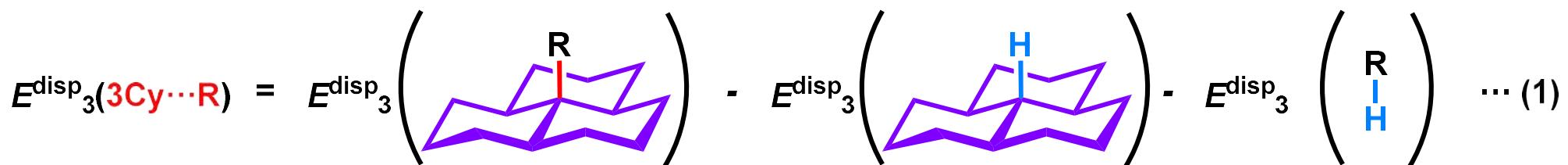
equatorial conformer to  
3 cyclohexyl rings

conformation is strictly fixed

axial conformer to  
3 cyclohexyl rings

- McFord, A. W.; Butts C. P.; Fey, N.; Alder, R. W. *J. Am. Chem. Soc.* **2021**, 143, 13573.
- Solel, E.; Ruth, M.; Schreiner, P. R. *J. Am. Chem. Soc.* **2021**, 143, 20837.

# Correction to Dispersion energy



$$E^{\text{disp}} = -[E(\text{B3LYP}) - E(\text{B3LYP-D3BJ})]$$

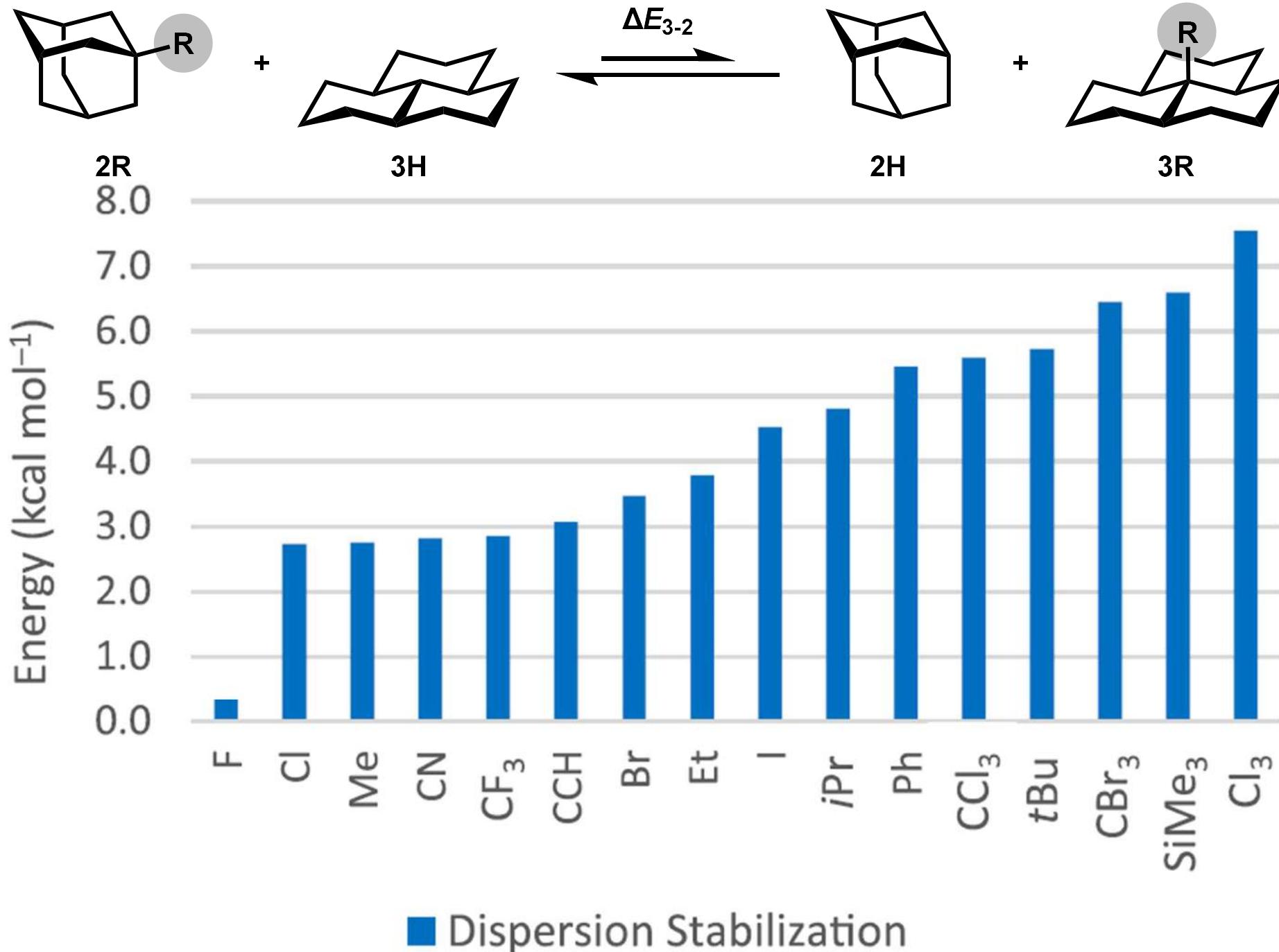
$$\text{Dispersion energy } \Delta E^{\text{disp}}_{3-2}(3\text{Cy}\cdots\text{R}) = E^{\text{disp}}_{\text{ax}}(3\text{Cy}\cdots\text{R}) - E^{\text{disp}}_{\text{eq}}(3\text{Cy}\cdots\text{R})$$

(1) - (2):

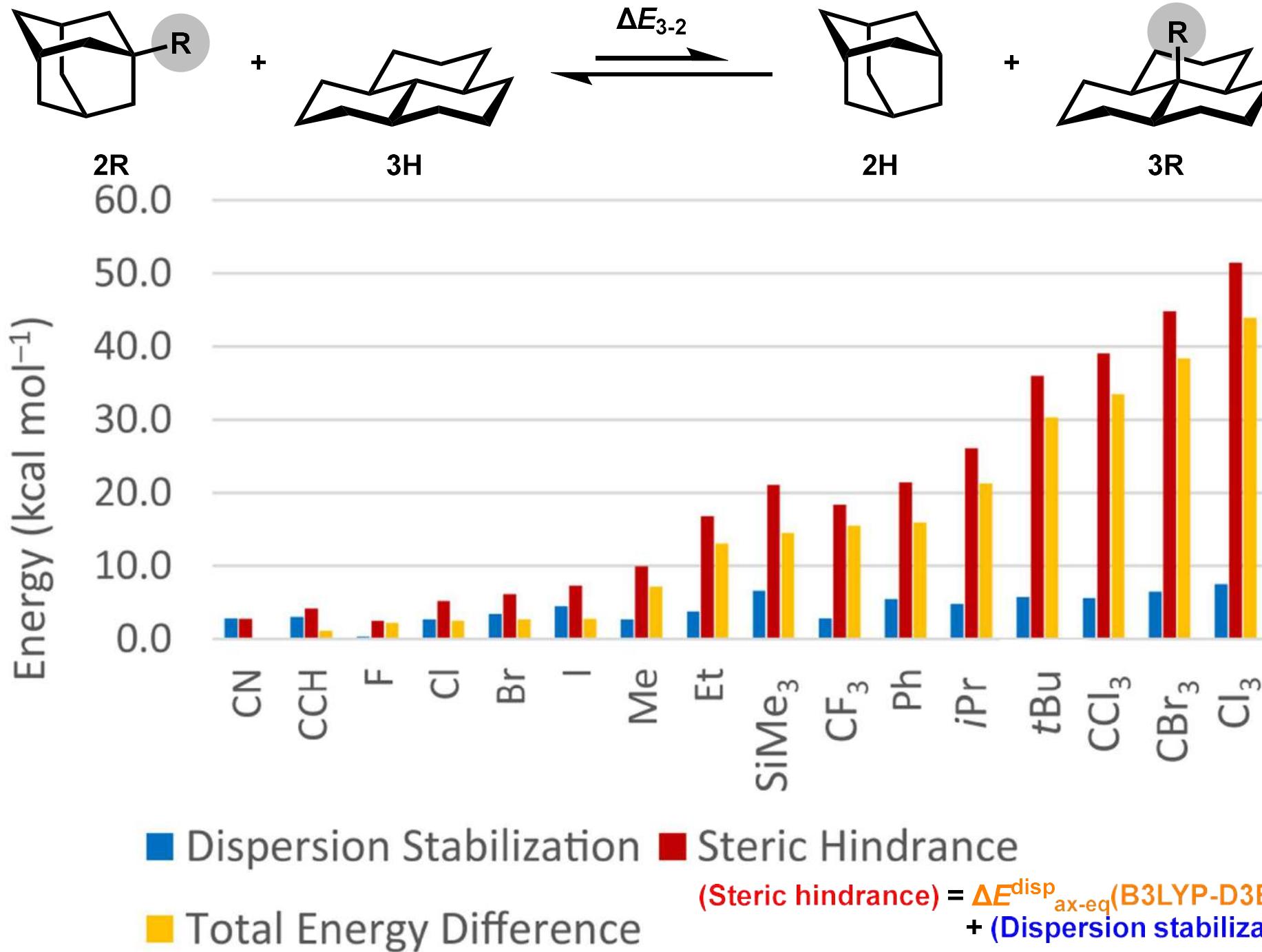
$$\Delta E^{\text{disp}}_{3-2}(3\text{Cy}\cdots\text{R}) = \Delta E^{\text{disp}}_{3-2} - \Delta E^{\text{disp}}_{3-2}(3\text{Cy}) - \Delta E^{\text{disp}}_{3-2}(\text{R})$$

$$(\text{Steric hindrance}) = \Delta E^{\text{disp}}_{\text{ax-eq}}(\text{B3LYP-D3BJ}) + (\text{Dispersion stabilization})$$

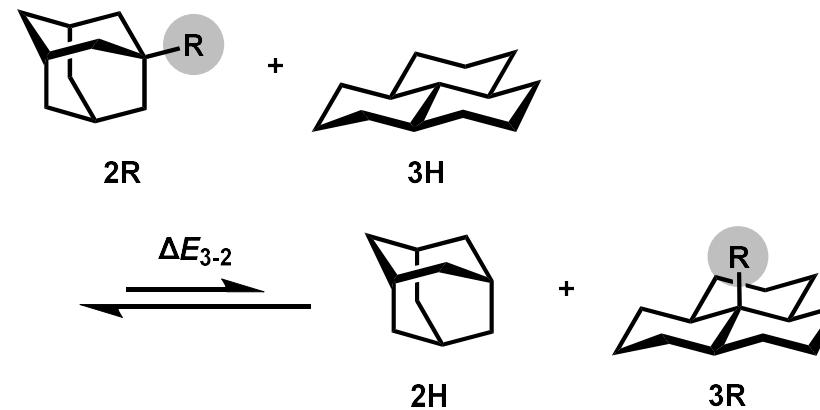
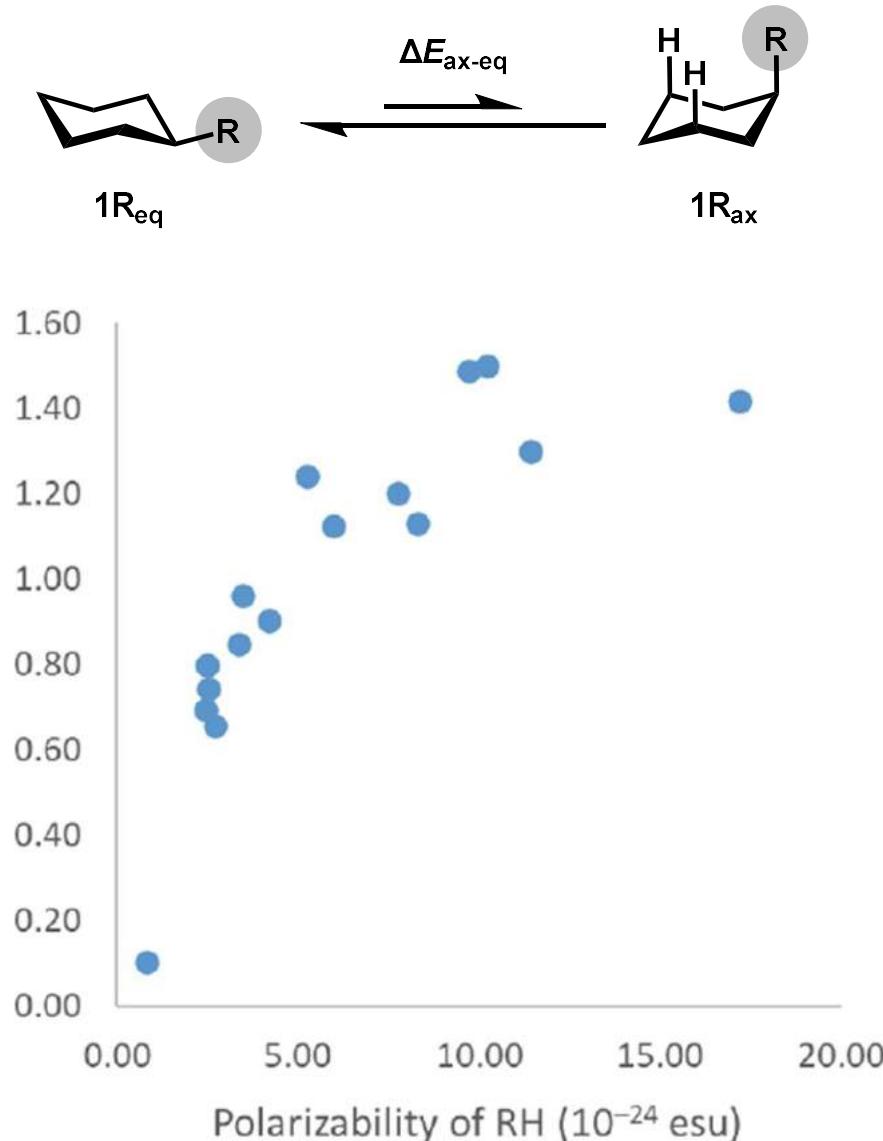
# Dispersion Effect in New System



# Steric Effect in New System

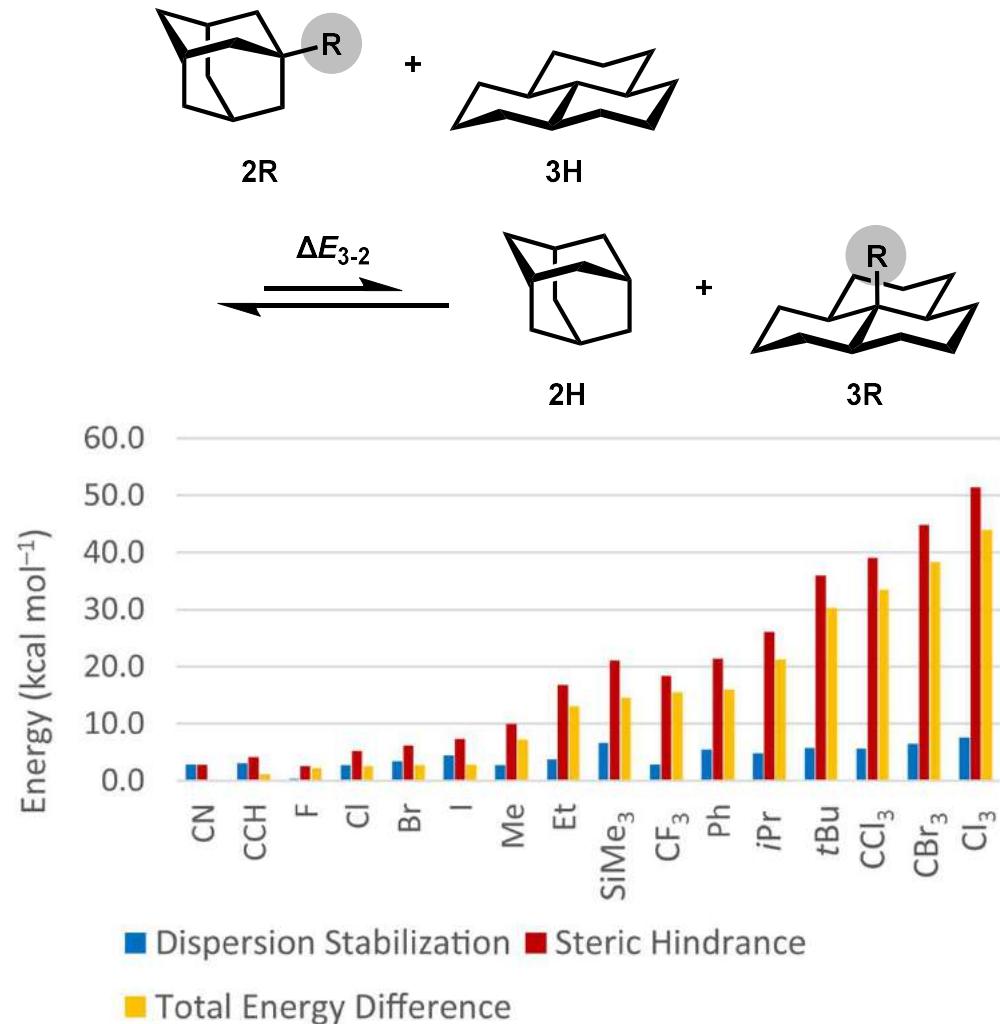
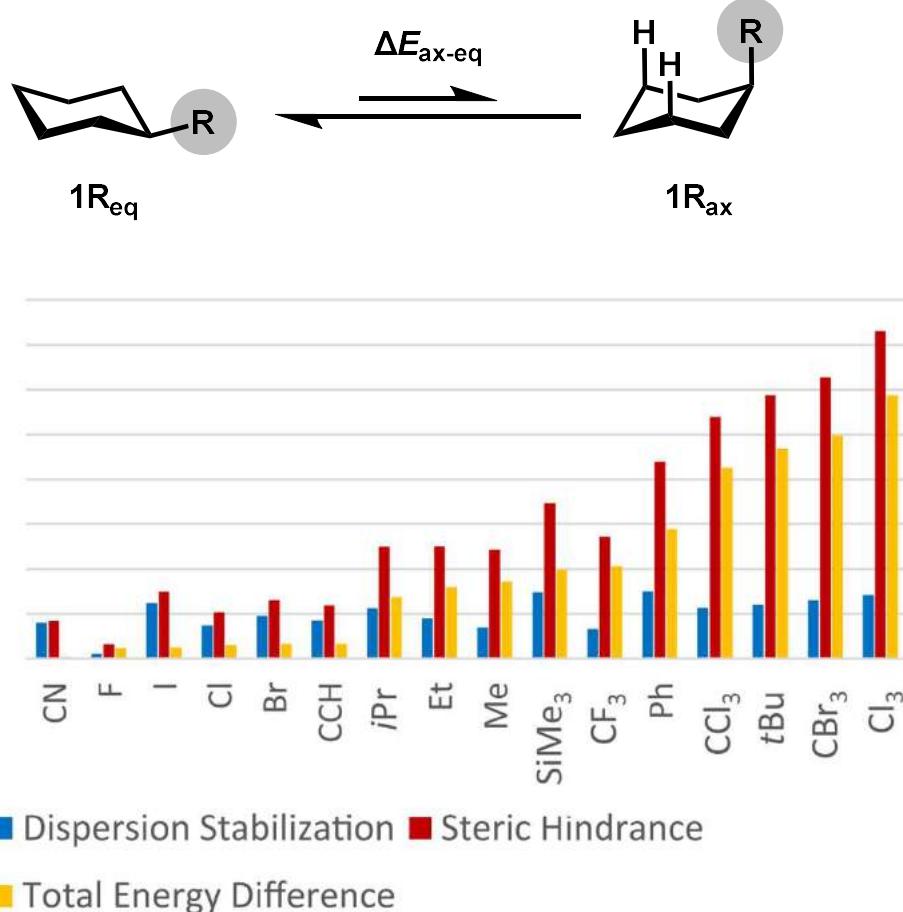


# Correlation between Polarizability



Good correlation was observed in these two systems. The right system shows better trend.

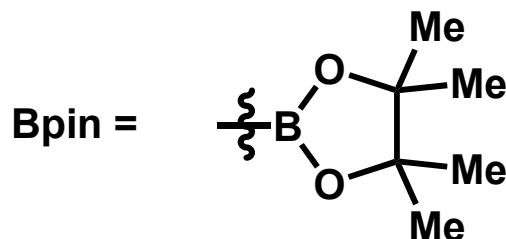
# Short Summary



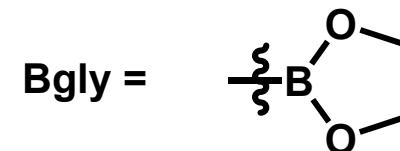
The group can rotate to reduce steric hindrance in the left system while the right one cannot.

→ Shows some different tendency in dispersion energy and steric hindrance.

# A-value of Bpin and Bgly



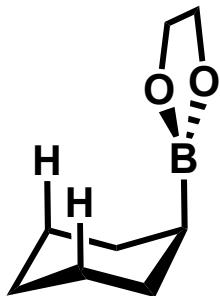
A-value: 0.42 kcal/mol



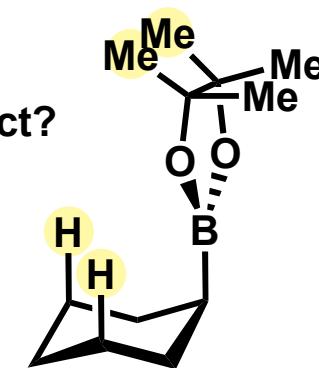
A-value: 0.73 kcal/mol

Bpin is larger group than Bgly, but A-value of Bpin is smaller than Bgly.

→ Dispersion affects the result?



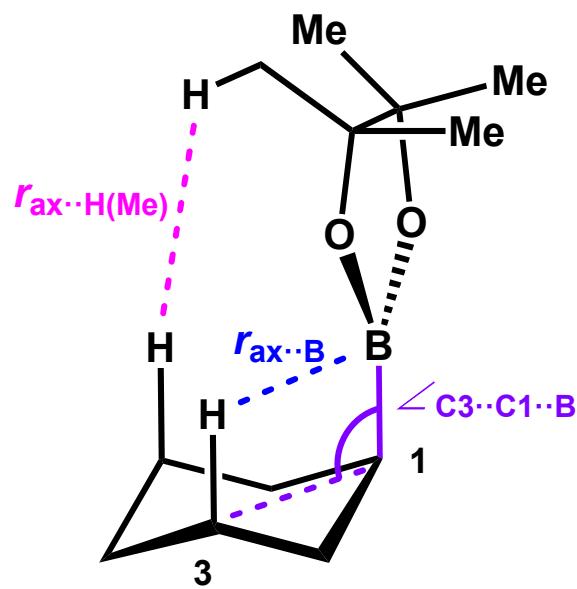
Dispersion effect?



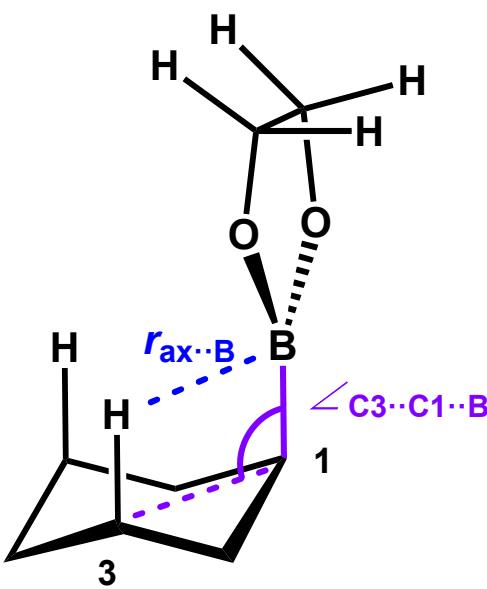
How large the dispersion/steric hindrance are?

# Steric Factors in Bpin and Bgly

| R    | $\Delta G_{\text{exp}}$<br>(A-value,<br>kcal/mol) | B3LYP/def2-TZVPP          |                                      |                                   |  | B3LYP-D3BJ/def2-TZVPP     |                               |                                   |   |
|------|---|---------------------------|--------------------------------------|-----------------------------------|--|---------------------------|-------------------------------|-----------------------------------|---|
|      |   | $\Delta G_{\text{ax-eq}}$ | $r_{\text{ax}\cdots\text{B}}$<br>(Å) | $r_{\text{ax}\cdots\text{H(Me)}}$ | $\angle \text{C3}\cdots\text{C1}\cdots\text{B}$<br>(°) | $\Delta G_{\text{ax-eq}}$ | $r_{\text{ax}\cdots\text{B}}$ | $r_{\text{ax}\cdots\text{H(Me)}}$ | $\angle \text{C3}\cdots\text{C1}\cdots\text{B}$ |
| Bpin | 0.42  | 1.46                      | 2.98                                 | 3.21                              | 102.0  | 0.36                      | 2.88                          | 2.95                              | 99.2  |
| Bgly | 0.73  | 1.32                      | 2.96                                 |                                   | 101.5  | 0.53                      | 2.88                          |                                   | 99.4  |



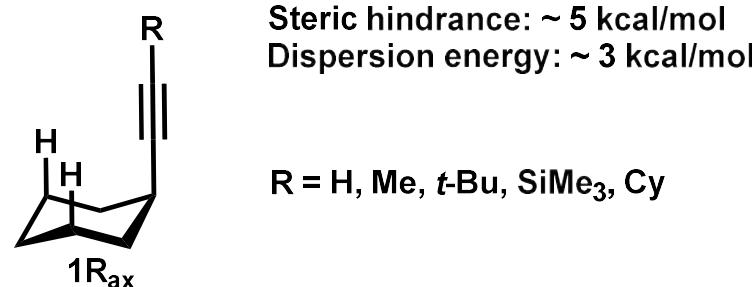
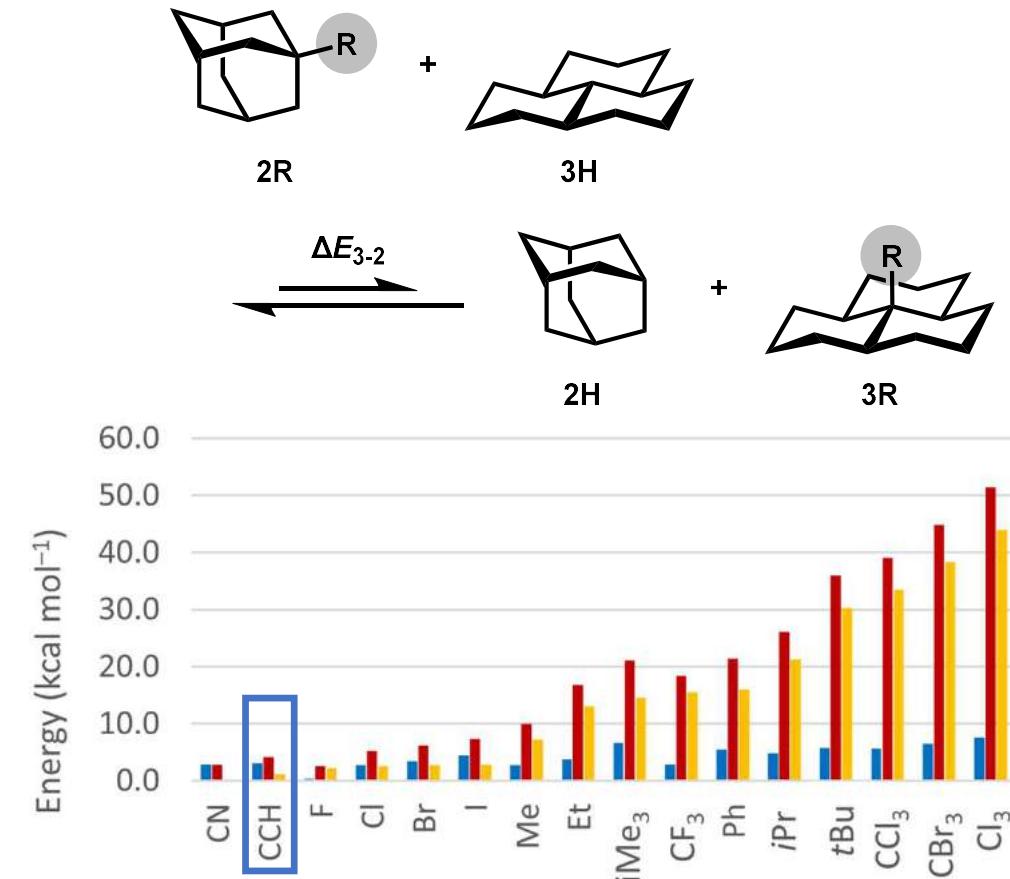
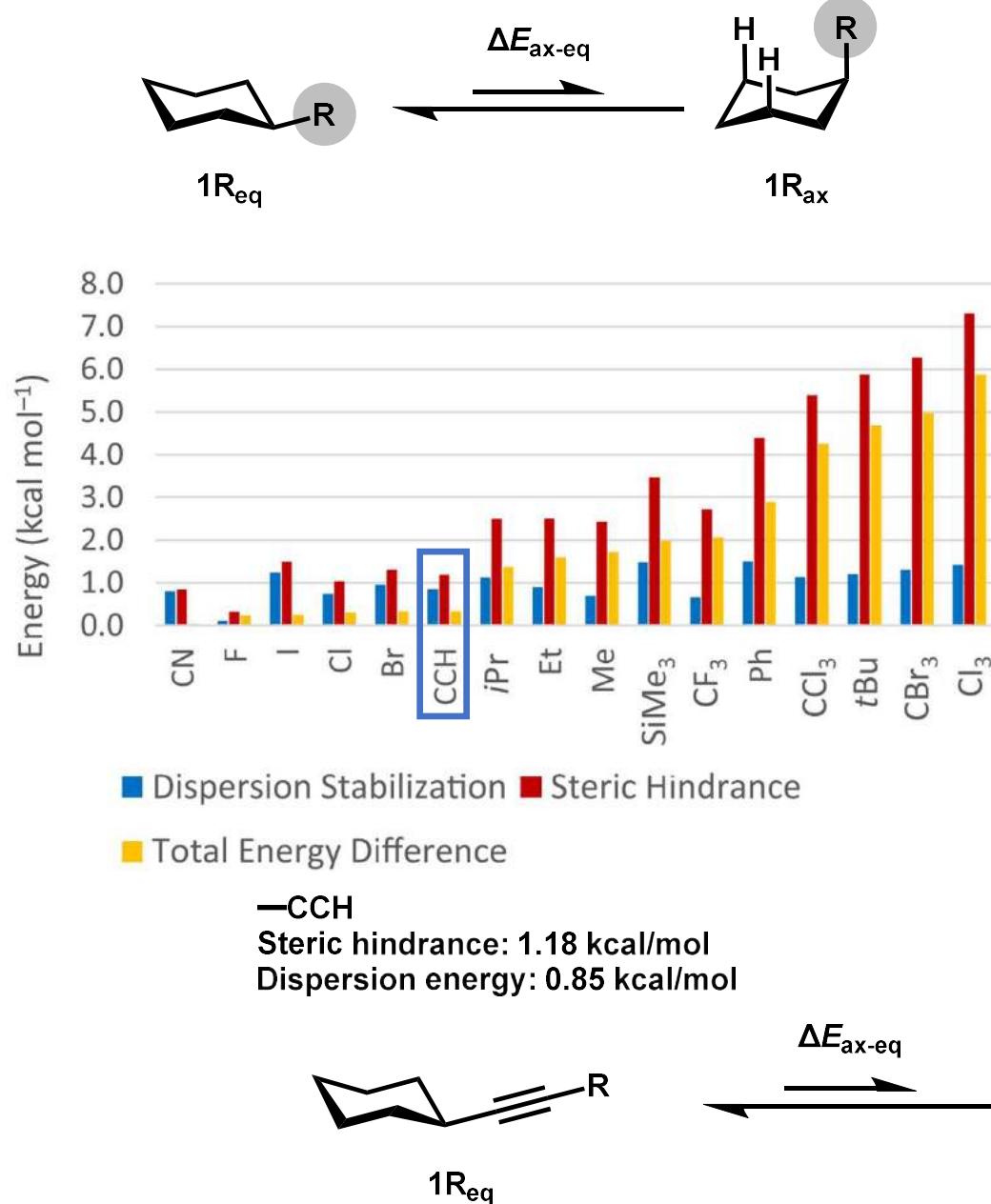
1Bpin<sub>ax</sub>



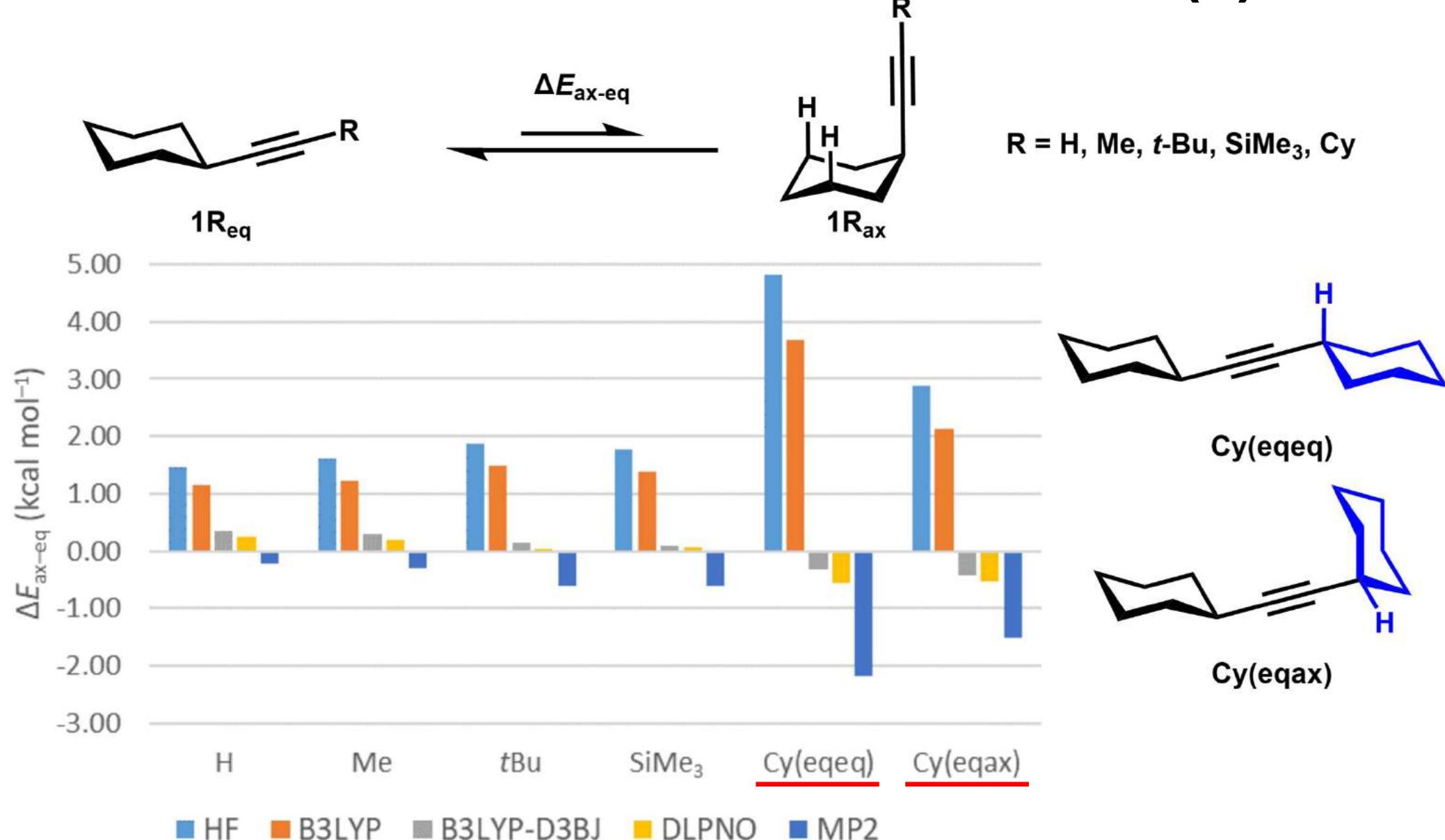
1Bgly<sub>ax</sub>

In computational calculation, Bpin is larger in steric hindrance, but dispersion energy is much more larger in Bpin.

# Search for Counterintuitive Trend (1)



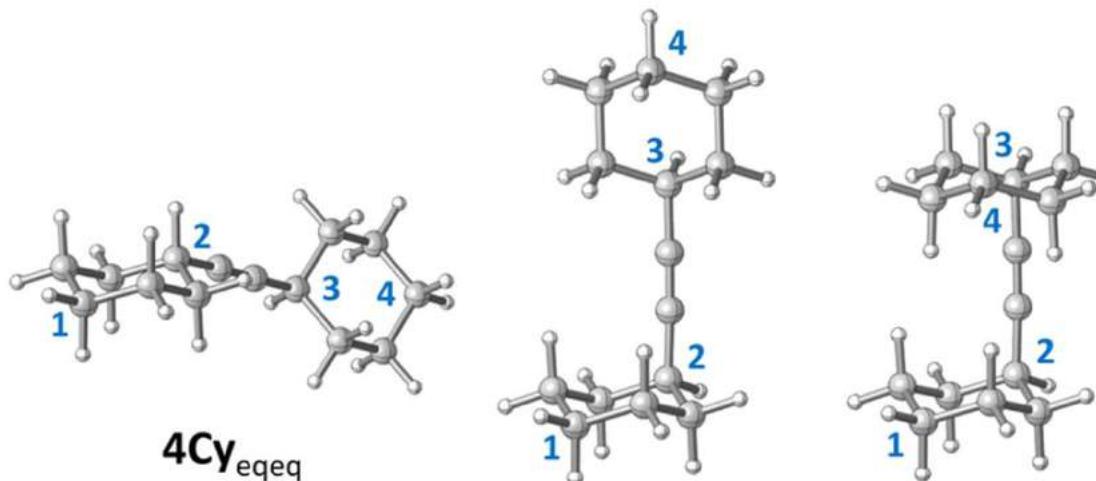
# Search for Counterintuitive Trend (2)



Levels of theory used are:

HF/aug-cc-pVTZ//MP2/aug-cc-pVTZ (HF), B3LYP/def2-TZVPP//MP2/aug-cc-pVTZ (B3LYP)  
 B3LYP-D3BJ/def2-TZVPP//MP2/aug-cc-pVTZ (B3LYP-D3BJ)  
 DLPNO-CCSD(T)/aug-ccpVQZ//MP2/aug-cc-pVTZ (DLPNO), MP2/aug-cc-pVTZ (MP2)

# **4Cy<sub>axax</sub> Can be the Most Stable Conformer**



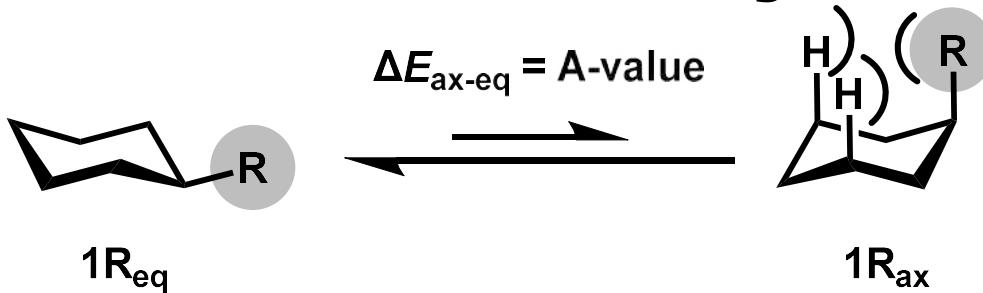
|                           | $\Delta H$<br>(kcal/mol) | $\Delta G$ (4 K) | $\Delta G$ (193 K) | $\Delta G$ (298 K) |
|---------------------------|--------------------------|------------------|--------------------|--------------------|
| <b>4Cy<sub>eqeq</sub></b> | 0.4                      | 0.2              | 0.0                | 0.0                |
| <b>4Cy<sub>eqax</sub></b> | 0.5                      | 0.4              | 0.8                | 1.3                |
| <b>4Cy<sub>axax</sub></b> | <b>0.0</b>               | <b>0.0</b>       | 0.8                | 1.4                |

computed at the B3LYP-D3BJ/def-TZVPP

**At cryogenic temperature (4 K), 4Cy<sub>axax</sub> is the most stable conformer.**

**At low temperature (193 K), although 4Cy<sub>eqeq</sub> is the most preferable, there is no difference between the energies of 4Cy<sub>eqax</sub> and 4Cy<sub>eqeq</sub>.**

# Summary

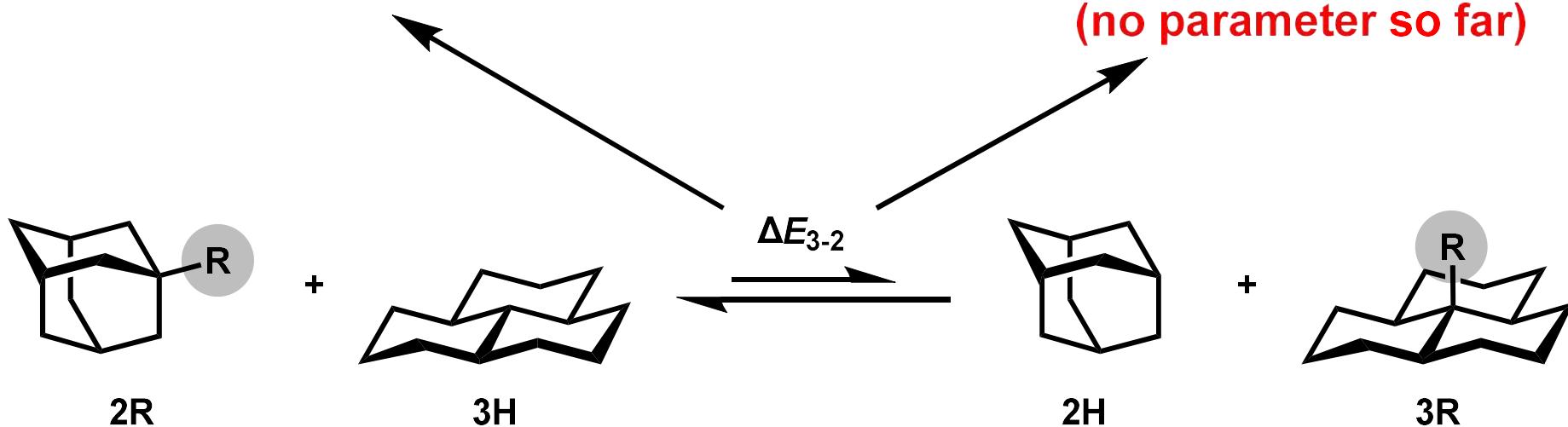


$$\Delta E_{ax-eq} = (\text{Steric hindrance}) + (\text{Dispersion stabilization})$$

by computational calculation

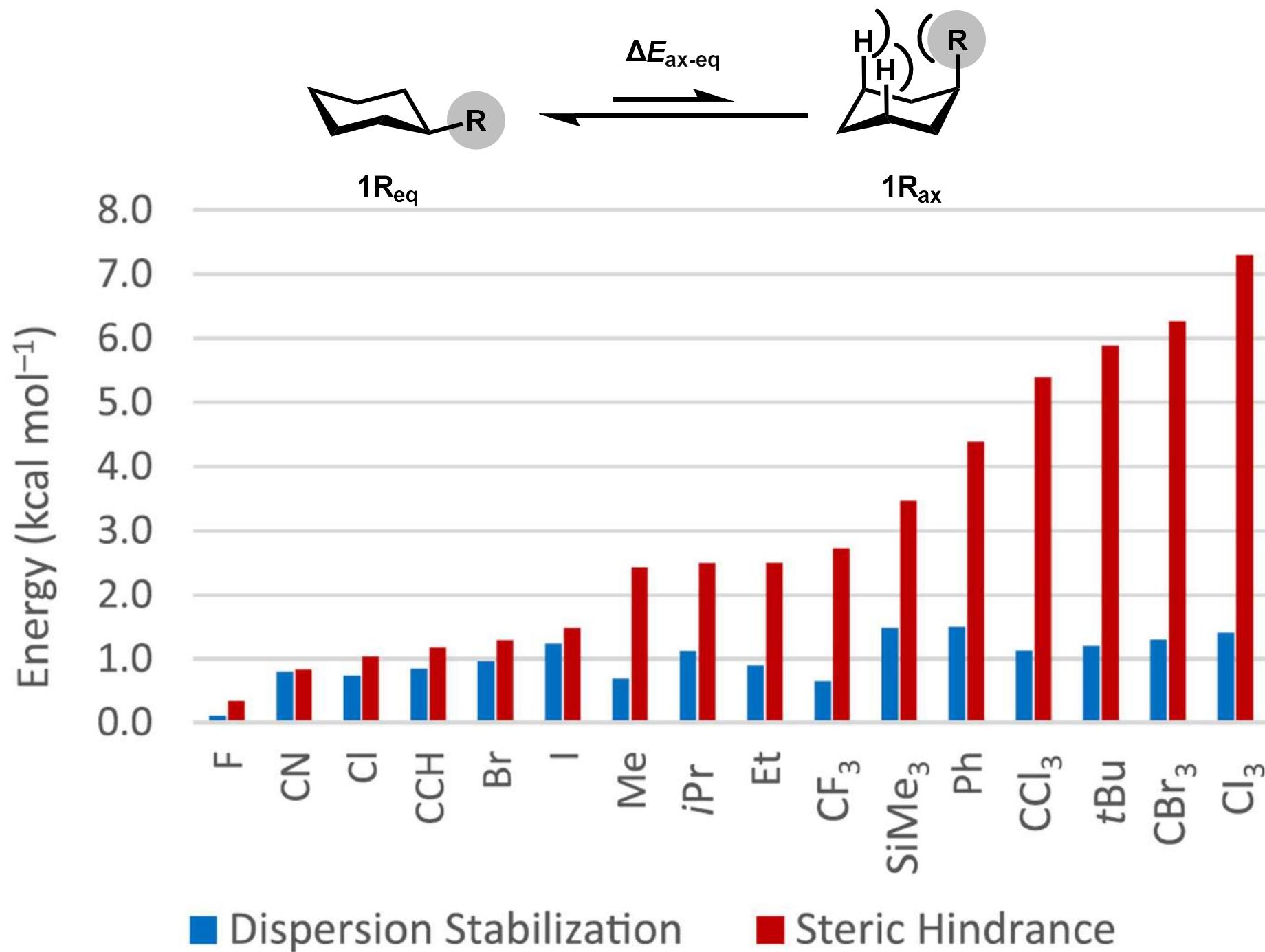
Steric hindrance

Dispersion stabilization  
(no parameter so far)

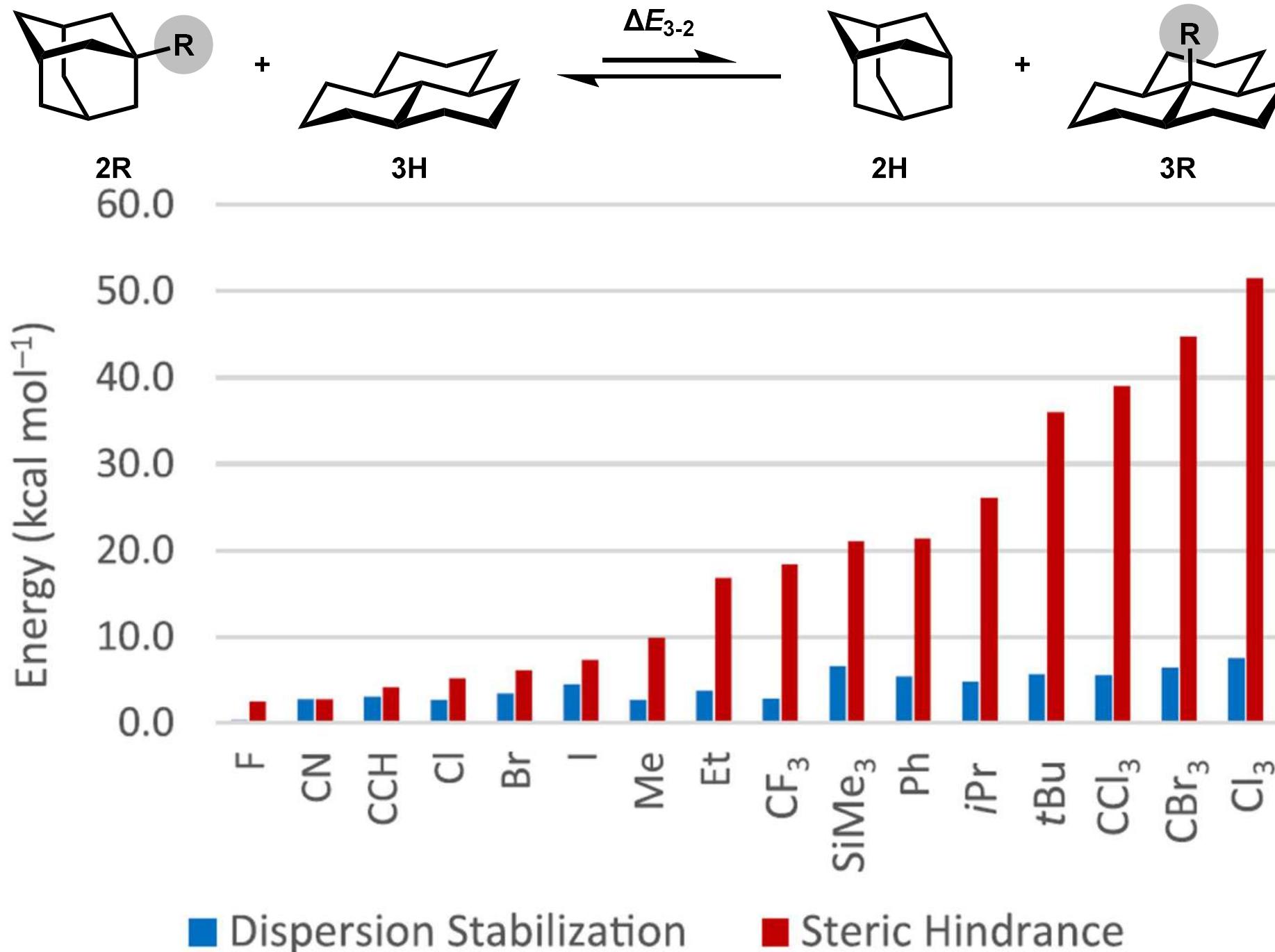


# **Appendix**

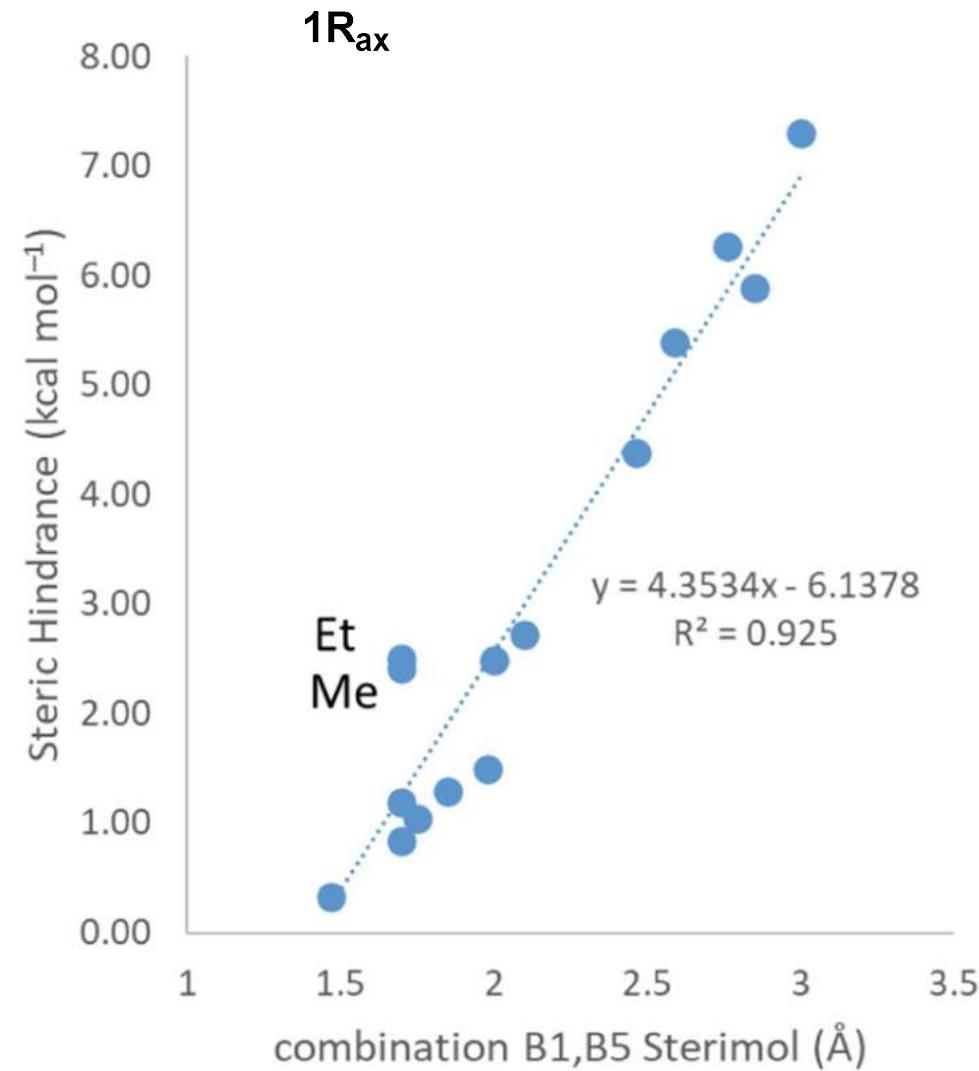
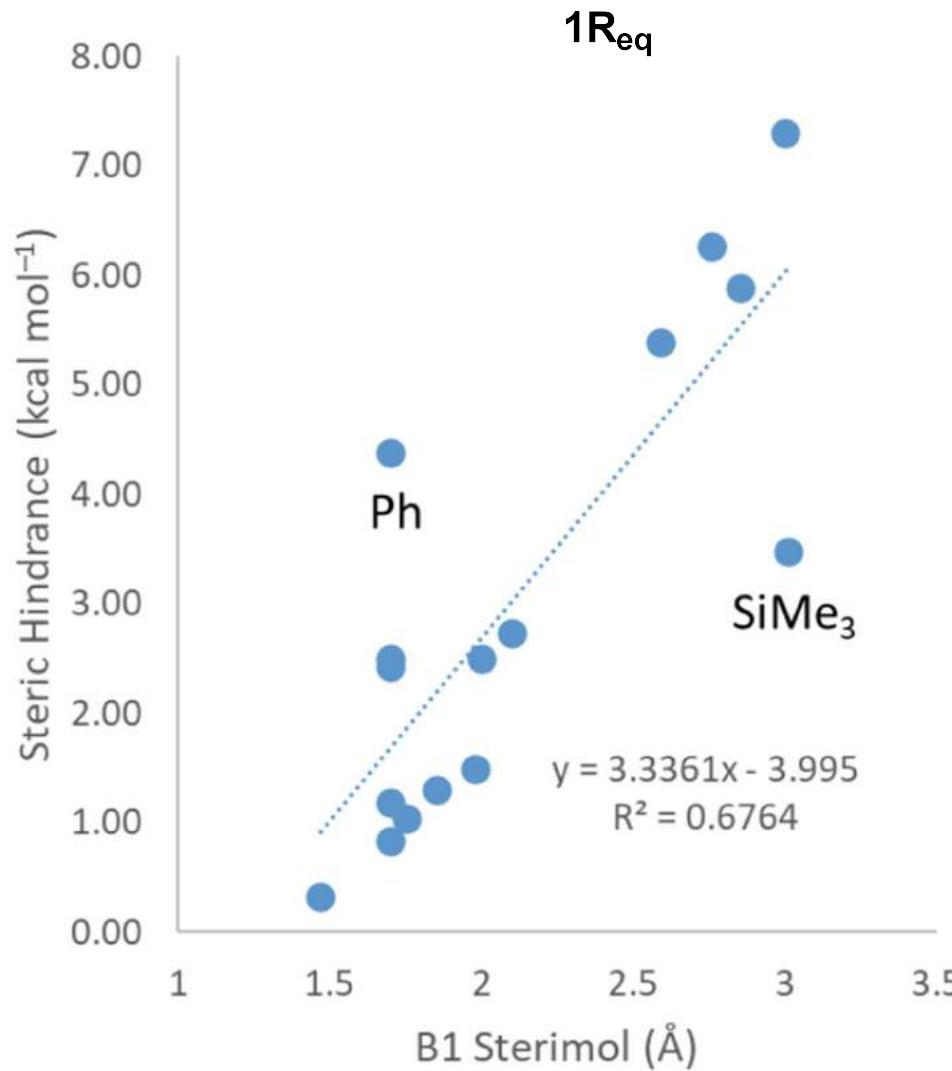
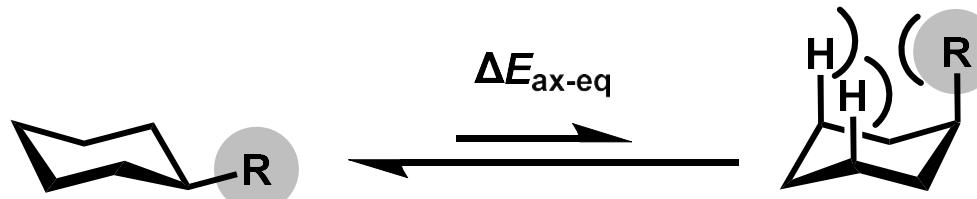
# Steric hindrance in Monosubstituted Cyclohexane



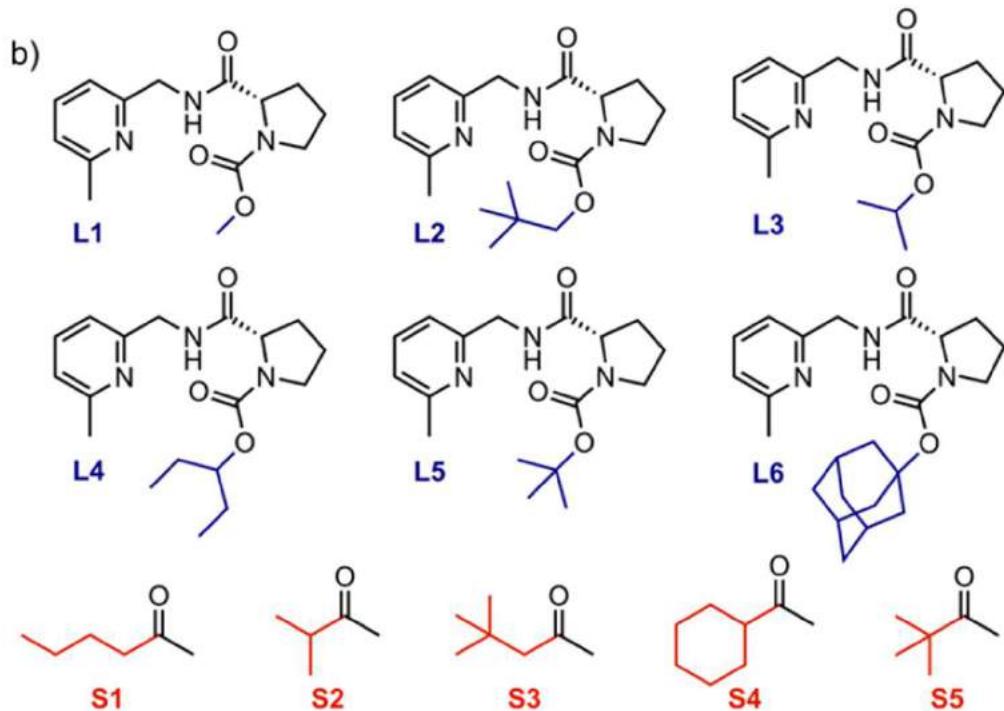
# Steric Effect in New System



# Correlation between Sterimol Parameters

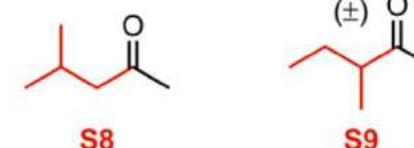
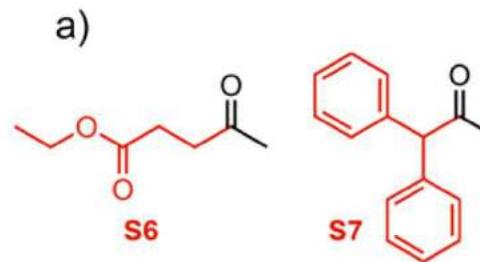


# Correlation between Sterimol Parameters



$$\begin{aligned}\Delta\Delta G^\ddagger = & z_0 + aB_{1L} + bB_{5L} + cL_L + dB_{1S} + fB_{5S} + gL_S \\ & + hB_{1L}B_{1S} + iB_{1L}B_{5S} + jB_{1L}L_S + kB_{5L}B_{1S} \\ & + mB_{5L}B_{5S} + nB_{5L}L_S + oL_LB_{1S} + pL_LB_{5S} \\ & + qL_LL_S\end{aligned}\quad (1)$$

$$\begin{aligned}\Delta\Delta G^\ddagger = & -2.19 + 1.47B_{1L} + 0.94B_{1S} - 0.27B_{1L}B_{1S} \\ & - 0.09B_{1L}B_{5S}\end{aligned}\quad (2)$$



b)  $\sigma_{n-}$

