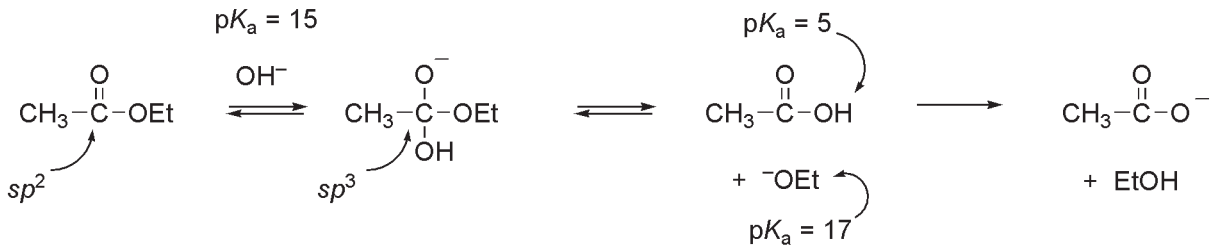
III. Reaction Mechanisms and Conformational Effects on Reactivity

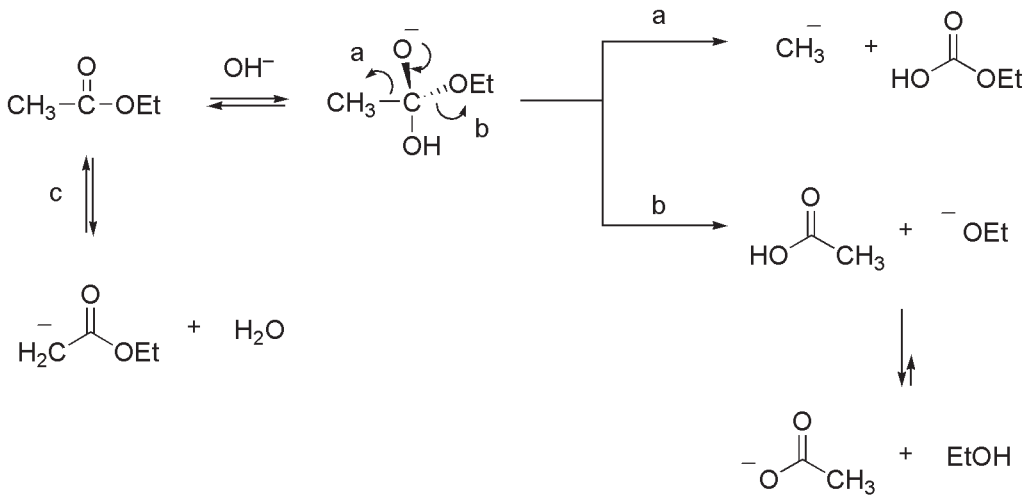
George de Hevesy received the 1943 Nobel Prize in Chemistry for the use of isotopes as markers in the study of chemical reactions.

C. N. Hinshelwood and N. N. Semenov received the 1956 Nobel Prize in Chemistry for their research on the mechanism of chemical reactions.

A. Ester Hydrolysis

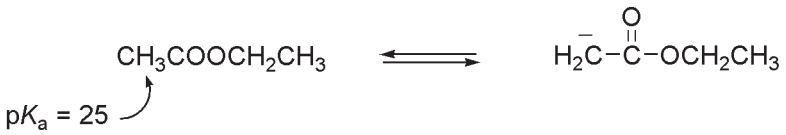


• Reaction driven to completion by final, irreversible step (compare pK_a = 17 to pK_a = 5).



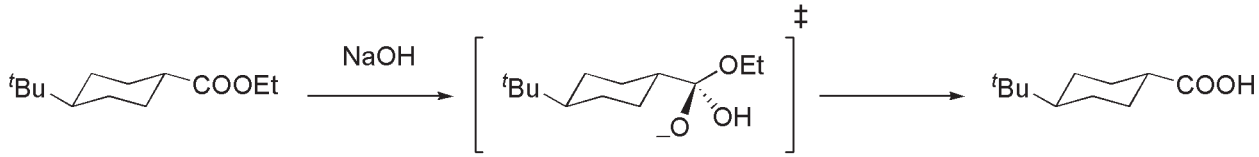
• Possible competing reaction is α-H removal, but pK_a difference means equilibrium strongly favors ester and OH^-, i.e.;

• To deprotonate an ester, must use a strong base which is non-nucleophilic, such as ^{t}BuOK or LDA.



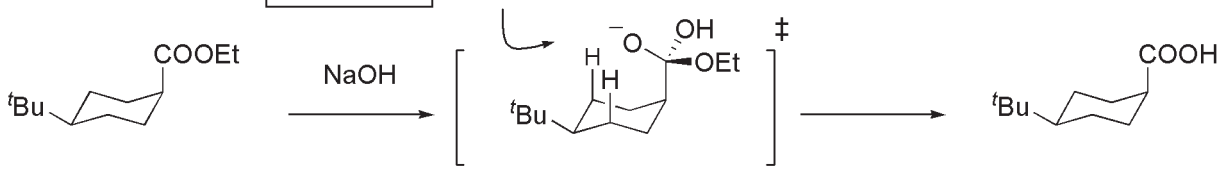
1. ^{t}BuOK (pK_a of ^{t}BuOH = 19) → generates low concentration of anion, and a significant amount of ester always present ⇒ self (Claisen) condensation
2. LDA (pK_a of ^{i}Pr$_2$NH = 36) → generates a high concentration of enolate and is a good base to carry out stoichiometric deprotonation and alkylation of ester

1. Kinetics of ester hydrolysis (stereochemistry and rates of reactions)



Steric Effect

no way to avoid a severe ^{t}Bu-like 1,3-diaxial interaction



A value = 1.2 kcal

A value = 2.3 kcal

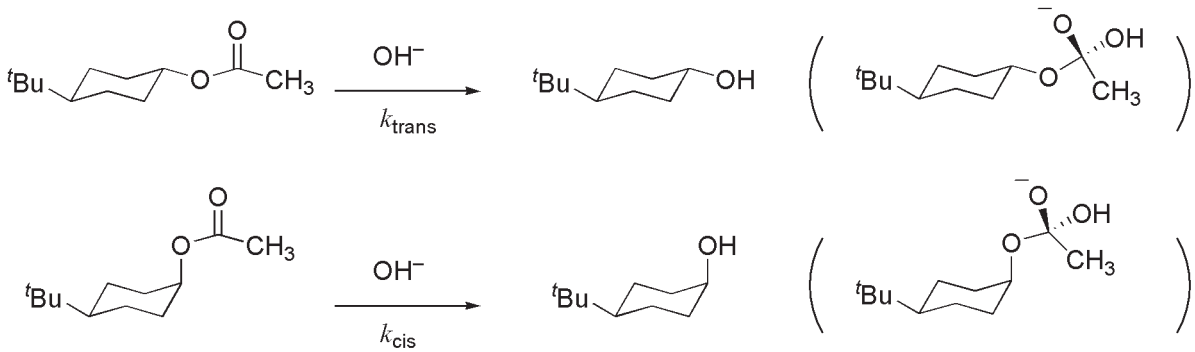
$$\frac{k_{trans}}{k_{cis}} = 19.8$$

The rate determining step for ester hydrolysis is the formation of tetrahedral intermediate and the ratio of k_{trans}/k_{cis} >> 1.

Eliel *J. Am. Chem. Soc.* **1961**, *83*, 2351.

- Difference in rates much greater than expected if simply considering the difference in either the product or reactant A values.
- Reaction of axial ester decelerated due to more severe developing 1,3-diaxial interactions in transition state (i.e., an axial ^{t}Bu-like group).

2. Same effect is observed, but to a lesser extent with acetate hydrolysis



A value = 0.7 kcal/mol

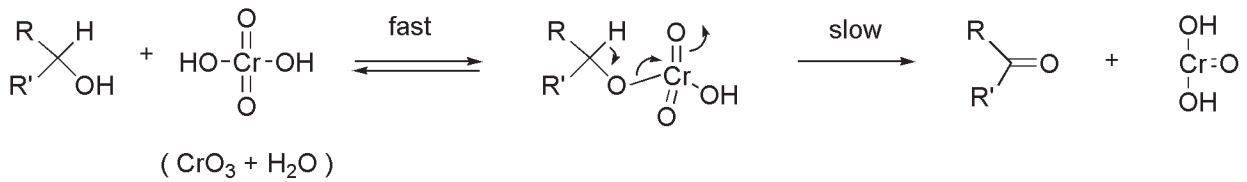
$$\frac{k_{trans}}{k_{cis}} = 6.65$$

- Effect is smaller because of the more remote distance of the steric interactions.

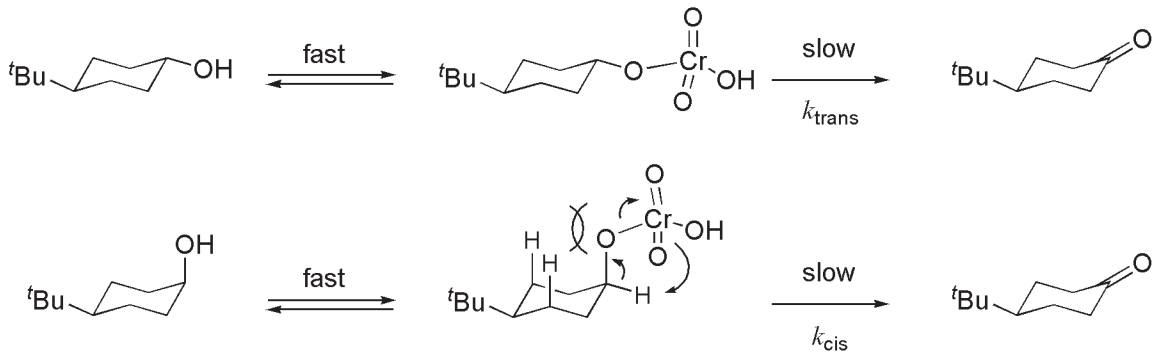
Similarly, the rates of acetylation are k_{trans} / k_{cis} = 3.7 This is in very good agreement with a simple prediction from the A value (k_{rel} = 3.25 for ΔG = 0.7 kcal/mol).

Eliel *J. Am. Chem. Soc.* **1966**, *88*, 3334.

B. Alcohol Oxidation



Westheimer *J. Am. Chem. Soc.* **1951**, *73*, 65.



Eliel *J. Am. Chem. Soc.* **1966**, *88*, 3327.

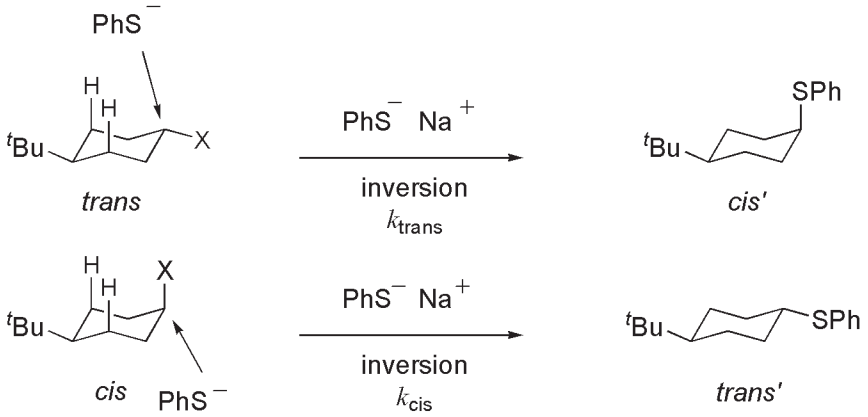
$$\frac{k_{cis}}{k_{trans}} = 4$$

The rate determining step for alcohol oxidation is break down of the chromate ester with cleavage of C–H bond and O–Cr bond.

- Destabilizing 1,3-diaxial interactions in *cis* chromate ester accelerate its breakdown to the ketone (would be slower if the slow step for the reaction were formation of chromate ester).

Eschenmoser *Helv. Chim. Acta* **1955**, *38*, 1529.

C. S_N2 Reaction



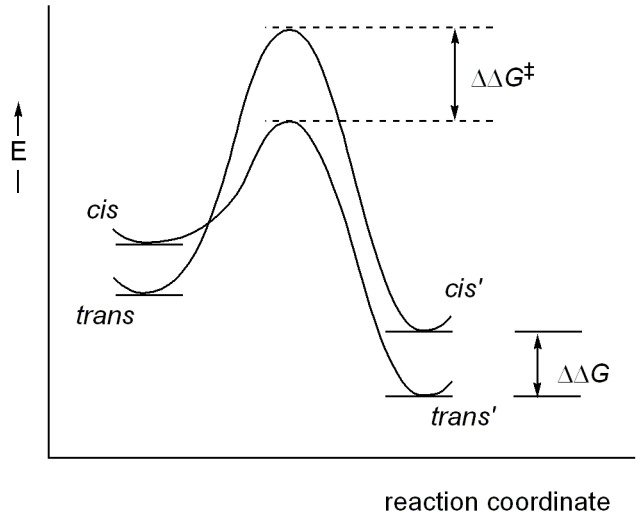
less stable product formed and proceeds through a less stable T.S.

• The free energy of activation (E_a, or $\Delta G^{\ddagger}$) for reaction of the *trans* isomer is higher due to steric interactions felt in the transition state (interactions of incoming nucleophile with axial H's).

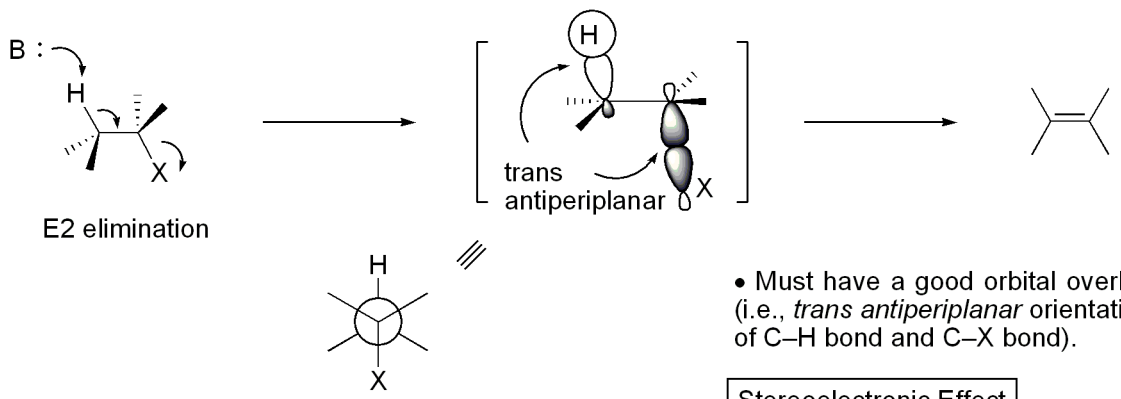
→ $k_{cis} > k_{trans}$

$\Delta\Delta G^{\ddagger}$ greater than $\Delta\Delta G$ of products.

• The reaction of the *trans* isomer is kinetically slower and thermodynamically less favorable.



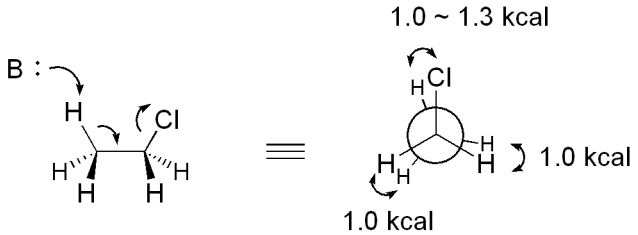
D. Elimination Reaction



• Must have a good orbital overlap (i.e., *trans antiperiplanar* orientation of C–H bond and C–X bond).

Stereoelectronic Effect

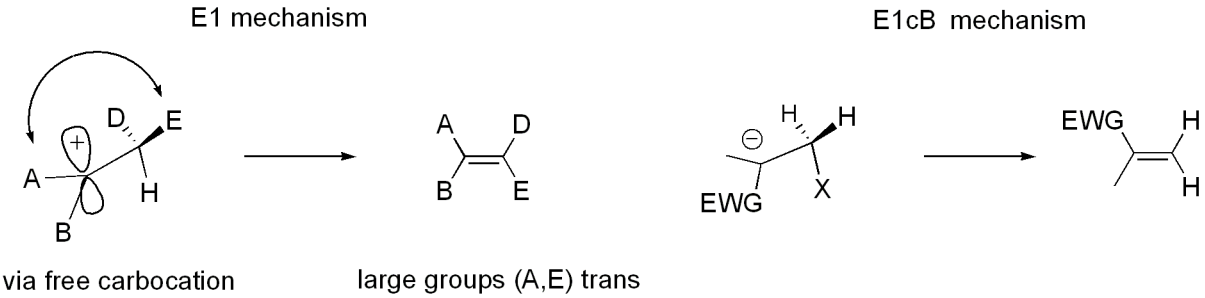
- Alternatively, if dihedral angle = 0° (i.e., eclipsed X and H), elimination can take place (orbital overlap good).



• Syn elimination

• Eclipsed conformation is 3.0–3.3 kcal/mol higher in E, so elimination takes place mainly through *trans antiperiplanar* arrangement.

- Alternate mechanisms also possible:



via free carbocation

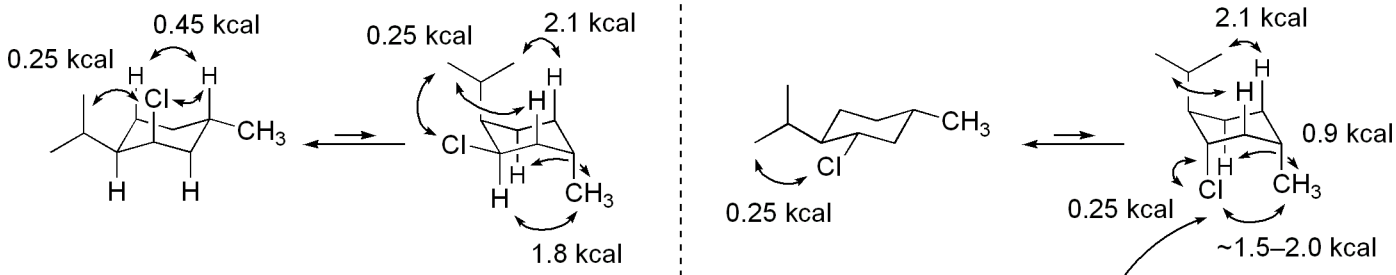
large groups (A,E) trans

Cyclic Substrate

Consider E2 elimination of

neomenthyl chloride menthyl chloride

Look at all conformations of each:



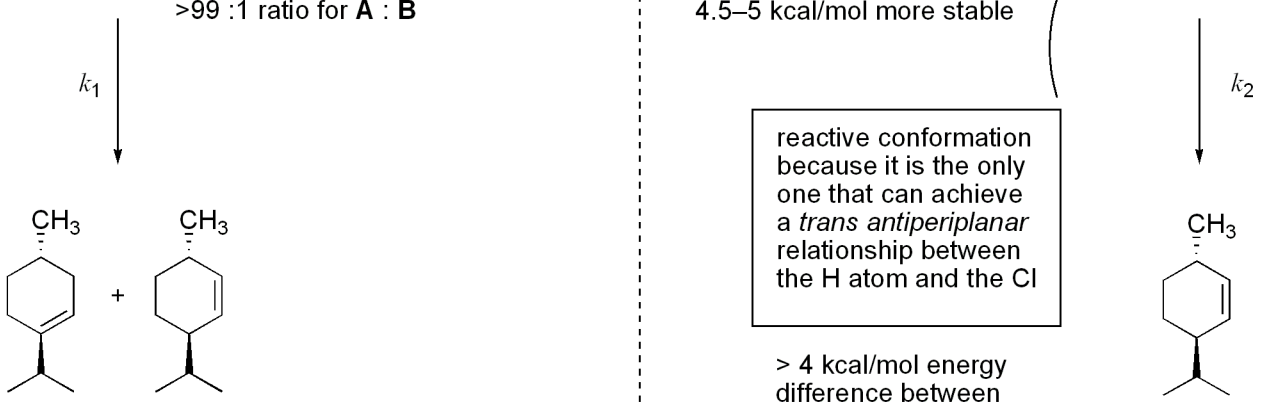
A ΔE= ~3.4 kcal/mol **B**

>99 :1 ratio for **A** : **B**

C

4.5–5 kcal/mol more stable

D



78 : 22

reactive conformation because it is the only one that can achieve a *trans antiperiplanar* relationship between the H atom and the Cl

> 4 kcal/mol energy difference between ground state and the reactive conformation

only product !

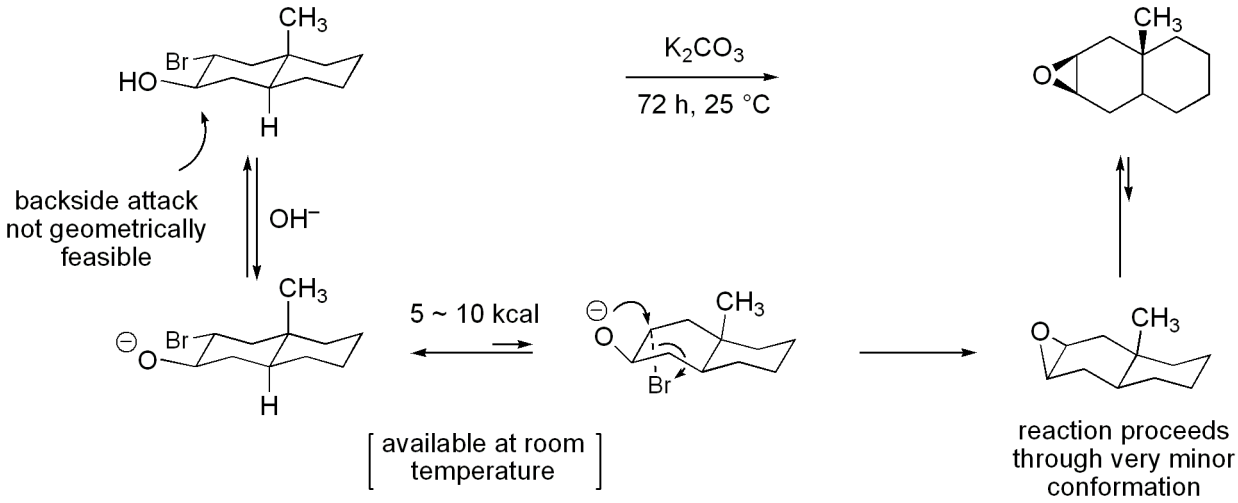
The reaction of the neomenthyl chloride is much faster (k_1/k_2 = 193:1)

From **D** (menthyl chloride) – only one product is possible

Curtin–Hammett principle :	Ground state conformation need not be decisive in determining product of a reaction.

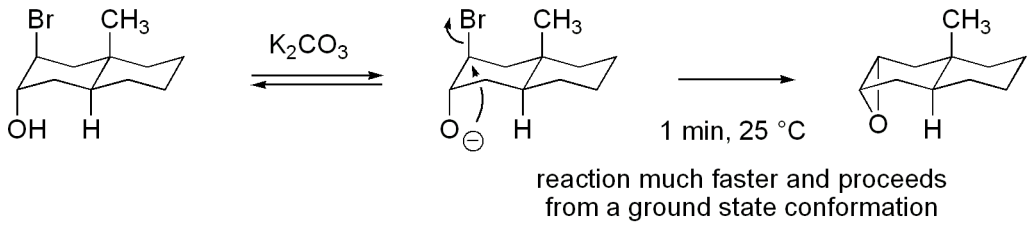
E. Epoxidation by Intramolecular Closure of Halohydrins

- Must involve backside displacement → geomerical constraints !

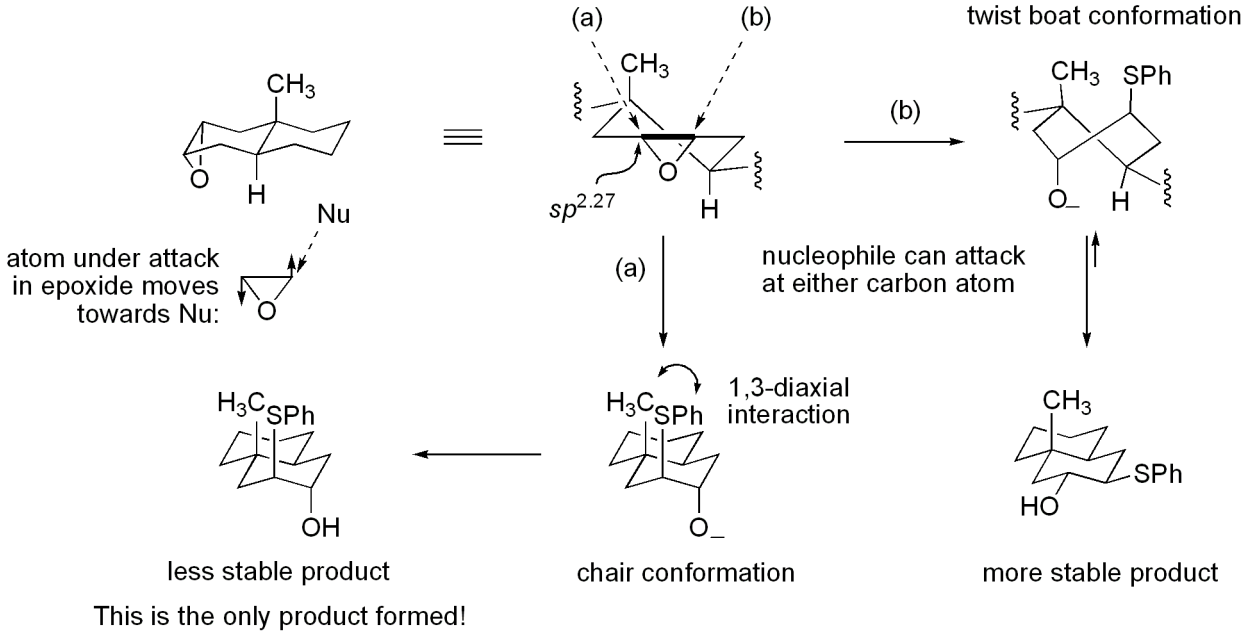


- Again, ground state conformation of reactant is not a determinant in reaction product (Curtin–Hammett principle).

Another example:



F. Epoxide Opening (S_N2)

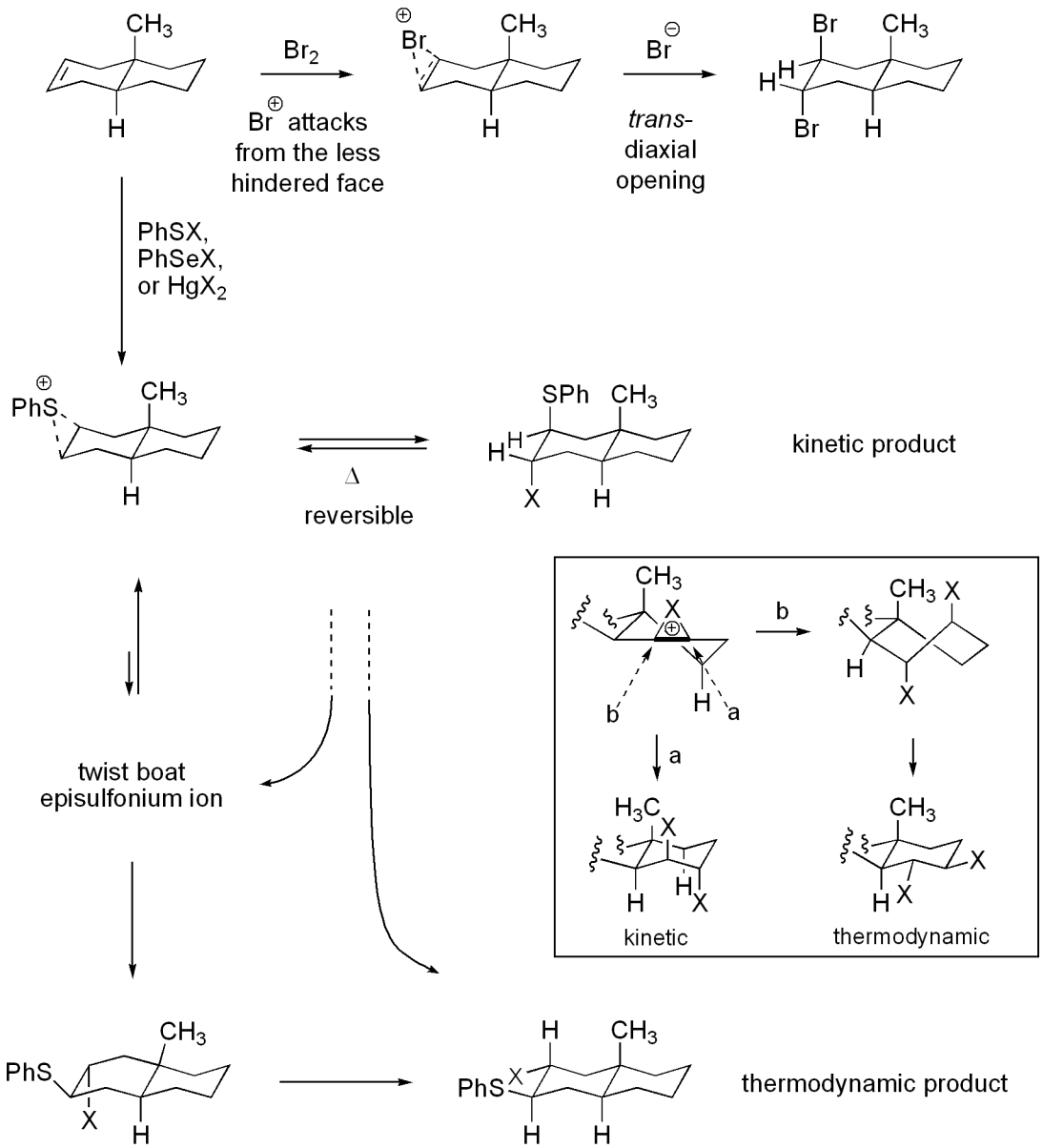


⟹ Product ratio dependent on $\Delta\Delta G^{\ddagger}$ (i.e., relative energy of two T.S.): route (a) proceeding through chair conformation and destabilizing 1,3-diaxial interaction is of lower energy than route (b) proceeding through twist boat T.S.

- Conformational effects determine regioselectivity

G. Electrophilic Addition to Alkenes

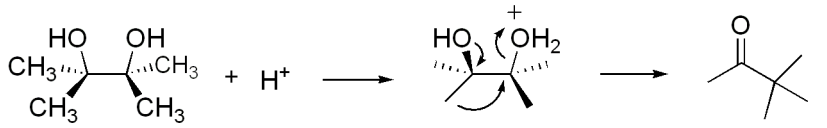
Follows the same principles



- Conformational effects control regioselectivity and stereochemistry
  But, it is not always possible to obtain the thermodynamic product
  ⇒ must have the 20–30 kcal/mol of energy required and a mechanism to reverse the reaction.

H. Rearrangement Reactions

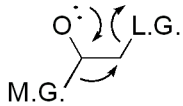
Pinacol → Pinacolone Rearrangement



pinacolone

- Prototype of rearrangement:

heteroatom



leaving group

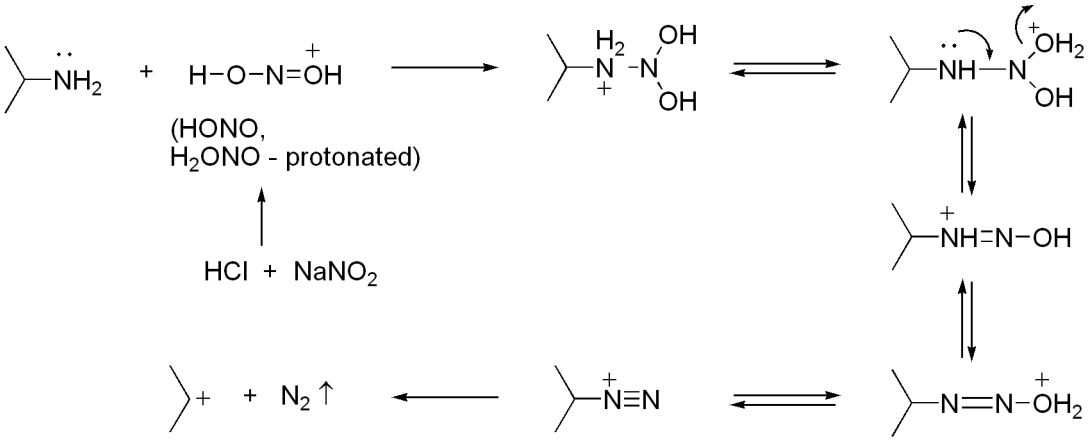
$-OH_2^+$

$-OSO_2R$

$-N_2^+$ diazonium ion

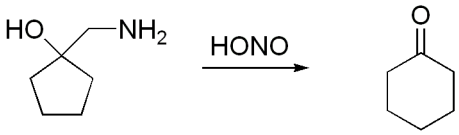
migrating group

• This process is conformationally dependent!



Tiffeneau–Demjanov Reaction

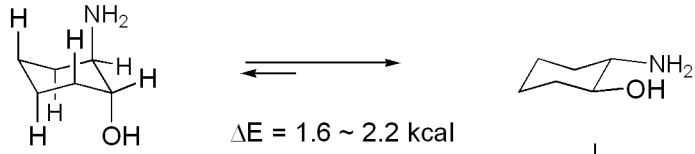
Ring expansion of cyclic β-amino alcohols



Tiffeneau *Compt. rend.* **1937**, *205*, 54.
Review: *Org. React.* **1960**, *11*,157.

The course of rearrangement is conformationally dependent:

A value of NH_2/NH_3^+ (1.8–1.4 kcal)



A value of OH
(0.7 kcal)

ΔE = 1.6 ~ 2.2 kcal

gauche (0.35–0.9 kcal)

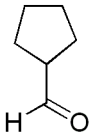
HONO

Stereoelectronic Effect

backside attack

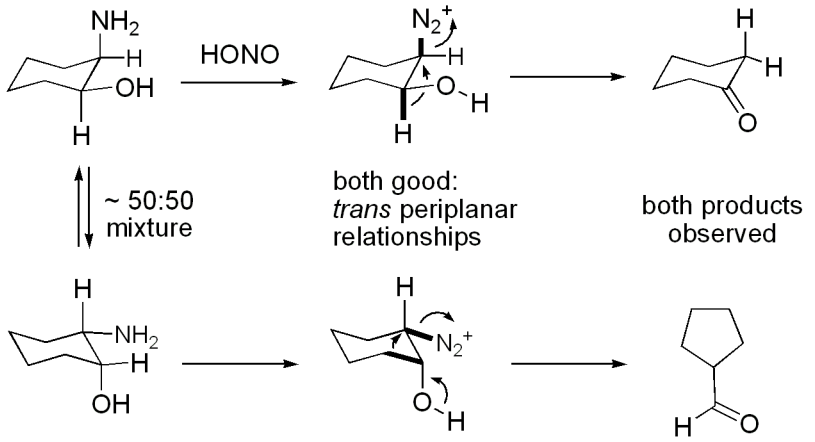
≡

trans periplanar arrangement



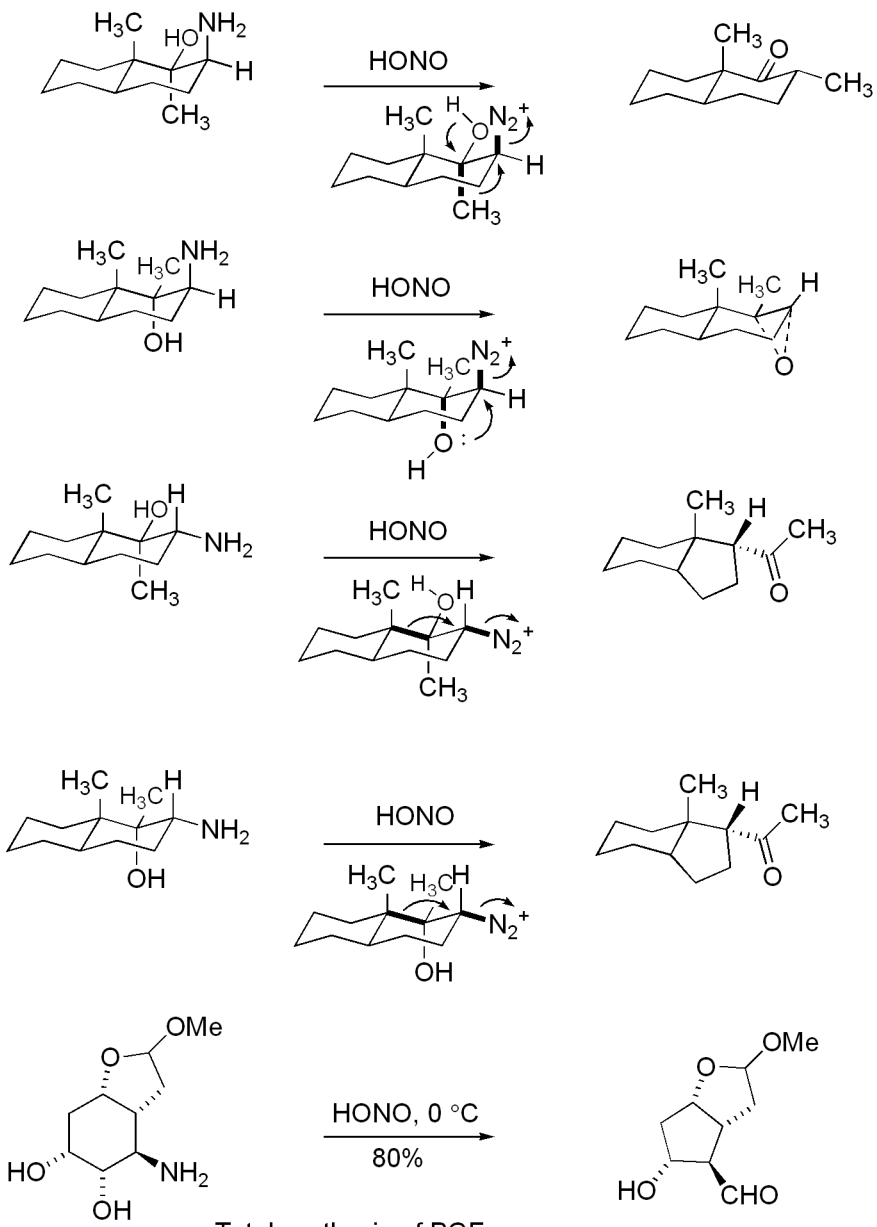
only product observed

Compare:



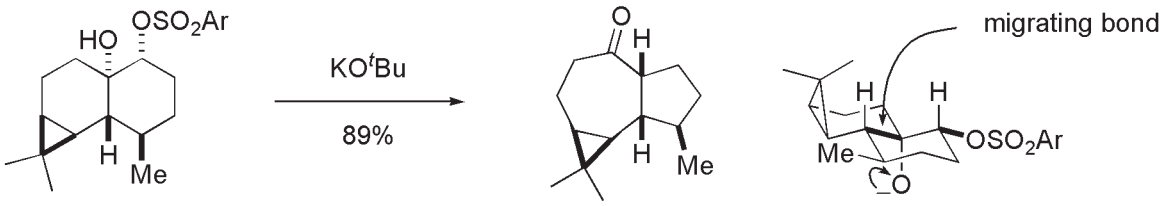
Stereoelectronic effects dominate the control of regioselectivity

Explain the following results:

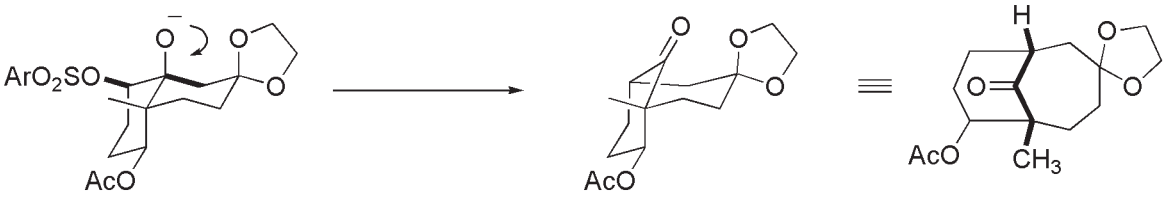


Total synthesis of $PGF_{2\alpha}$
Woodward *J. Am. Chem. Soc.* **1973**, *95*, 6853.

- Additional examples



Büchi *J. Am. Chem. Soc.* **1966**, *88*, 4113.



Heathcock *J. Am. Chem. Soc.* **1982**, *104,* 1907.

I. Pericyclic Reactions

1. Conservation of Orbital Symmetry, FMO Analysis

- Concerted reactions where there is a single transition state and no intermediates that proceed through cyclic transition states.
- Cyclic transition state corresponds to an allowed arrangement of participating orbitals that can maintain a bonding interaction between the reaction components throughout the course of the reaction. This dictates features of relative reactivity, regioselectivity, and diastereoselectivity.

- This also established the viability of utilizing Frontier Molecular Orbitals (FMO) composed of the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO) to analyze pericyclic reactions.

Woodward, Hoffmann *The Conservation of Orbital Symmetry,* Academic: New York, 1970.
J. Am. Chem. Soc. **1965**, *87*, 395, 2046, 2511, 4388, 4389.
Acc. Chem. Res. **1968**, *1*, 17.

Fukui *Acc. Chem. Res.* **1971**, *4*, 57; *Angew. Chem., Int. Ed. Eng.* **1982**, *21*, 801.

Encouraged by E. J. Corey, R. Hoffmann began examining mechanistic problems in organic chemistry and, as a junior fellow at Harvard, entered into a collaboration with R. B. Woodward that combined his insights in MO theory with Woodward's knowledge of experimental pericyclic reactions. This led to five papers in 1965 before he was 30 years old, that were the foundation of what we now refer to as the **Woodward–Hoffmann rules**.

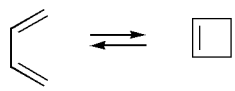
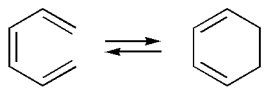
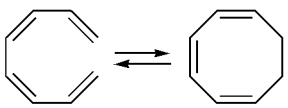
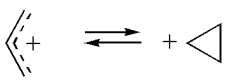
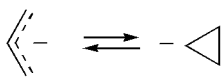
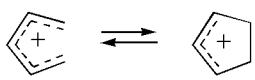
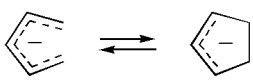
R. Hoffmann received the 1981 Nobel Prize in Chemistry for the launch and development of the concept of orbital symmetry conservation.

K. Fukui received the 1981 Nobel Prize in Chemistry for his Frontier Orbital theory of chemical reactivity.

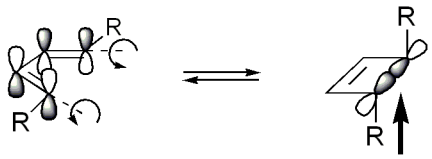
This followed the 1965 Nobel Prize in Chemistry awarded to R. B. Woodward for his contributions to the "art of organic synthesis".

2. Electrocyclic Reactions

- This is composed of a series of reactions in which a ring closure occurs with formation of a single bond at the ends of a linear, conjugated system of π electrons and the corresponding reverse reaction with ring opening.

System	π electrons	Thermal Reaction Ground State (HOMO)	hν Reaction Excited State (LUMO)
	4 π e⁻	conrotatory	disrotatory
	6 π e⁻	disrotatory	conrotatory
	8 π e⁻	conrotatory	disrotatory
	2 π e⁻	disrotatory	conrotatory
	4 π e⁻	conrotatory	disrotatory
	4 π e⁻	conrotatory	disrotatory
	6 π e⁻	disrotatory	conrotatory

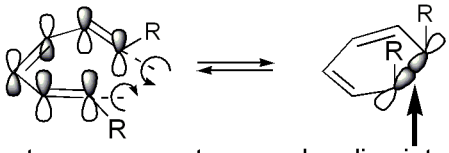
4 π e⁻ thermal reaction (ground state, HOMO)



conrotatory movement ⟶ bonding interaction

• Stereochemistry dictated by the orbital symmetry allowed reaction course

6 π e⁻ thermal reaction (ground state, HOMO)



disroratory movement ⟶ bonding interaction

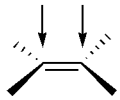
- Generalization:

No. of π electrons	Thermal	hν
4n π electrons (n = 0,1,...)	conrotatory	disrotatory
4n + 2 π electrons (n = 0,1,...)	disrotatory	conrotatory

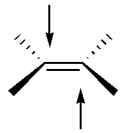
3. Cycloadditions and Cycloreversions

- These are discussed in terms of suprafacial or antarafacial addition to the ends of a π system.

Suprafacial



Antarafacial



- Generalization:

Total π electrons	Allowed in Ground State	Allowed in Excited State
4n	$m_s + n_a$	$m_s + n_s$
	$m_a + n_s$	$m_a + n_a$
4n + 2	$m_s + n_s$	$m_s + n_a$
	$m_a + n_a$	$m_a + n_s$

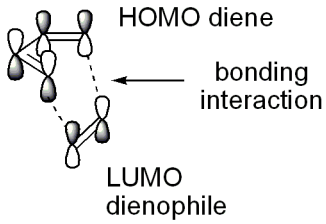
- Notations

orbital type (π, σ, ω) ⇨ $\pi 2_s$ ⇦ suprafacial (s) or antarafacial (a)

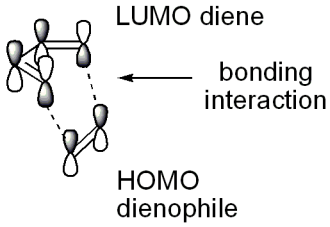
⇧ number of e^-

- Diels–Alder Reaction (6π e^-), Ground State Thermal Reaction

Normal Diels–Alder Reaction



Inverse Electron Demand Diels–Alder Reaction

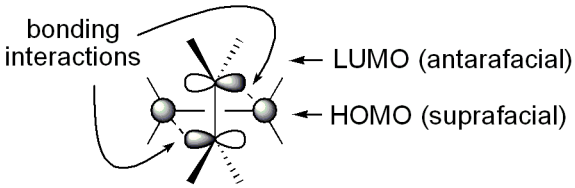


$[\pi 4_s + \pi 2_s]$ cycloaddition

- Suprafacial with respect to both reacting components and this defines the orientation with which the two reactants approach: boat transition state.
- The FMO analysis may also be used to predict relative rates, regioselectivity, and diastereoselectivity (*endo* effect) and we will discuss this in detail along with the Diels–Alder reaction.

- [2 + 2] Cycloaddition (4π e^-)

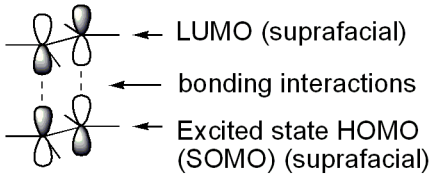
Ground State (thermal)



$[\pi 2_a + \pi 2_s]$ cycloaddition

- Antarafacial with respect to one olefin and suprafacial with respect to the second: dicates perpendicular approach to permit bonding.

Excited State ($h\nu$)



$[\pi 2_s + \pi 2_s]$ cycloaddition

- Suprafacial with respect to both olefins: dictates parallel (stacked) approach to permit bonding.

4. Sigmatropic Rearrangements

- Class of reactions characterized by migration of an allylic group from one end of a π system to the other.
- Generalization:

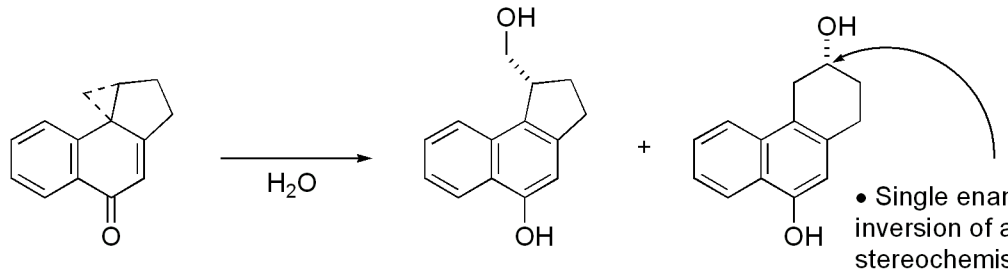
Total π electrons	Ground State	Excited State
4n	antara - supra supra - antara	antara - antara supra - supra
4n + 2	supra - supra antara - antara	antara - supra supra - antara

- These include a wide range of rearrangements including [1,3]-, [1,5]-, [1,7]-, [3,3]-, and [2,3]-sigmatropic reactions that we will discuss in detail.

J. Subtle Conformational and Stereoelectronic Effects on Reactivity and Reaction Regioselectivity

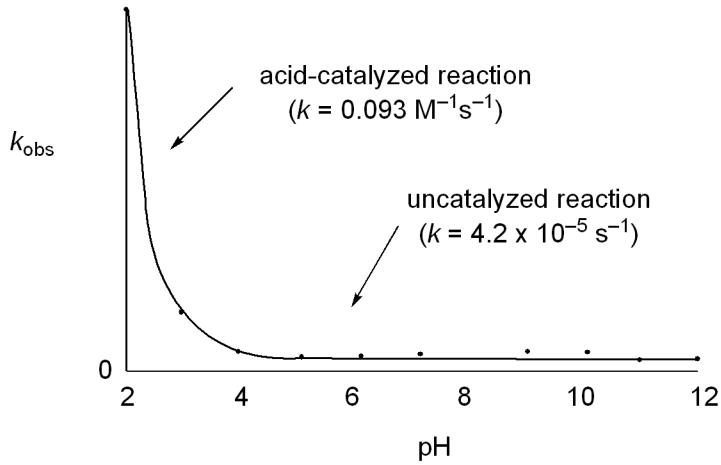
1. Kinetics, Stereochemistry, and Reaction Mechanisms

- Two of the cornerstones of defining a mechanism rest with the establishment of the stereochemistry of the reaction in conjunction with kinetic studies of the reaction.
- For example, for a reaction that might entail acid or base catalysis, it is common to examine a pH rate profile.



optically active 1 : 15

- Single enantiomer with inversion of absolute stereochemistry: therefore S_N2, not S_N1, ring opening.

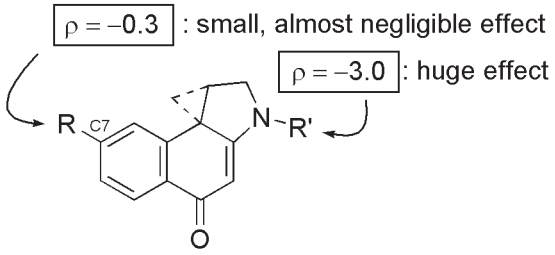


- Below pH 4, H^+ catalyzed reaction dominates.
- Above pH 4 (pH 4–12), the uncatalyzed direct S_N2 addition reaction dominates.

Boger *J. Org. Chem.* **1998**, *63*, 8004; *J. Org. Chem.* **1999**, *64*, 5666.

2. Substituent Effects

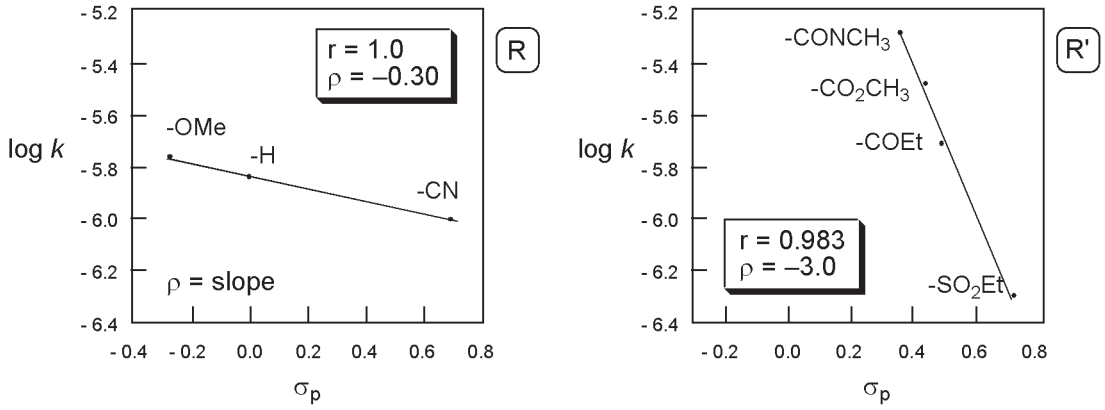
- These can be quantitated using a Hammett treatment and provide insights into reaction mechanisms.



- C7 substituents (R) have little effect on reactivity.
- N substituent (R') has a pronounced effect on reactivity and even subtle perturbations will change reactivity greatly ($-SO_2R \rightarrow -CO_2R$, 10×).

ρ values are characterized in a log scale

- The negative ρ value indicates δ^+ charge buildup in the rate-determining step of the reaction.



Boger *J. Am. Chem. Soc.* **1994**, *116*, 5523.
J. Org. Chem. **1996**, *61*, 1710 and 4894.

3. Structure versus Reactivity and Reaction Regioselectivity

- Structure can have a pronounced effect on reactivity and reaction regioselectivity.

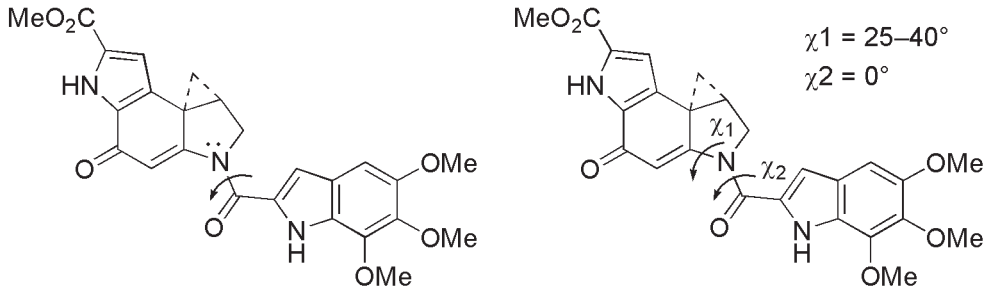
One nice example of this can be illustrated with a series of analogues related to CC-1065 and the duocarmycins which are potent antitumor antibiotics that derive their biological properties from a sequence-selective DNA alkylation reaction. The reactivity changes that one sees as a result of the loss of the vinylogous amide stabilization are related to the source of DNA alkylation catalysis.

Alexander R. Todd received the 1957 Nobel Prize in Chemistry for his work on the synthesis of nucleotides and nucleotide coenzymes.

Francis Crick and James Watson shared the 1962 Nobel Prize in Medicine for their elucidation of the structure of DNA.

Sydney Brenner, a part time resident at The Scripps Research Institute, received the 2002 Nobel Prize in Medicine for his discoveries concerning genetic regulation of organ development. He is also responsible for the discovery of messenger RNA.

Binding-induced conformational change: shape-selective catalysis



- DNA bound agent adopts helical conformation, twist adjusted at linking amide.
  - DNA bound agent maintains full amide. ($\chi 2 = 0°$)
  - Vinylogous amide stabilization diminished. ($\chi 1 = 25–40°$)
  - Cyclohexadienone structure destabilized.
- **Shape-dependent catalysis**: Preferential activation in AT-rich minor groove.

Binding induced twist greatest in the narrower, deeper AT-rich minor groove.

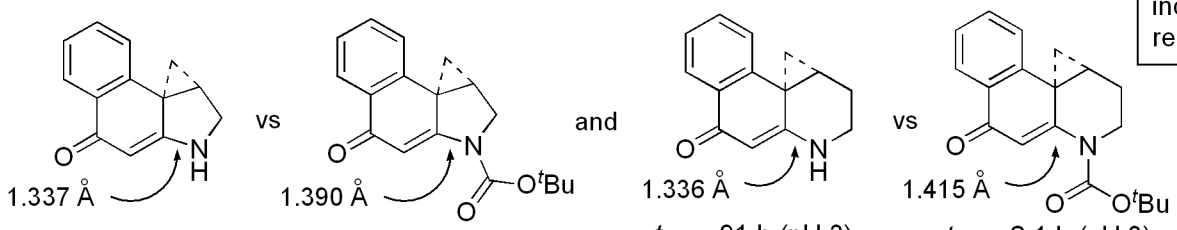
- **Shape-selective recognition**: Preferential binding in AT-rich minor groove.

Boger *J. Am. Chem. Soc.* **1997**, *119*, 4977 and 4987.
Boger, Garbaccio *Bioorg. Med. Chem.* **1997**, *5*, 263.
Acc. Chem. Res. **1999**, *32*, 1043.

- *N*-Acylation and its effect on vinylogous amide and cyclopropane conjugation.

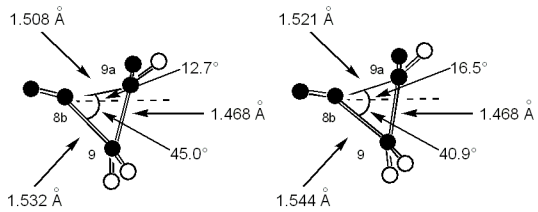
ca. 10–50× increase in reactivity

(+)-CBI vs (+)-*N*-BOC-CBI and (–)-CBQ vs (–)-*N*-BOC-CBQ

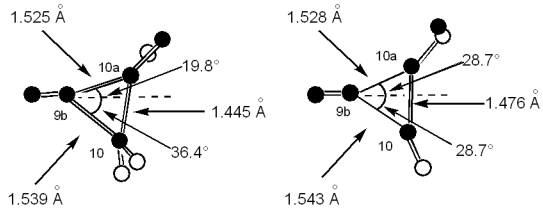


$t_{1/2}$ = 920 h (pH 3) | $t_{1/2}$ = 133 h (pH 3) | $t_{1/2}$ = 91 h (pH 3), $t_{1/2}$ = stable (pH 7) | $t_{1/2}$ = 2.1 h (pH 3), $t_{1/2}$ = 544 h (pH 7)

X-ray

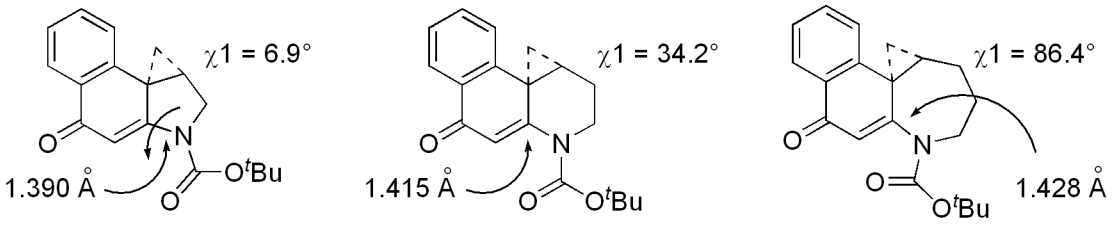


X-ray



- *N*-acylation decreases the cross-conjugated vinylogous amide conjugation, increases the cyclopropane conjugation and bond lengths, and increases cyclopropane reactivity. This is observed in the corresponding X-ray crystal structures.

- Amide twist effect on the vinylogous amide and cyclopropane conjugation.



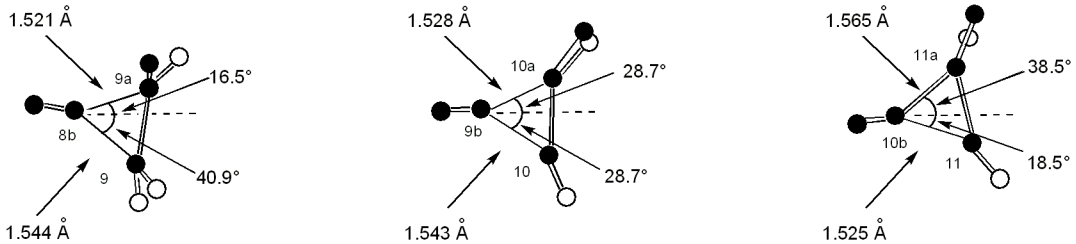
H^+ catalyzed reaction → $t_{1/2}$ = 133 h (pH 3) | $t_{1/2}$ = 2.1 h (pH 3) | $t_{1/2}$ = 0.03 h (pH 3)

Uncatalyzed reaction → $t_{1/2}$ = stable (pH 7) | $t_{1/2}$ = 544 h (pH 7) | $t_{1/2}$ = 2.1 h (pH 7)

- Decreases in vinylogous amide cross-conjugation
- Increases cyclopropane conjugation (bond lengths)
- Increases cyclopropane reactivity

10^4× increase in reactivity

X-ray



regioselectivity: > 20 : 1 | 3 : 2 | < 1 : 20

- Note the change in solvolysis regioselectivity where the stereoelectronically aligned cyclopropane bond is the bond which is cleaved. The stereoelectronically aligned bond is that which is positioned to best overlap with the developing π-system of the product phenol.

complete reversal of reaction regioselectivity

- In each case, the ring expansion occurred with generation of a single enantiomer by a S_N2 mechanism.

Boger *J. Org. Chem.* **1997**, *62*, 5849; *J. Am. Chem. Soc.* **1997**, *119*, 4977.

K. Methods for the Synthesis of Optically Active Materials

Morrison *Asymmetric Synthesis*, Academic: New York, 1983; Vol. 1–5.

Note: A summary of approaches which will be highlighted throughout the following material.

1. Partial Synthesis

- From readily available, naturally-derived optically active materials. Some examples include:

a. Progesterone from sapogenin diosgenin

b. Synthetic penicillins from the fermentation product 6-aminopenicillanic acid (6-APA)

c. Vitamin D_3 (1-hydroxycholecalciferol) from cholesterol

Louis Pasteur (1822–1895) conducted the first separation of a racemate into its enantiomers (by hand!) and by fractional crystallization. Thus, he conducted the first diastereomeric resolution (tartaric acid + quinine). His investigations into the process of fermentation led to the development of microbiology and the important method of preserving foods known as pasteurization. His research into immunity led to preventative vaccinations using weakened strains of bacteria. He developed the first vaccines for rabies.

2. Resolution

a. Diastereomeric salts and selective crystallization

b. Diastereomeric derivatization and chromatography or selective crystallization

c. Direct chromatographic resolution of enantiomers on an optically active stationary support

d. Enzymatic resolution

e. Kinetic resolution with selective production of desired enantiomer or selective consumption of undesired enantiomer

Advantage: Both enantiomers are made available

Disadvantage: 1/2 of the material is wasted if only one enantiomer is desired
Ambiguous assignment of absolute configuration

See: Jacques, Collet, Wilen *Enantiomers, Racemates, and Resolutions*, Wiley: New York, 1981.

A. J. P. Martin and B. L. M. Synge shared the 1952 Nobel Prize in Chemistry for developing the technique of liquid–liquid partition chromatography. The collaboration also led to the invention of gas–liquid partition chromatography (GLC). The use of chromatography can be traced back to a Russian botanist, M. Tswett, who separated plant pigments by such methods in 1906. Martin and Synge pioneered the rapid progress in this area made in the 1940's and early 1950's.

M. Tswett's work, published in 1906, described a column that was made of powdered $CaCO_3$ (chalk) and was used to separate chlorophyll into several colored bands and also identified the presence of carotene. He named the technique chromatography (Latin for color writing).

3. Synthesis from Chiral Pool

- Readily available, abundant or naturally occurring starting materials

a. Carbohydrates

b. Amino acids

c. α-Hydroxy carboxylic acids

d. Terpenes

e. Readily available, abundant natural products

O. Wallach, a colleague and collaborator of A. Kekule, received the 1910 Nobel Prize in Chemistry for his work on essential oils that converted the field of natural products from a disorganized collection of confusing observations into a complete, organized and integrated field. He established the isoprene rule.

4. Asymmetric Synthesis

a. Optically active reagent (Stoichiometric)
b. Optically active auxiliary incorporated into substrate (Stoichiometric)
c. Optically active catalyst (Catalytic)

See: Koskinen *Asymmetric Synthesis of Natural Products,* Wiley: New York, 1993.
Gawley, Aube *Principles of Asymmetric Synthesis,* Elsevier: Amsterdam, 1996.

5. Microbial, Enzymatic, or Catalytic Antibody Transformation

See: Wong, Whitesides *Enzymes in Synthetic Organic Chemistry,* Pergamon: Oxford, 1994.

Leonor Michaelis and Maude L. Menten published their work that created the foundation for modern enzyme kinetics in 1913. The Michaelis – Menten equation $V_o = V_{max}[S] / K_m + [S]$, was one of the earliest mathematical principles applied in biochemistry and was done at a time when the nature of enzymes remained mysterious.

Hans Lineweaver and Dean Burk are responsible for the most highly cited paper ever to appear in *J. Am. Chem. Soc.* **1934**, *56*, 658 - "The determination of enzyme dissociation constants." When it was published, Lineweaver was a 26 year old graduate student working with Burk, then 30 years old. Lineweaver transformed the Michaelis – Menten equation into $1 / V_o = K_m / V_{max}[S] + 1 / V_{max}$ where a plot of $1 / V_o$ vs $1 / [S]$, the double reciprocal plot, yields a straight line (vs hyperbolic curve for Michaelis – Menten) that provides K_m, V_{max}, and mechanistic insights into inhibitor action. Six referees and two rounds of reviews of the paper initially rejected its acceptance, but an editor accepted and published it anyway.