

# **CHM-4328**

## **Tactics and Strategies for the Construction of Complex Natural Products**

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# Some interesting quotes

*The World is made of the two parts, the full and the empty. The fullness is divided into small particles called atoms (indivisible). The atoms are infinite in number, eternal and absolutely simple. They are alike in quality but differ in shape, order and position. Every substance, every single object, is made up of those atoms. The possible combinations of which are infinite in an infinity of ways. The objects exist as long as the atoms constituting them remain together. They cease to exist when their atoms move away from one another. The endless changes of reality are due to the continual aggregation and disaggregation of atoms.*<sup>1</sup>

Democritus, fifth century B.C.

1. Sarton, G. In *Ancient Science Through in the Golden Age of Greece*, Dover Publications:New York, **1980**, p.253

*“The synthesis of substances occurring in Nature, perhaps in greater measure than activities in any other area of organic chemistry, provides a measure of the condition and power of the science”*<sup>2</sup>

R. B. Woodward (Nobel Laureate, 1965)

2. Woodward, R. B. In *Perspective in Organic Chemistry*, Todd, A.R., Ed., Interscience: New York, **1956**, p.155

*“The organic chemist is more than a logician and strategist; he is an explorer strongly influenced to speculate, to imagine, and even to create. These added elements provide the touch of artistry which can be included in a cataloging of the basic principles of synthesis but they are very real and extremely important”*<sup>3</sup>

E. J. Corey (Nobel Laureate, 1990)

3. Corey, E. J. *Pure and Appl. Chem.* **1967**, 14, 19.

# Kinetics and Thermodynamics of Organic Reactions

## A. Free Energy Relationship

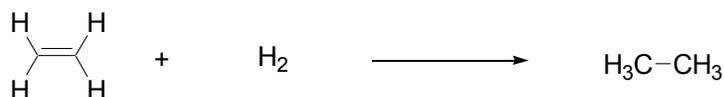
$$\Delta G = \Delta H - T\Delta S$$

The equilibrium for the reaction can be described by  $\ln K_{eq} = -\Delta G / RT$

In order to achieve a high ratio of products in a thermodynamically controlled reaction run under reversible conditions, one needs the following  $\Delta G$ 's:

$K(25\text{ }^\circ\text{C})$	$\Delta G$ (kcal/mol)	$K(0\text{ }^\circ\text{C})$	$\Delta G$ (kcal/mol)	$K(-78\text{ }^\circ\text{C})$	$\Delta G$ (kcal/mol)
2 (67:33)	0.41	2.1 (68:32)	0.41	2.9 (75:25)	0.41
5 (83:17)	0.95	5.7 (85:15)	0.95	11.6 (92:8)	0.95
9 (90:10)	1.30	10.9 (92:18)	1.30	28.5 (97:3)	1.30
20 (95:5)	1.74	27.5 (96:4)	1.80	103.3 (99:1)	1.80
99 (99:1)	2.73				
999 (99.9:0.1)	4.09				

Example:



Bonds broken:      1 C=C      163kcal/mol  
                           1 H-H      104 kcal/mol  
                           total      267 kcal/mol

Bonds formed:      1 C-C      88 kcal/mol  
                           2 C-H      2X98 kcal/mol  
                           total      284 kcal/mol

Overall:  $\Delta G = -17$  kcal/mol thus reaction favorable

## B. Transition State Theory

The nature of the rate constant  $k_r$  can be discussed in terms of Transition State (TS) Theory. This is a general theory for analyzing the energetic and entropic components of a reaction process. In TS theory, a reaction is assumed to involve the attainment of an activated complex that goes on to product at an extremely rapid rate. The rate of decomposition of the activated complex has been calculated from the assumptions of the theory to be  $6 \times 10^{12} \text{ s}^{-1}$  at room temperature and is given by the following expression:

$$\text{Rate of activated complex decomposition} = \kappa kT/h$$

$\kappa$  = transmission coefficient (usually 1)

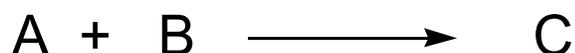
$k$  = Boltzmann's constant

$h$  = Planck's constant

$T$  = Absolute temp.

Thus,

$$\text{Rate of reaction} = (\kappa kT/h) [\text{TS}]$$



$$K^\ddagger = [\text{TS}]/[\text{A}][\text{B}]$$

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

$\Delta G^\ddagger$  = Free Energy of Activation

$\Delta H^\ddagger$  = Enthalpy of Activation: Difference in bond energy between reactants and transition state.

$-T\Delta S^\ddagger$  = Entropy of Activation:  $\Delta S^\ddagger$  usually negative thus making the change more endothermic.

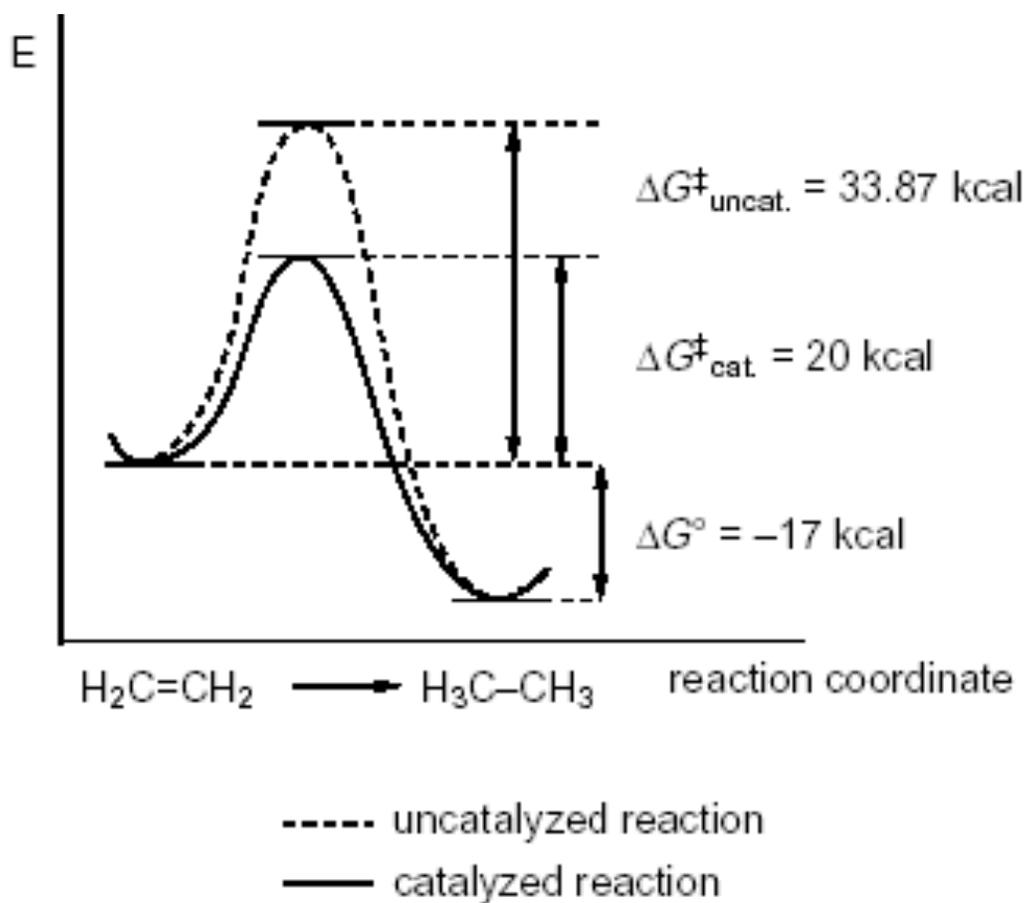
$$\text{From } \Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger, \Delta G^\ddagger = -RT \ln K^\ddagger$$

$$\text{Rate} = (\kappa kT/h) [\text{TS}]$$

$$[\text{TS}] = K^\ddagger [\text{A}][\text{B}] \text{ and } K^\ddagger = e^{-\Delta G^\ddagger/RT}$$

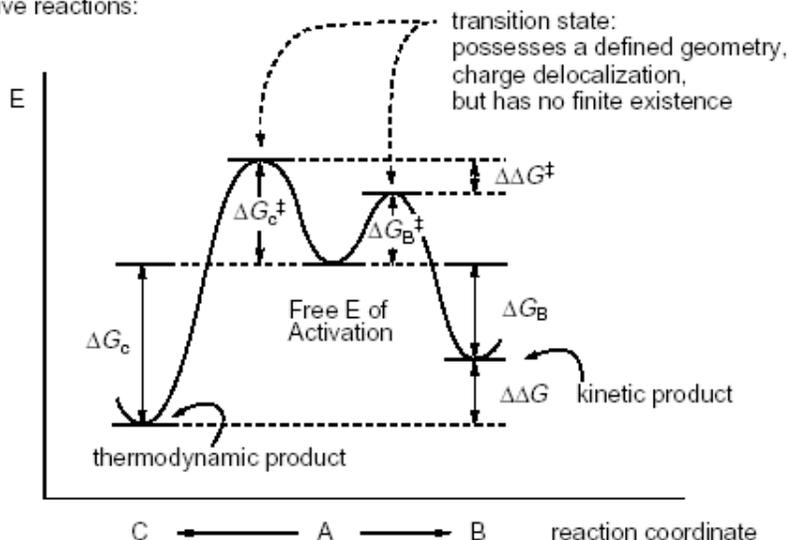
$$\text{Rate} = (\kappa kT/h) (e^{-\Delta G^\ddagger/RT}) [\text{A}][\text{B}]$$

$$\text{Rate} = k_f [\text{A}][\text{B}]$$



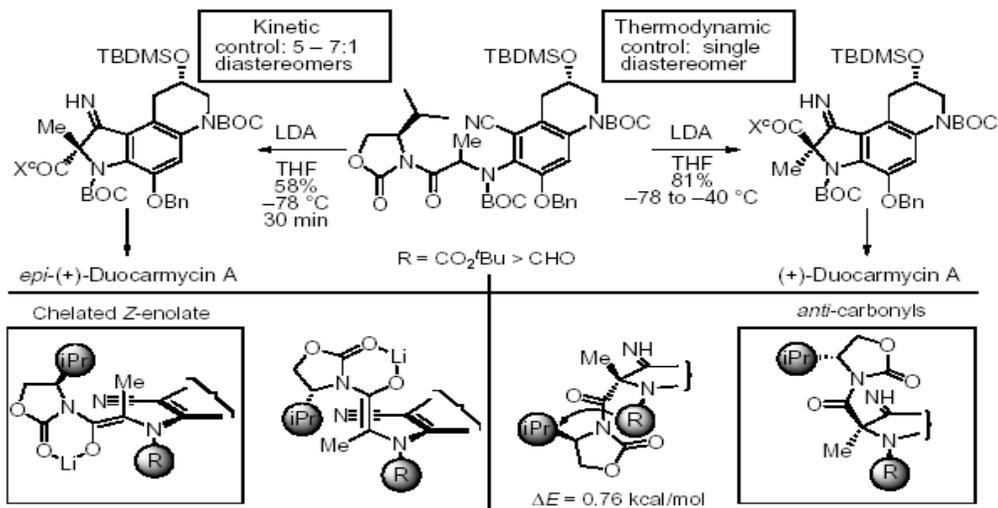
## C. Kinetic and Thermodynamic Control

– For competitive reactions:



If this is an irreversible reaction, most of the reaction product will be B (kinetic product).  
 If this is a reversible reaction, most of the product will be C (more stable, thermodynamic product).

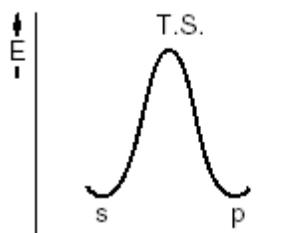
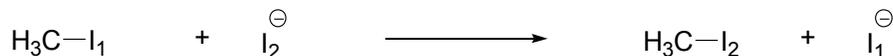
A beautiful example by Boger et al (J. Am. Chem. Soc. 1997, 119, 311) illustrated the kinetic versus thermodynamic asymmetric Dieckmann-like condensation. The most stable product (lower  $\Delta G$ ) was observed upon conducting the reaction under equilibrating conditions (thermodynamic conditions) for the reversible reaction. The alternative kinetic product (lower  $\Delta G^\ddagger$ ) was observed when the reaction was conducted under lower temperature and nonequilibrating conditions (kinetic conditions)



## D. Hammond Postulate

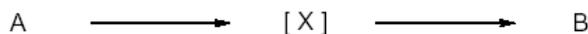
The geometry of the transition state for a step most closely resembles the reactant or product to which it is closer in energy. In other words, *reactions endothermic will have a late transition state which resemble to the final product. Reactions exothermic will have an early transition state which resemble to the reactant.*

Example:

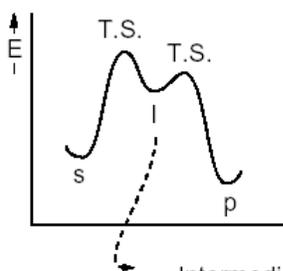
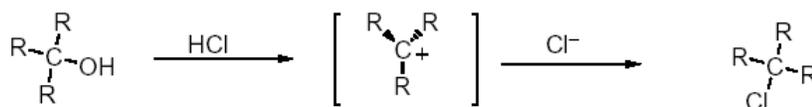


Thermoneutral reaction – transition state resembles both starting material and product equally

For reactions which proceed through an intermediate: solvolysis of tertiary alcohol



X: discrete intermediate



G. A. Olah received the 1994 Nobel Prize in Chemistry for his contributions to carbocation chemistry.

Resemble the geometry of the carbocation intermediate and not that of the reactant (alcohol) or product (alkyl chloride).

Intermediate (for this reaction it will be  $\text{C}^+$  so T.S.  $\Rightarrow$  I)

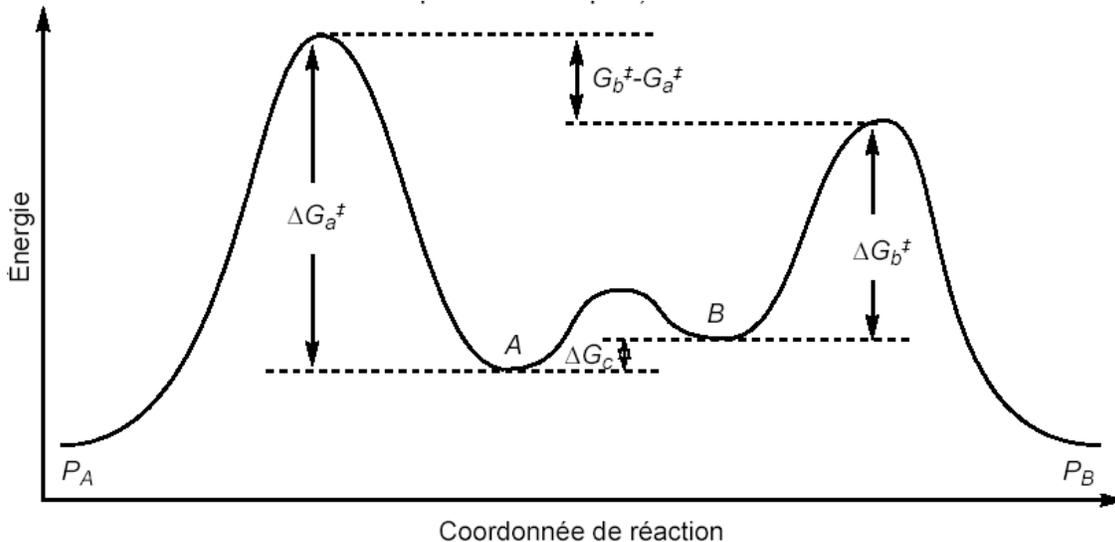
### Notes

- 20 kcal/mol energy available at 25 °C for free energy of activation.
- Increase reaction temperature, increase the rate of reaction.
- Decrease reaction temperature, decrease the rate of reaction, but increase the selectivity of the reaction.

Hammond *J. Am. Chem. Soc.* **1955**, 77, 334.  
Farcasiu *J. Chem. Ed.* **1975**, 52, 76.

## E. Curtin-Hammett Principle

The conclusion that the ratio of products formed from conformational isomers is not determined by the population ratio is known as the Curtin-Hammett principle. In most cases, the energy of activation for a chemical reaction will be greater than that for a conformational equilibrium as is illustrated in the figure below. If it is the case  $\Delta G_a^\ddagger$  and  $\Delta G_b^\ddagger \gg \Delta G_c^\ddagger$ . The conformers of the reactant are in equilibrium and are interconverted at a rate much faster than that at which the competing reactions occur.



rate of the formation of product P<sub>A</sub> = dP<sub>A</sub>/dt = k<sub>a</sub>[A] = k<sub>a</sub>K<sub>c</sub>[B]

rate of formation of product P<sub>B</sub> = dP<sub>B</sub>/dt = k<sub>b</sub>[B]

Product ratio = (dP<sub>A</sub>/dt)/(dP<sub>B</sub>/dt) = k<sub>a</sub>K<sub>c</sub>[B]/k<sub>b</sub>[B] = k<sub>a</sub>K<sub>c</sub>/k<sub>b</sub>

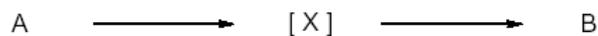
According to transition theory,

$$k_r = (\kappa kT/h) (e^{-\Delta G^\ddagger/RT}) \text{ and } K_c = e^{-(\Delta G_c)/RT}$$

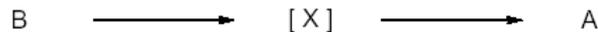
$$\text{Thus, product ratio} = e^{(-\Delta G_a^\ddagger + \Delta G_b^\ddagger + \Delta G_c)/RT} = e^{(G_b^\ddagger - G_a^\ddagger)/RT}$$

## F. Principle of Microscopic Reversibility

The forward or reverse reactions, run under identical conditions, must proceed by the same mechanism i.e., if forward reaction proceeds via intermediate X



then reverse reaction also goes through X.



# Fragmentation Reactions

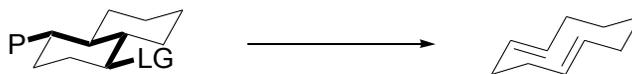
Grob et al. *Angew. Chem., Int. Ed. Eng.* **1969**, 8, 535.

## Different types of fragmentation

### *Interannular*



### *Intraannular*



### *Extraannular*

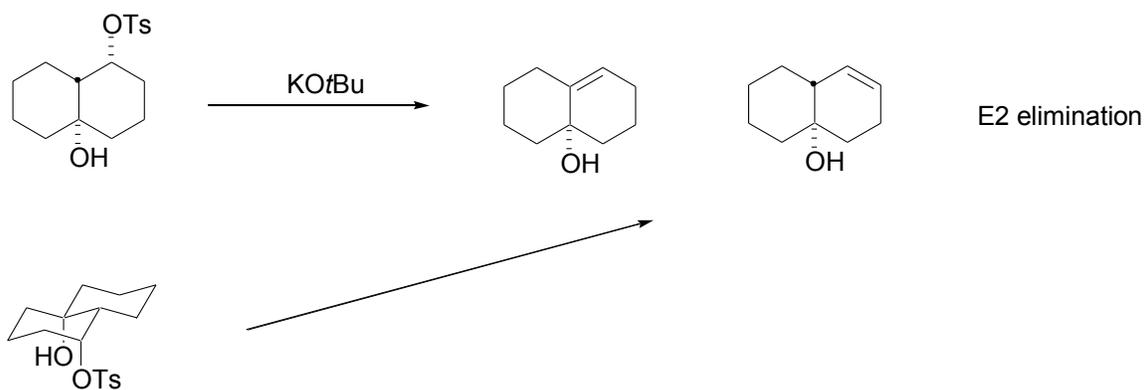


- ***Trans antiperiplanar arrangement of participating bond orbital and departing bond orbital.***

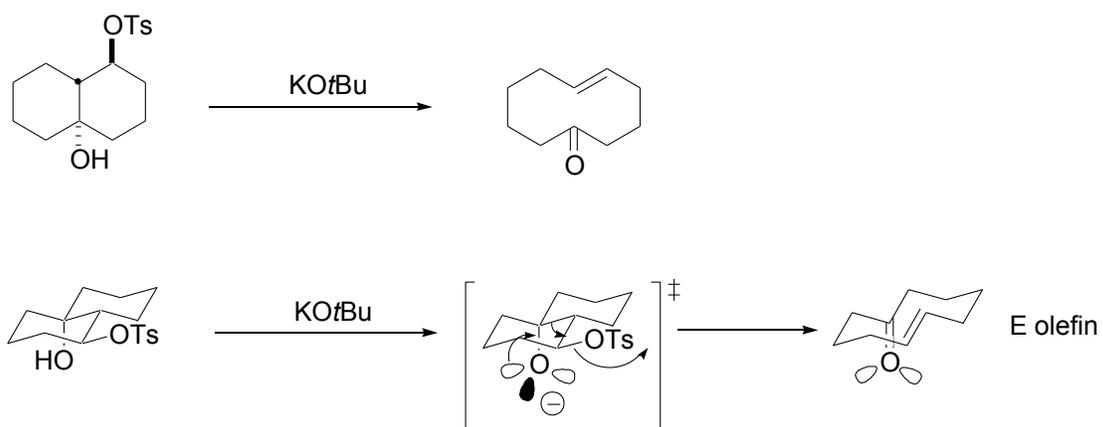
Wharton *J. Org. Chem.* **1965**, 30, 3254

Fuchs *J. Am. Chem. Soc.* **1979**, 101, 3567

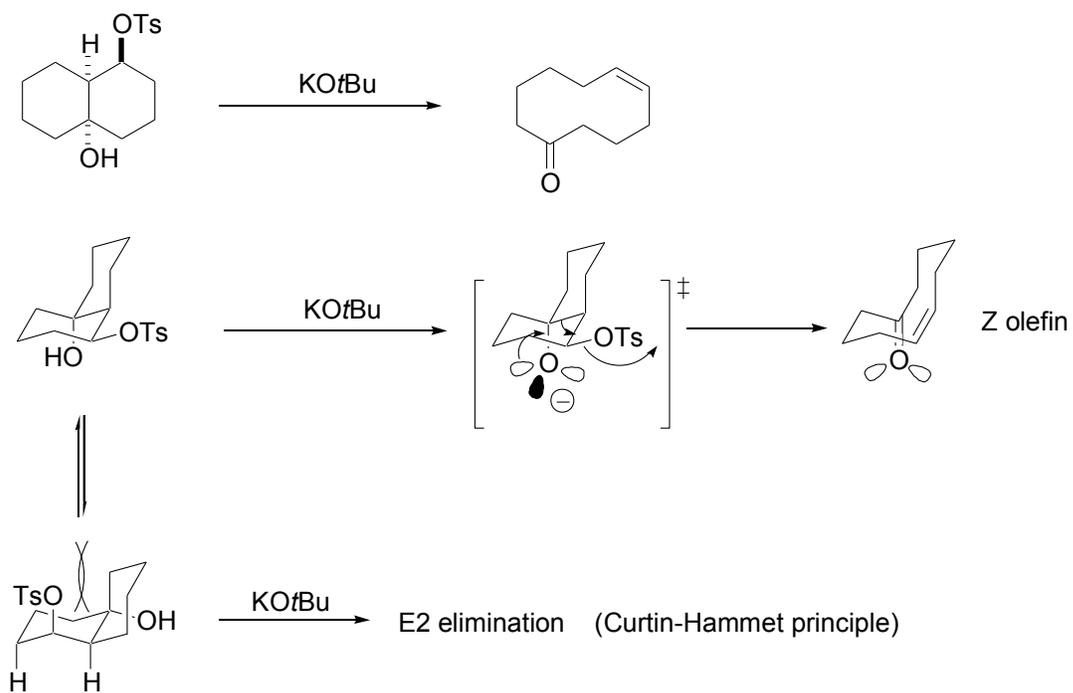
### Case 1



### Case 2



### Case 3



### Case 4

