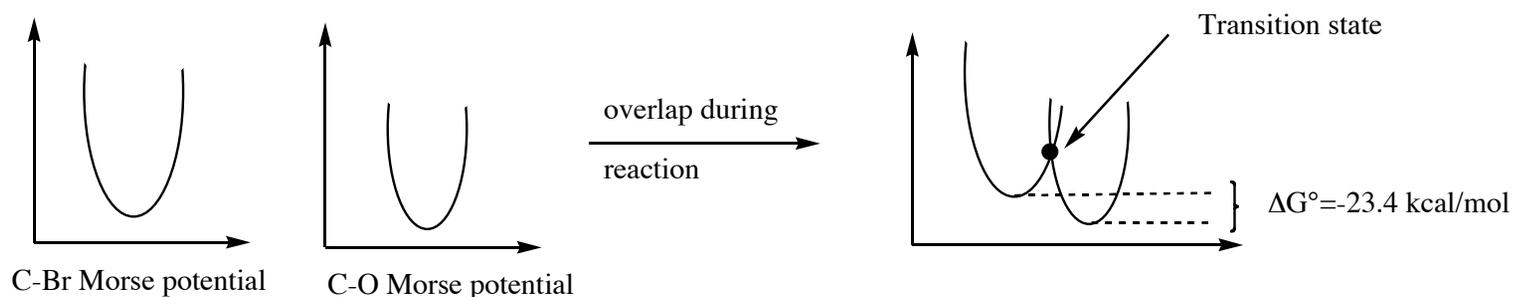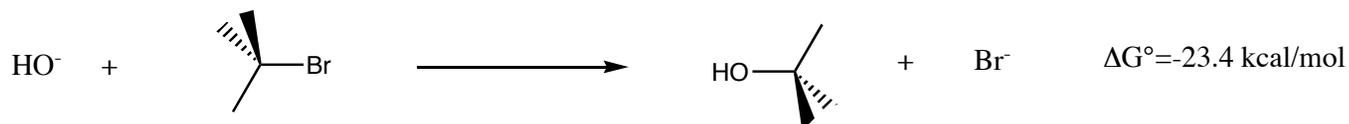# Marcus Theory

The relationship of reaction energy barrier height to exo- or endothemricity of a reaction

Consider an SN2 reaction (single step process, no intermediates)

HO^- +   [structure]—Br $\longrightarrow$ HO—[structure]   + Br^- $\Delta G°=-23.4$ kcal/mol

C-Br Morse potential   C-O Morse potential

overlap during reaction

Transition state

$\Delta G°=-23.4$ kcal/mol

As the reaction becomes more exothermic, the energy barrier (s.m=>T.S.) becomes zero, and then increases again, leading to a **Marcus Inverted Region**

$\Delta G°$

Zero energy barrier for reaction

$\Delta G°$

Transition state in Marcus inverted region

$\Delta G°$
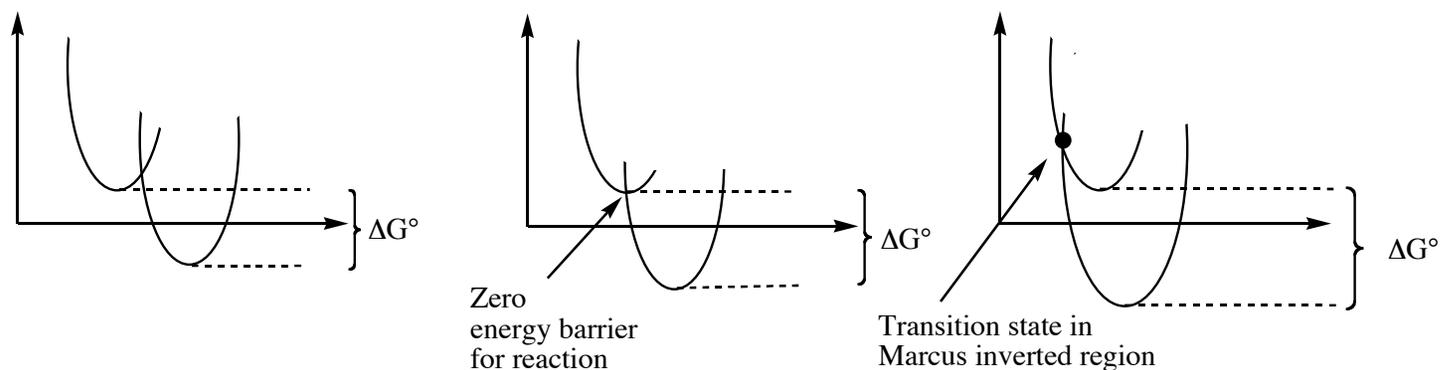
Discovery of Marcus inverted region: *JACS*, **106**, *3047* (1984); *Science*, **240**, *440* (1988)

Tunneling

When $k_H/k_D = 50$ or greater, indicative of Quantum Mechanical Tunneling

Tunneling involves penetration of the wavefunction for a molecule <u>through</u> a barrier rather than over it tunneling is very sensitive to the mass of the tunneling particle, thus tunneling is usually associated with proton or hydrogen transfers or electron transfers. Tunneling rate is much less sensitive to temperature than typical reactions, thus tunneling becomes a very important process at low temperatures, where even the smallest barrier could not be overcome, but it can be tunneled through.

$$k=QAe^{-Ea/RT}$$
$$Q= e^{\alpha}/\beta-\alpha(\beta e^{-\alpha}-\alpha e^{-\beta})$$
$$\alpha=E/RT$$
$$\beta = 2a\pi^2(2mE)^{1/2}/h$$

Example:

$k_H/k_D=74$
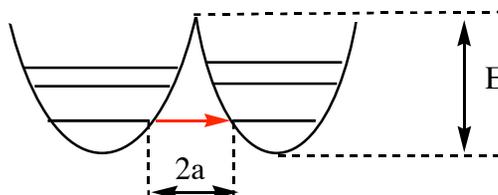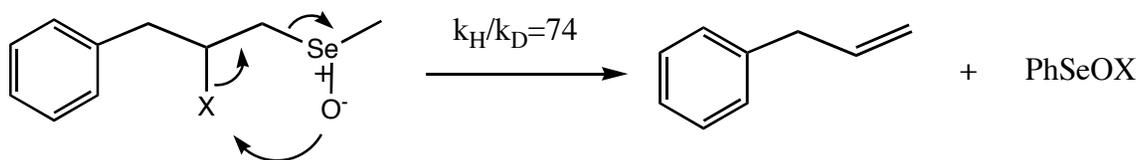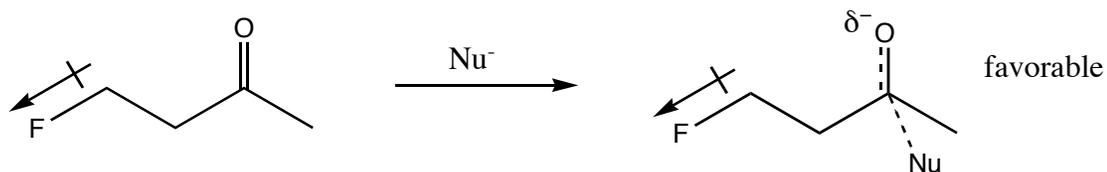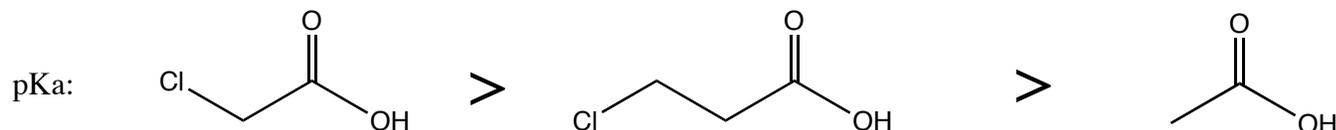
JACS, **103**, *1232* (1981)
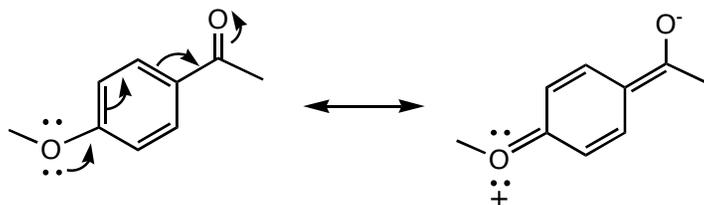
Substitutent Effects

Field Effects: through space electrostatic interaction resulting from the orientation of dipoles within molecules.

Inductive Effects: ability of an atom or group to withdraw or donate electron density through sigma bonds

Resonance Effects: ability of an atom or group to withdraw or donate electron density through pi bonds

Polarizability Effects: the extent to which the electron cloud of an atom can undergo distortion: hard/soft nucleophiles/leaving groups. Thus, sulfide, RS^- is a better nucleophile and a better leaving group than alkoxide RO^-, because in both leaving group departure and nucleophilic attack, the electron clouds must be distorted.

Steric Effects: The size of a group influences the rate of reaction: SN2, rate $CH_3-I > Et-I > iPr-I > tBu-I$

Solvation Effects: Field effects in the substrate/T.S. can become important because solvent dipoles may become directly involved in the reaction

Linear Free-Energy Relationships

Structure-Reactivity Relationships

Describes the manner in which the reactivity of a molecule changes when substitutents are introduced
Thus, we are studying several different reactions, and asking the question: "How do free energies of
reaction and activation vary with structure?"
What varies from reaction type to reaction type is the magnitude of the effect

1. Hammett Plot: a general method for examining changes in charge during a reaction

Reference Reaction: assess the ability of substitutents in the meta or para position to influence the acidity
of benzoic acid. Steric effects are avoided in this analysis.
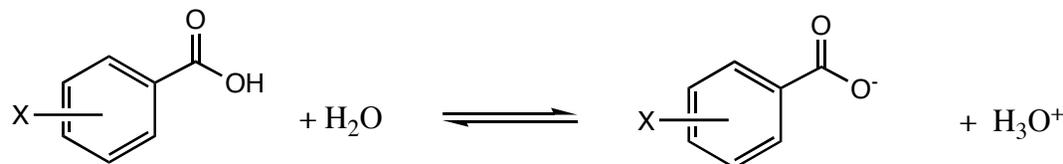
$$\text{Define} \implies \quad \log(K_X/K_H) = \sigma_X \qquad \text{Tables for } \sigma_{meta} \text{ and } \sigma_{para} \text{ have been tabulated}$$

when $\sigma < 0$, the substituted benzoic acid is less acidic than benzoic acid (an electron donating group)
when $\sigma > 0$, the substituted benzoic acid is more acidic than benzoic acid (an electron withrawing group)

EDG's destabilize carboxylate negative charge, EWG's stabilize carboxylate negative charge

Note: some groups have positive σ_{meta} and negative σ_{para} and vice-versa.

$$-OCH_3: \quad \sigma_{meta} = 0.1 \qquad \sigma_{para} = -0.12$$

good   bad
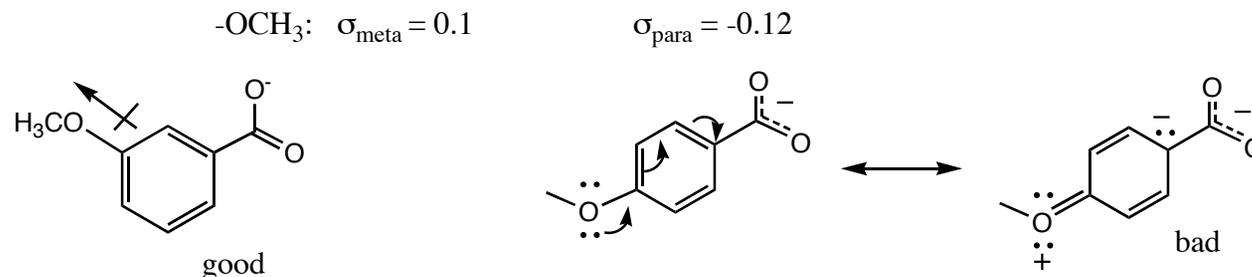
σ Values for Several Commonly Encountered Substituents

Substituent	σ_{meta}	σ_{para}	σ^+	σ^-
-NH$_2$	-0.09	-0.30	-1.3	
-OCH$_3$	0.10	-0.12	-0.78	
-CH$_3$	-0.06	-0.14	-0.31	
-Ph	0.05	0.05	-0.18	0.08
-I	0.35	0.18	0.13	
-Br	0.37	0.26	0.15	
-Cl	0.37	0.24	0.11	
-CF$_3$	0.46	0.53		0.74
-CN	0.62	0.70		0.99
-NO$_2$	0.71	0.81		1.23

Hammet Relation, I

Structure-Reactivity Relationships

We now have a reference reaction for a case where negative (or positive) charge is created in the course of a reaction.

1. For a Thermodynamic Analysis of other reaction types according to this reference:

$$\log (K_X/K_H) = \rho\sigma_X$$

2. For a Kinetic Analysis of other reaction types according to this reference:

$$\log (k_X/k_H) = \rho\sigma_X$$

Note that ρ is the slope of a plot of $\log (K_X/K_H)$ vs. σ_X or of $\log (k_X/k_H)$ vs σ_X.

ρ describes the sensitivity of the new reaction to the substitutent effects relative to the substitutent effect on the ionization of benzoic acid. ρ is called the **reaction constant** or **sensitvity constant**

When $\rho>1$, the reaction under study is more sensitive to substitutents than benzoic acid, and negative charge is building during the reaction

When $0<\rho<1$, the reaction is less sensitive to substituents than benzoic acid, but negative change is still building
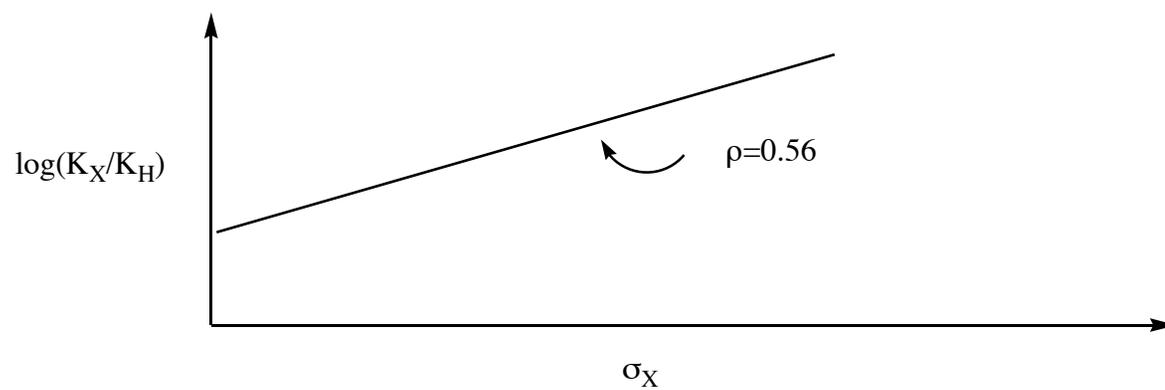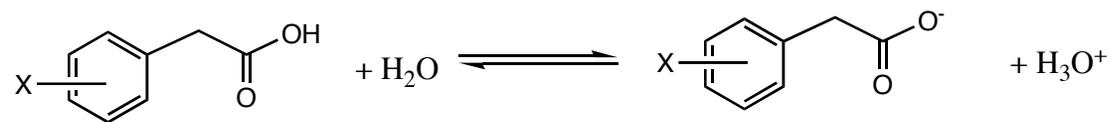
When $\rho=0$, there is no substituent effect

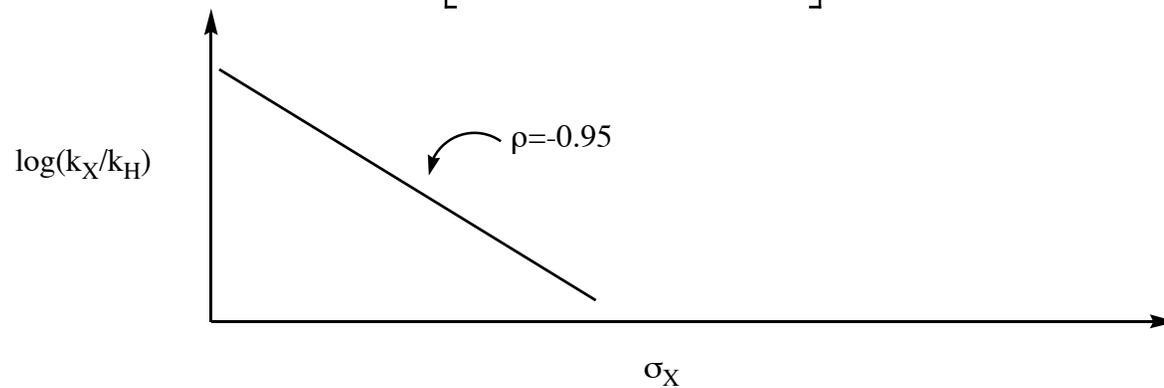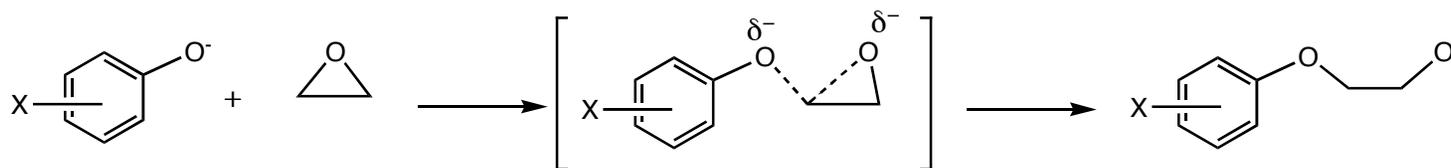**When $\rho<0$ the reaction is either diminishing in negative charge or creating a positive charge.**
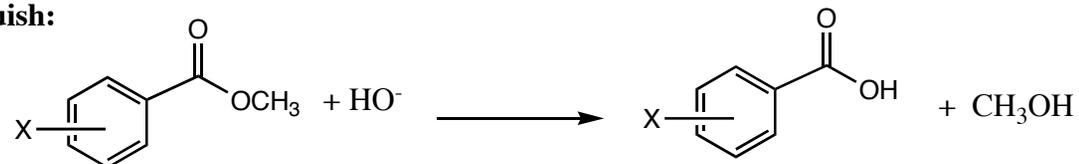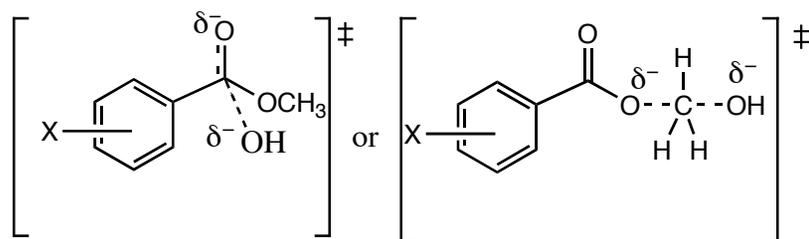
Hammet Relation, II

Examples

A

B

Hammet Relation, III

ρ indicates a change in charge when comparing reactant to transition state (kinetic) or product (thermodynamic)

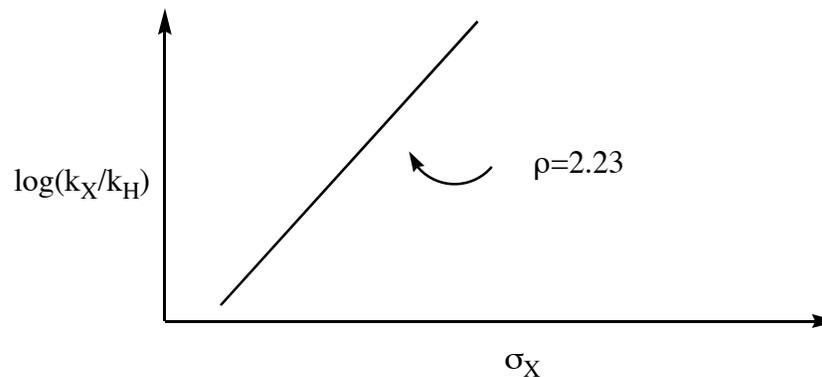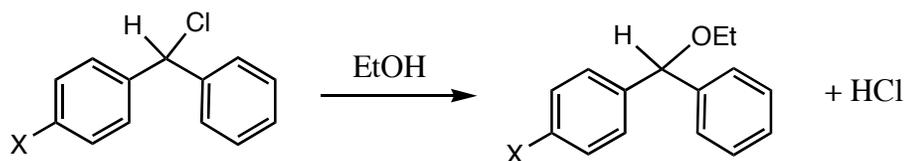**A. Cannot distinguish:**

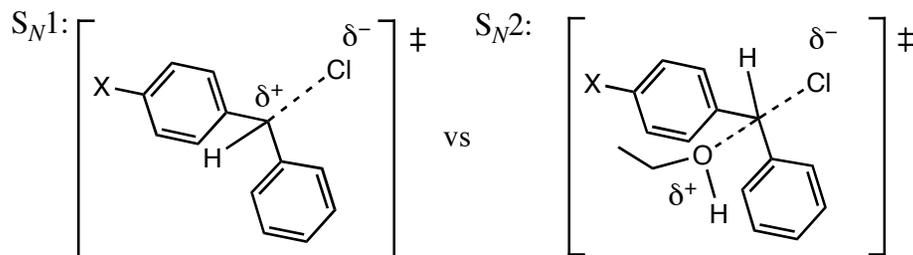Transition state for rate determining step:

negative charge buildup in T.S. stabilized by EWG's

$\rho = 2.23$

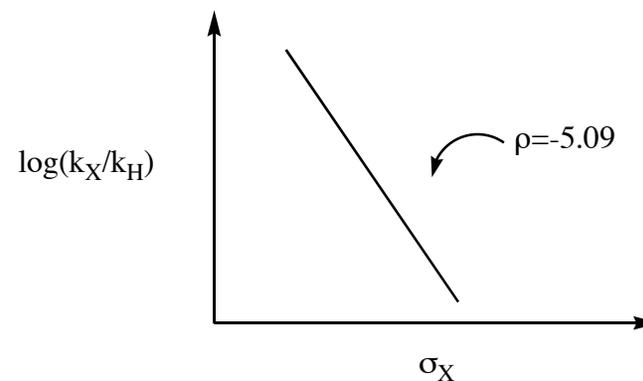$\log(k_X/k_H)$ vs σ_X

B. Can distinguish:

Transition state for rate-determining step:

S_N1: expect large negative ρ

vs

S_N2: not much change in charge on C

$\rho = -5.09$

$\log(k_X/k_H)$ vs σ_X

Hammet Relation, IV
Non-Linear Hammet plots

ρ will be linear if there is a consistent amount of charge in the transition state regardless of the substitutent attached
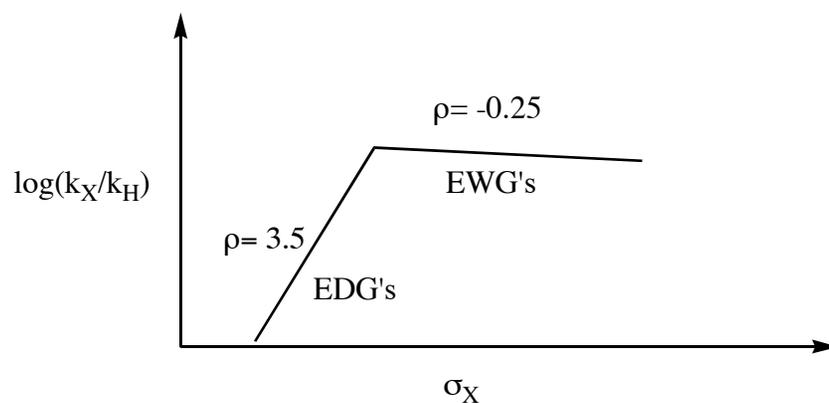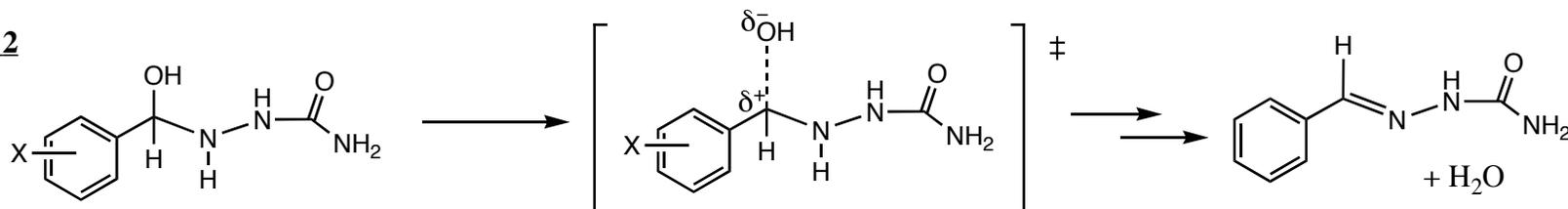
When the transition state does change significantly with regard to the extent of charge development, the Hammett plot will not be linear.

An abrupt change in the slope of the plot with two intersecting lines can indicate a change in the rate-determining step or a change in mechanism

Step 1

Step 2

$\rho = -0.25$

$\log(k_X/k_H)$

$\rho = 3.5$

EWG's

EDG's

σ_X
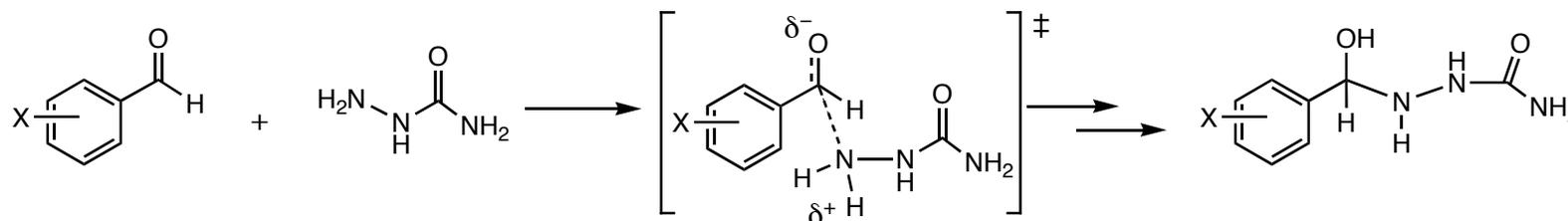
For EWG's, first step is fast and second step is slow (RDS)

For EDG's, first step is slow (RDS) and second step is fast.

Taking into account Resonance

A new scale was developed to account for resonance in a way that the ordinary σ_X values could not (there is no resonance between the carboxylate ion and the substituent)
Define:
σ^- :groups that stabilize negative charge by resonance
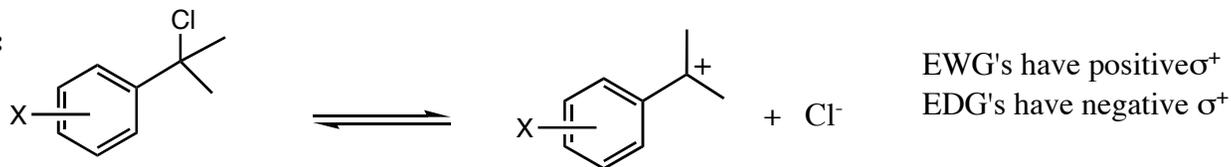**σ^+ :groups that stabilize positive charge by resonance**

Reference reactions for development of new substitutent constants

σ^- scale:

σ^+ scale:

EWG's have positiveσ^+
EDG's have negative σ^+

With σ_X, σ^-, σ^+ values ,one develops plots based on the various σ values and determines which has the least amount of scatter , thereby indicating if the charge involved is dominated by inductive (σ_X) or resonance (σ^-, σ^+) effects.

The sensitivity of a reaction to resonance relative to benzoic acid ionization: r

$$\log (k_X/k_H) = \rho[\sigma + r(\sigma^+ - \sigma)]$$
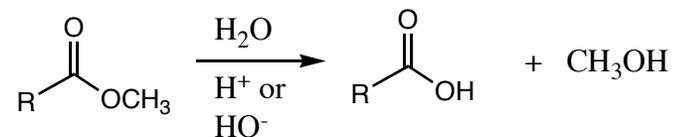
r=0 no difference relative to benzoic acid ionization
r>0 the new reaction is more sensitive to resonance effects than benzoic acid
r<0 the new reaction is less sensitive to resonance effects than benzoic acid

Taft Parameters

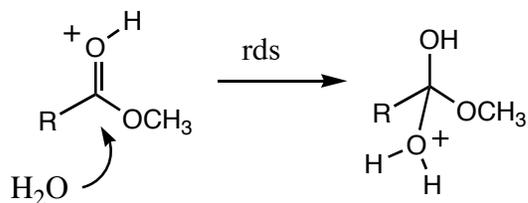**Taking into account steric and polar effects, new parameters E_S and σ^* were defined by Taft**

Reference Reaction:

$$\log (k_S/k_{CH3})=E_S \quad \text{where } E_S \text{ is the steric constant}$$

Steric constant defined from acid-catalyzed reaction where there is little influence of polar effects:
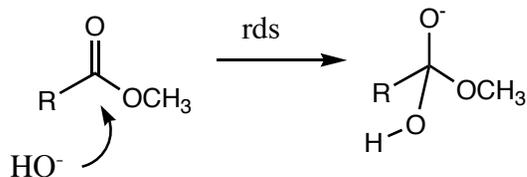
A:

$$\log (k_S/k_{CH3})= \rho^*\sigma^* + \delta E_S$$

| R Group	E_S	σ^*
-H	1.24	0.49
-Et	-0.07	-0.10
-i-Pr	-0.47	-0.19
-t-Bu	-1.54	-0.30
-CH$_2$Ph	-0.38	0.22
-Ph	-2.55	0.60

B:

$$\sigma^*= 1/2.48 \left[\log(k/k_o)_B - \log (k/k_o)_A \right]$$

Thus, ρ^* and δ are the sensitivity factors for a new reaction to polar (field, induction) and steric effects relative to the reference reaction, hydrolysis of methyl esters.

Solvent Effects: Grunwald-Winstein Plots

**Evaluating the extent of solvent participation/ charge build-up
in the rate-determining step transition-state**

Reference Reaction: SN1 reaction of *t*-BuCl

in 80% EtOH

$+ Cl^-$
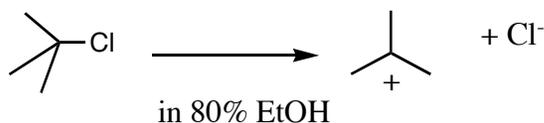
$\log (k_{tBuCl, solv}/k_{tBuCl, 80\%EtOH}) = Y$
and
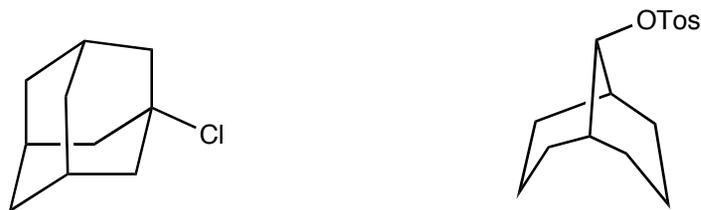$\log (k_{new, solv}/k_{new, 80\%EtOH}) = mY$

tabulate a solvent scale:
**Y a measure of
ionizing ability of solvent**

m is the sensitivity factor for the new reaction to a change in solvent

m=1   full ionization in rate determining step (no nucleophilic participation by solvent); maximum sensitivity to ionizing ability
       of solvent (completely SN1)
m<1 reaction not as sensitive to ionizing ability of solvent as tBuCl and there is less charge buildup
        in the transition state (nucleophilic participation by solvent involved); in other words, the reaction
        has some SN2 character

Alternative reference reactions:

Nucleophilic participation by solvent:

$solv. + CH_3OTs \longrightarrow solv\text{-}CH_3 + {}^-OTs$

$N_{OTs} = \log (k_{solv}/k_{80\%EtOH})$

$\log (k_{new,solv}/k_{new, 80\%EtOH}) = l\,N_{OTs} + m\,Y_{Cl}$

$\log(k_{1\text{-ada-Cl,sol}}/k_{1\text{-ada-Cl, }80\%EtOH}) = Y_{Cl}$ $\log(k_{2\text{-ada-OTs,sol}}/k_{2\text{-ada-OTs, }80\%EtOH}) = Y_{OTs}$

represent pure ionization

Swain-Scott Nucleophilicity Parameters

Evaluating extent of bonding of the nucleophile in the transition state
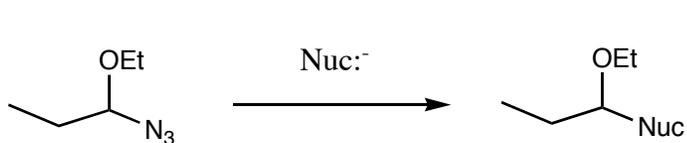
Reference Reaction: SN2 reaction

$$CH_3-I \ + \ H_2O \longrightarrow CH_3-OH \ + \ HI$$

$$\log(k_{CH3I, NucX}/k_{CH3I, H2O}) = n_X \longleftarrow \text{nucleophile parameter}$$

$$\log (k_{new, NucX}/k_{new, H2O}) = s\, n_X \qquad \text{s=sensitivity of the reaction to the type of nucleophile used (good/poor)}$$
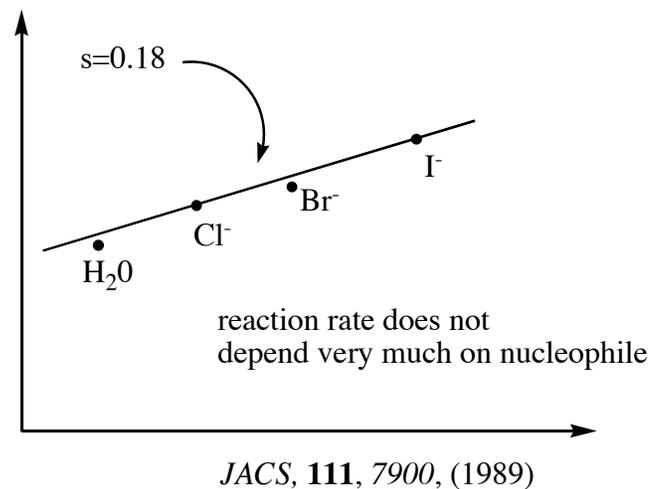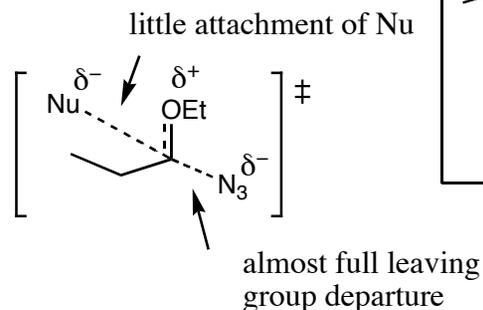
low s values: little bonding of nucleophile in the transition state, an early T.S. The reaction is not sensitive to the type of of nucleophile used.

high s values: strong bonding of nucleophile in the transition state, a late transition state, very sensitive to the type of nucleophile used

Nucleophile	n_X
H_2O	0.0
F^-	2.7
Cl^-	4.37
Br^-	5.79
I^-	7.42

little attachment of Nu

almost full leaving group departure

s=0.18

reaction rate does not depend very much on nucleophile

JACS, **111**, *7900*, (1989)

Bronsted Relationships

Correlating nucleophilicity and leaving group ability with pKa

$$\log k = \beta_{Nuc}\, pKa + \log(C')$$

pKa of conjugate acid of nucleophile
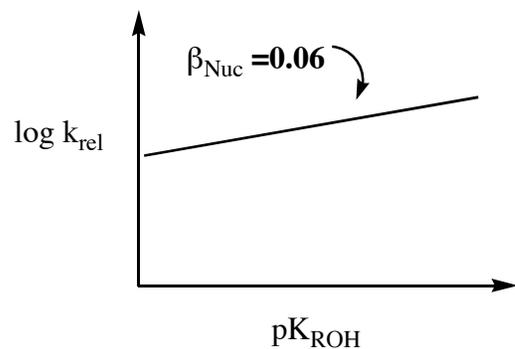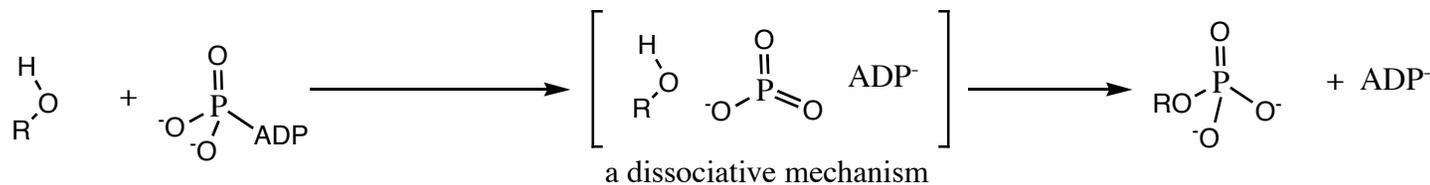or leaving group.

$$\log k = \beta_{LG}\, pKa + \log(C)$$

β_{Nuc} , β_{LG} are the sensitivity factors

A straight line is obtained when the dominant factor effecting nucleophile reactivity in the reaction is basicity.
β_{LG} gives the sensitivity of the reaction to the acidity of the conjugate acid of the leaving group.
Insight into the relative amounts of nucleophilic attack and leaving group departure in the rate-determining transition state

ATP hydrolysis: *Curr. Biol.* **2**, 729 (1995)

a dissociative mechanism

$\beta_{Nuc} = 0.06$

log k_{rel}

pK_{ROH}

no sensitivity to nucleophile: very little
bond formation in transition state

$\beta_{LG} = -1.1$
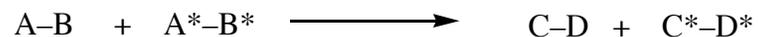
log k_{rel}

pK_{LG}
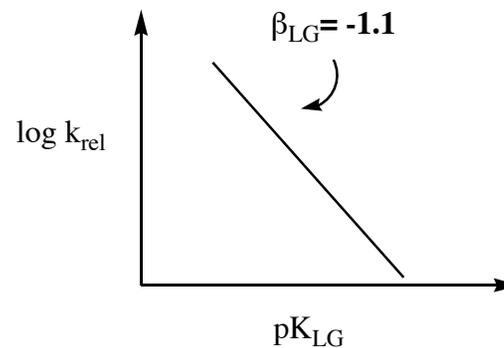
leaving group departure is sensitive to the
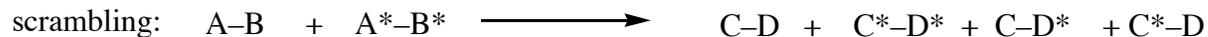structure and nature of the anion

Alternative Techniques to Study Reaction Mechanisms

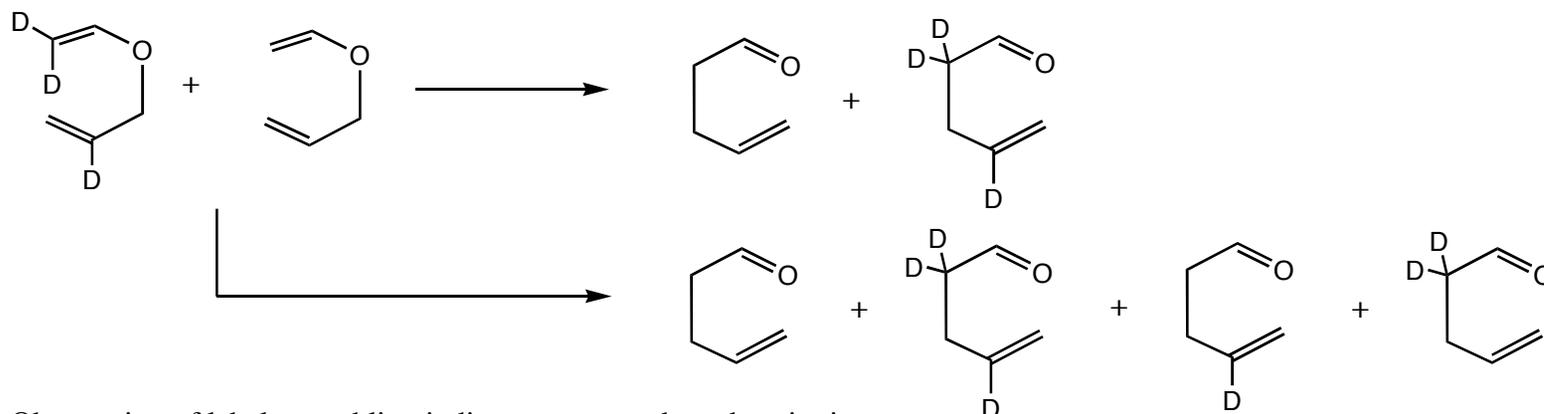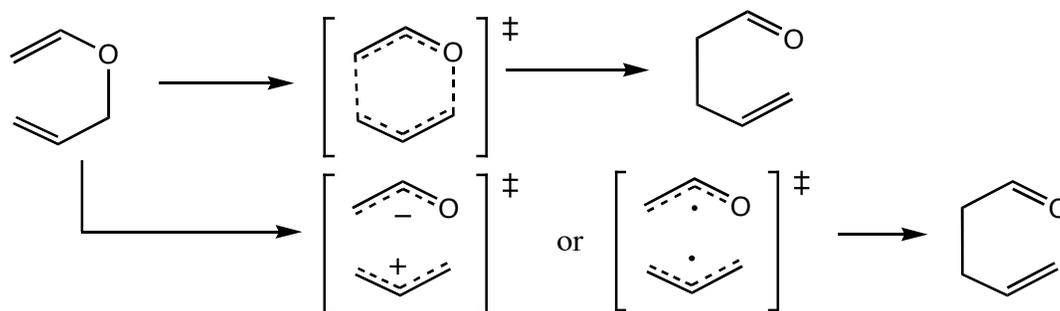## Cross-Over and Isotope Scrambling Experiments

Cross-Over Experiments: label one set of reactants so that one can observeif intermediates are released into solution before they combind to form products

$$A–B \ + \ A^*–B^* \longrightarrow C–D \ + \ C^*–D^*$$

or label
scrambling: $A–B \ + \ A^*–B^* \longrightarrow C–D \ + \ C^*–D^* \ + \ C–D^* \ + C^*–D$
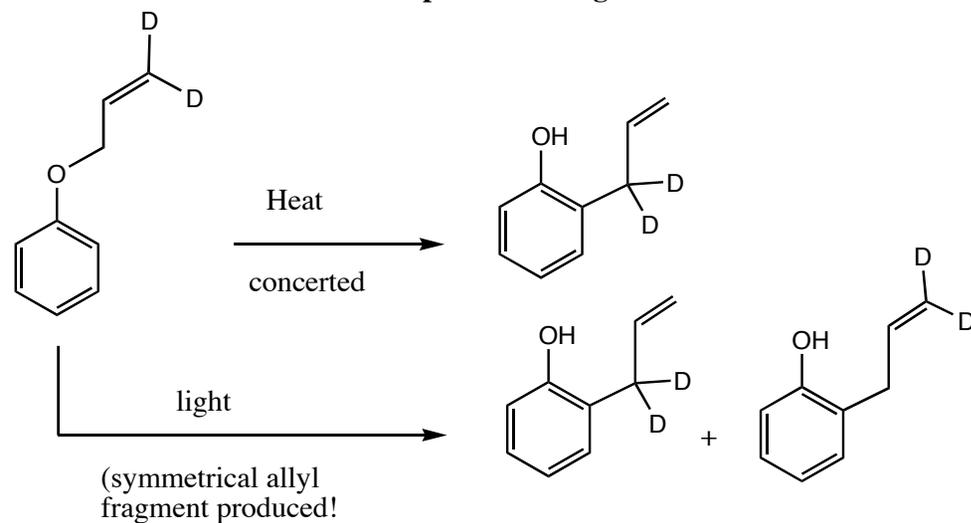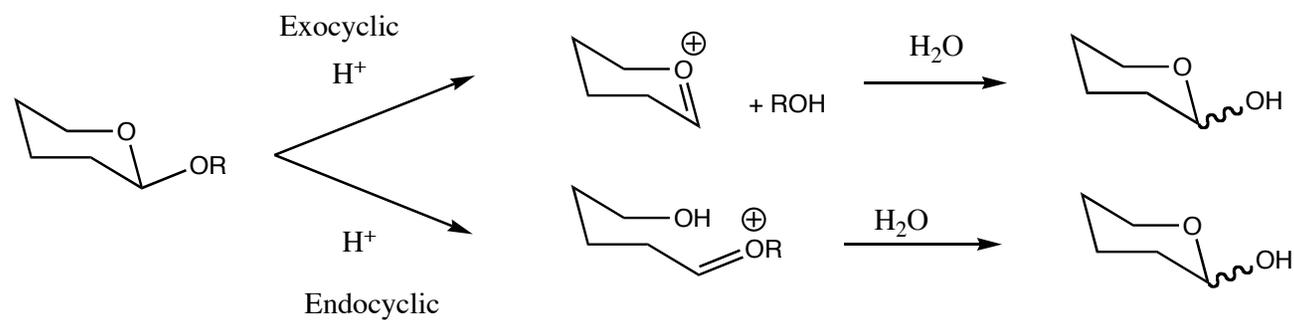
concerted or stepwise:

Observation of label scrambling indicates concerted mechansim is not
taking place. Observation of no scrambling does not prove concerted mechanism

Alternative Techniques to Study Reaction Mechanisms
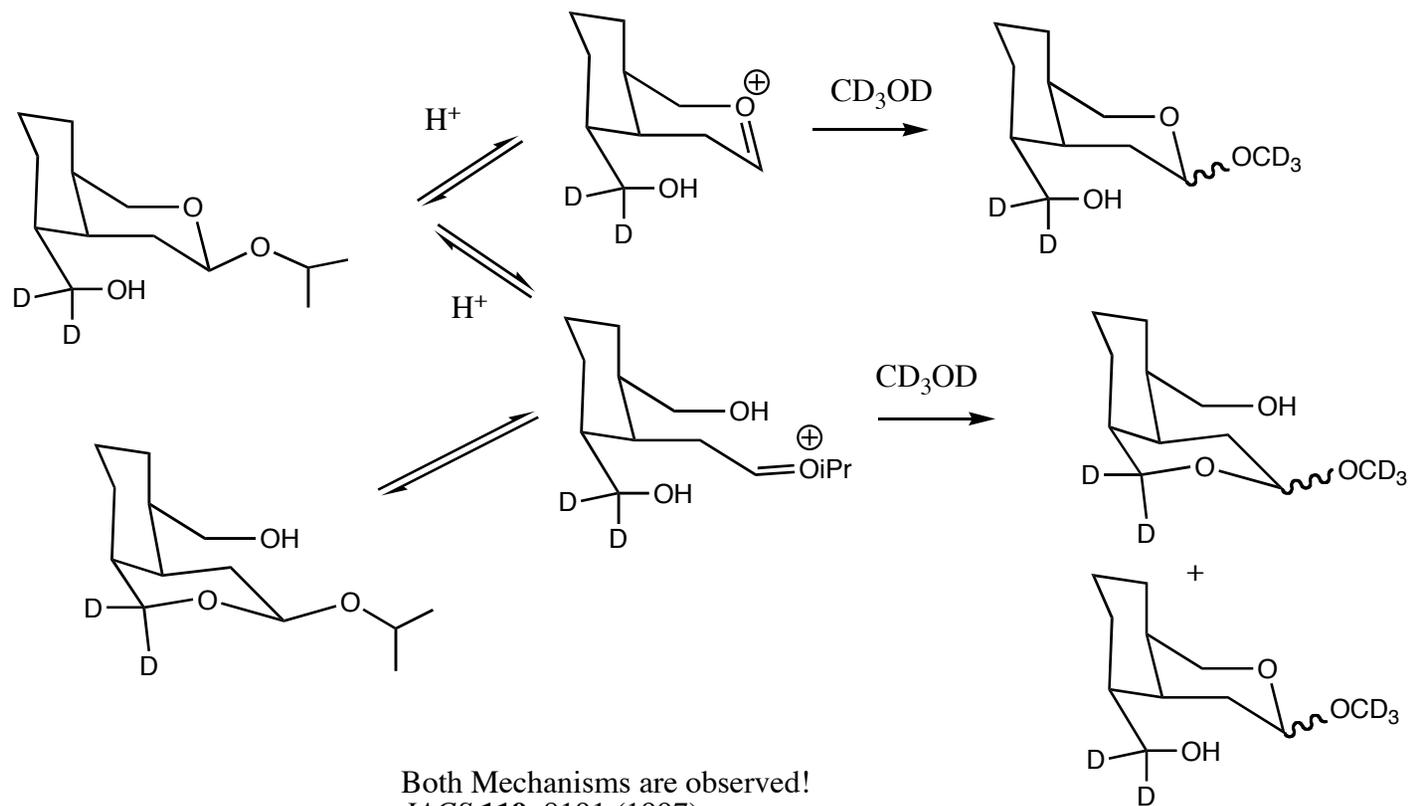
Isotope Scrambling

How to distinguish? endocyclic or exocyclic cleavage in acid-catalyzed hydrolysis

JACS **119**, 8191 (1997)

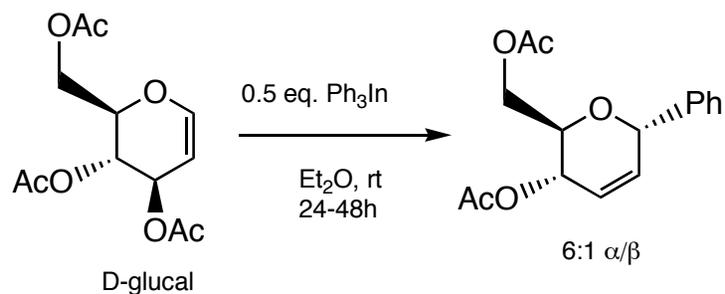# Alternative Techniques to Study Reaction Mechanisms

Isotope Scrambling

Both Mechanisms are observed!
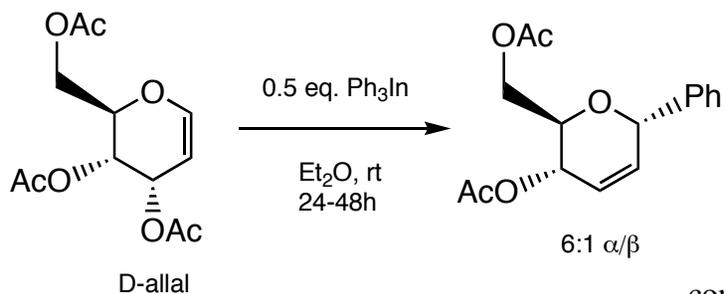*JACS* **119**, 8191 (1997)

Alternative Techniques to Study Reaction Mechanisms

Checking for a Common Intermediate: Stereochemical Studies

0.5 eq. Ph₃In

Et₂O, rt
24-48h

D-glucal

6:1 α/β

S$_N$1 (stepwise) or S$_N$2' (concerted)
mechanism operative?

Observation:

0.5 eq. Ph₃In

Et₂O, rt
24-48h

D-allal

6:1 α/β

A common intermediate is involved!
S$_N$2' mechanism would be stereospecific

Proposed mechanism:

TL, 25, 45, 5197 (2004)

common cationic intermediate: