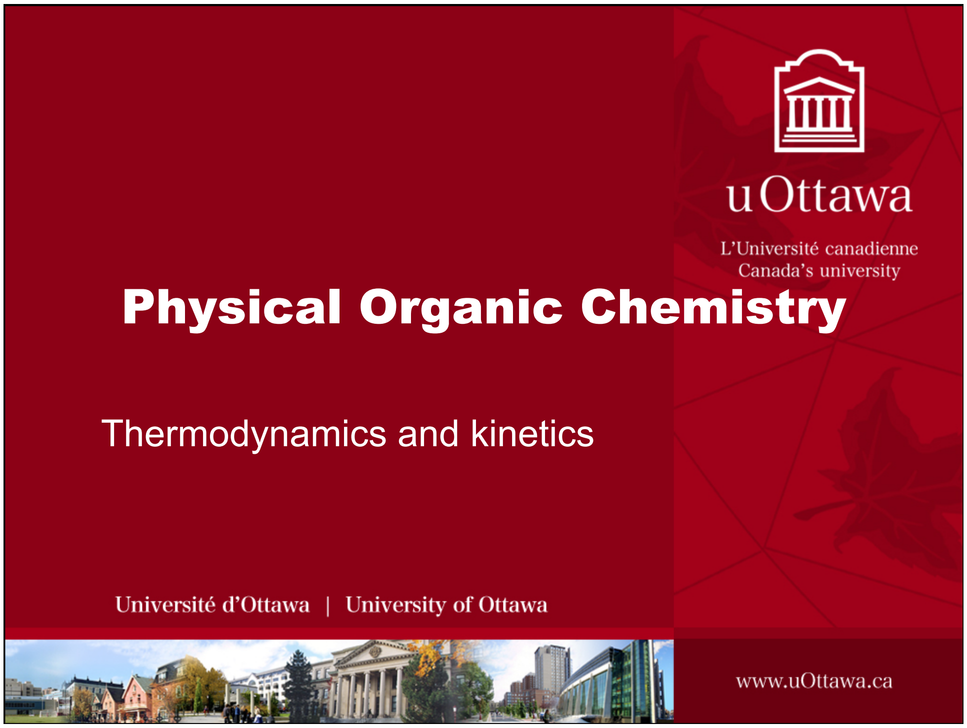

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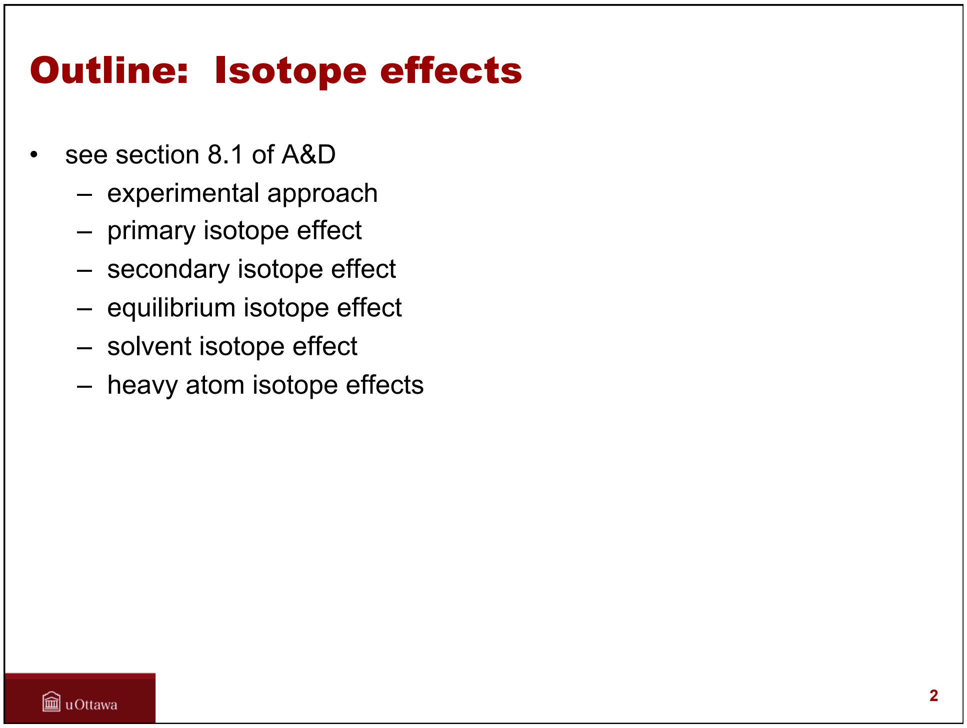


Outline: Isotope effects

- see section 8.1 of A&D
  - experimental approach
  - primary isotope effect
  - secondary isotope effect
  - equilibrium isotope effect
  - solvent isotope effect
  - heavy atom isotope effects

Measurement of an isotope effect

- performed to determine if a bond changes in a certain way during the rate-limiting step
- expressed as a ratio whose numerator is the rate constant measured for the naturally abundant isotope and the denominator is the rate constant measured for the varied isotope
  - e.g. k_H/k_D

Types of isotope effects

- **kinetic** isotope effects **(kie)**: result from a change in the rate constant of a reaction :
  - **normal** effect: ratio > 1
  - **inverse** effect: ratio < 1
  - **primary** isotope effect: when the isotopically substituted bond is cleaved during the rate-limiting step
  - **secondary** isotope effect : attributable to a change of hybridation state, not cleavage of bonds
- **equilibrium** isotope effects: result from displacement of an equilibrium

Origin of isotope effects

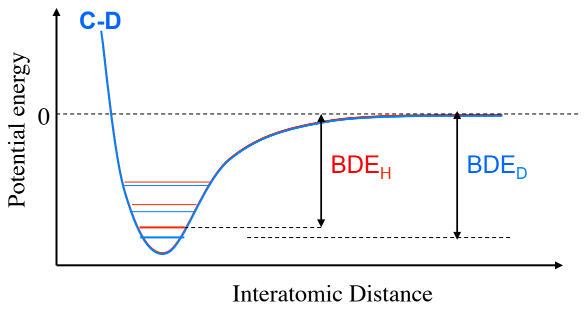
- the origin of all isotope effects is a difference in the *frequency of vibrational modes* of a substituted molecule with respect to an unsubstituted molecule

- it is these vibrational modes that principally affect the *shape* of the potential energy well on an energy surface

Zero point energy

- *zero point energy (ZPE)* is the energy level of the vibrational ground state for most molecules at ambient temperature

- the vibrational frequencies of C-D bonds are lower than those of C-H bonds, due to a the mass difference
  - therefore, a C-D bond is stronger and more difficult to cleave:



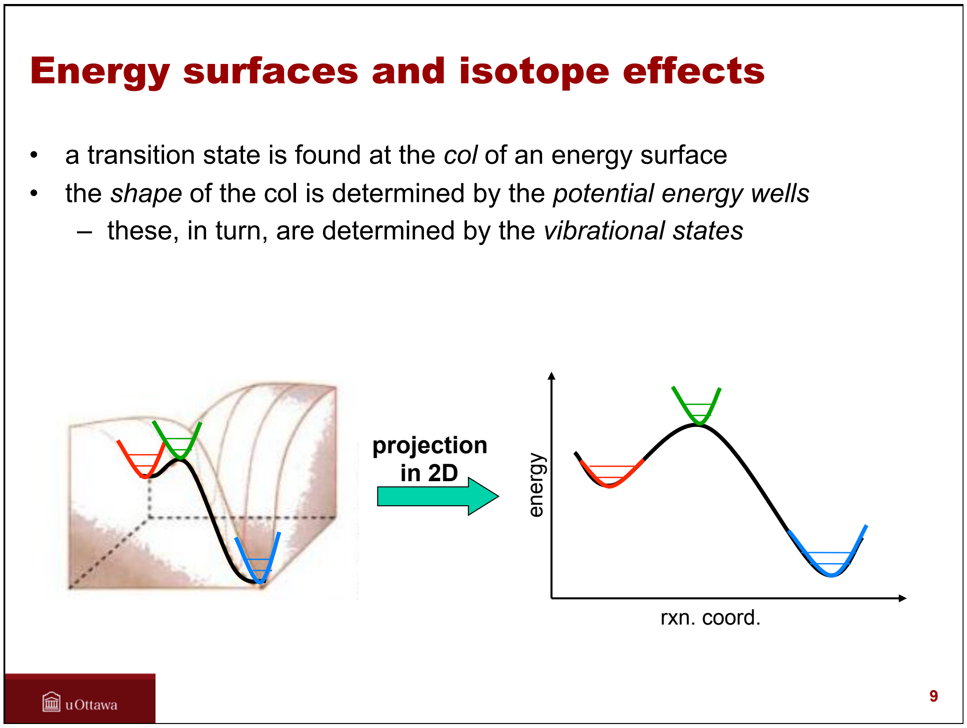
Primary isotope effects

- in general, bonds involving heavier isotopes are more stable and more difficult to break
- the cleavage of a C-D bond can be several fold slower than the cleavage of a C-H bond
- the *degree* of cleavage of the the bond at the transition state is given by the ratio:

$$\left(\frac{k_{\mathrm{H}}}{k_{\mathrm{D}}}\right)$$

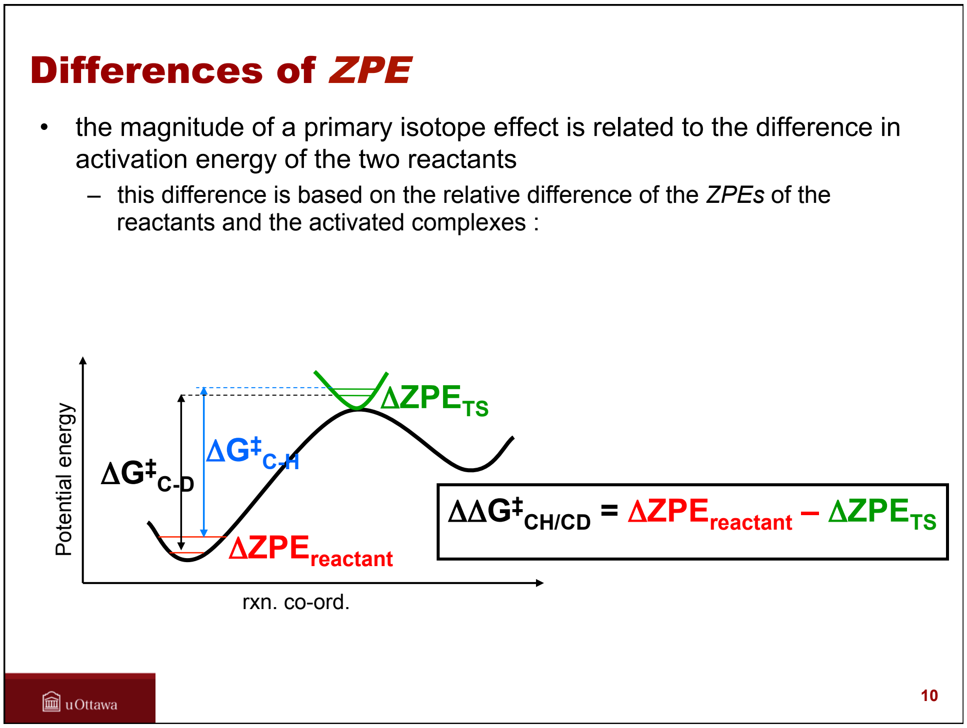
Values of primary isotope effects

- the magnitude depends on the relative mass difference between the two isotopes
  - e.g. H *vs* D, ^{12}C *vs* ^{13}C, ^{14}N *vs* ^{15}N, etc
- *maximum* normal values at 25 °C :
  - H *vs* D : 6.4 (typically 2-7)
  - H *vs* T : 13
  - ^{12}C *vs* ^{13}C : 1.04
  - ^{14}N *vs* ^{15}N : 1.03
- the value observed experimentally is related to the degree and the linearity of cleavage realised at the TS of the rds
  - 50% transfer, at 180°, gives the maximum effect



Energy surfaces and isotope effects

- a transition state is found at the *col* of an energy surface
- the *shape* of the col is determined by the *potential energy wells*
  - these, in turn, are determined by the *vibrational states*



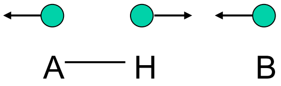
Differences of *ZPE*

- the magnitude of a primary isotope effect is related to the difference in activation energy of the two reactants
  - this difference is based on the relative difference of the *ZPEs* of the reactants and the activated complexes :

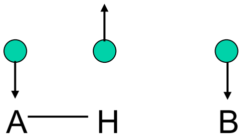
$$\boxed{\Delta\Delta G^{\ddagger}_{CH/CD} = \Delta ZPE_{reactant} - \Delta ZPE_{TS}}$$

Vibrational modes

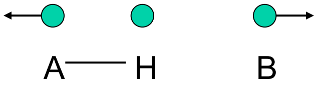
- one particular vibrational mode determines the reaction coordinate for the transfer of a proton:



- whereas other vibrational modes have little to do with the isotope effect :

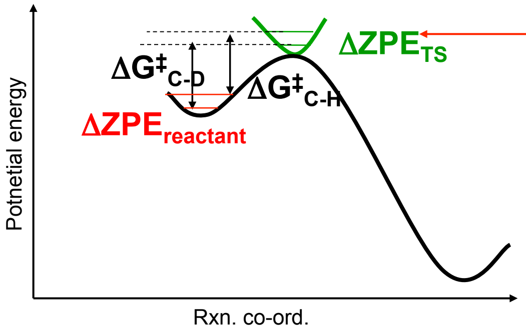


- and one mode is characteristic of the activated complex:

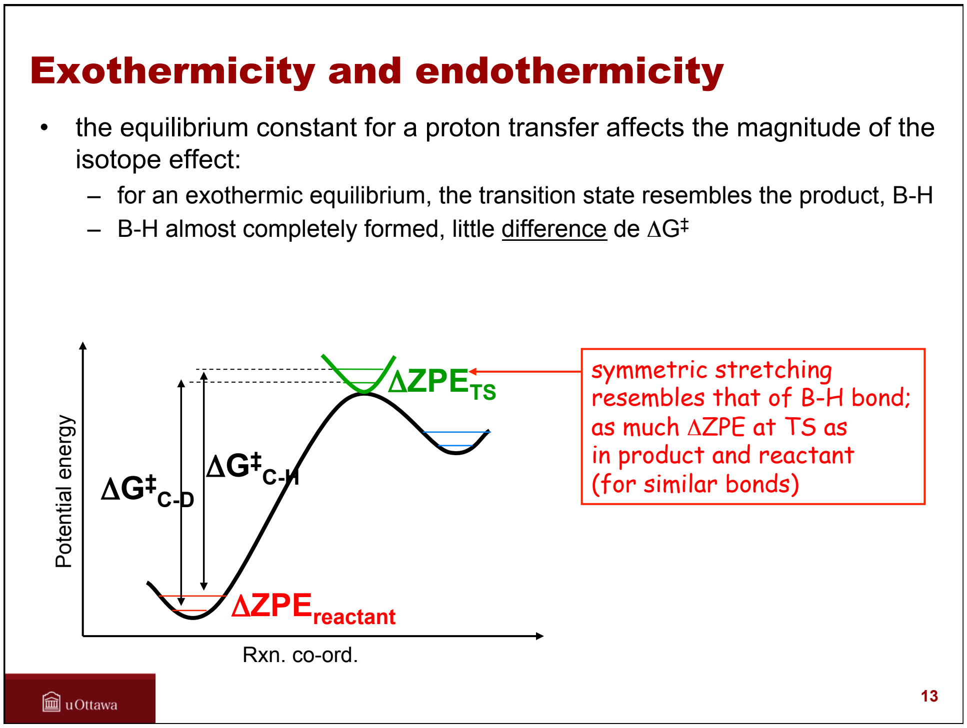


Exothermicity and endothermicity

- the equilibrium constant for a proton transfer affects the magnitude of the isotope effect:
  - for an exothermic equilibrium, the transition state resembles the reactant, A-H
  - little cleavage is achieved at the TS, so little difference of $\Delta G^\ddagger$



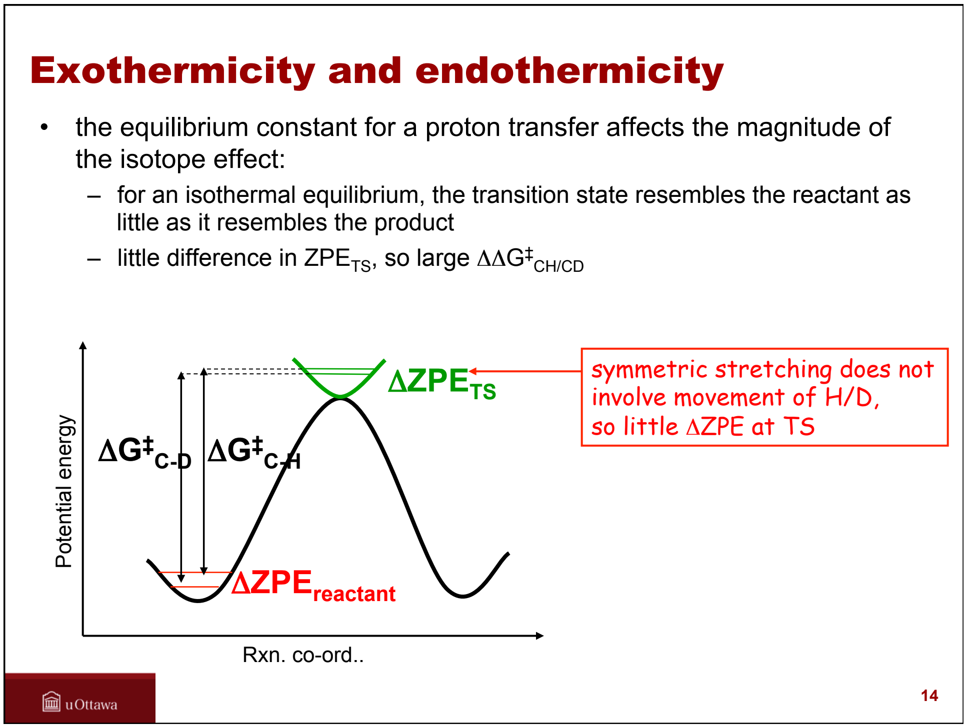
symmetric stretching resembles that of A-H bond; as much ΔZPE at TS than in reactant



Exothermicity and endothermicity

- the equilibrium constant for a proton transfer affects the magnitude of the isotope effect:
  - for an exothermic equilibrium, the transition state resembles the product, B-H
  - B-H almost completely formed, little <u>difference</u> de $\Delta G^{\ddagger}$

symmetric stretching resembles that of B-H bond; as much ΔZPE at TS as in product and reactant (for similar bonds)



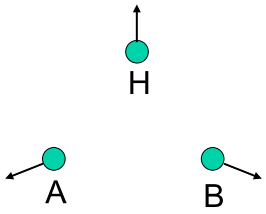
Exothermicity and endothermicity

- the equilibrium constant for a proton transfer affects the magnitude of the isotope effect:
  - for an isothermal equilibrium, the transition state resembles the reactant as little as it resembles the product
  - little difference in ZPE_{TS}, so large $\Delta\Delta G^{\ddagger}_{CH/CD}$

symmetric stretching does not involve movement of H/D, so little ΔZPE at TS

Non-linear transition states

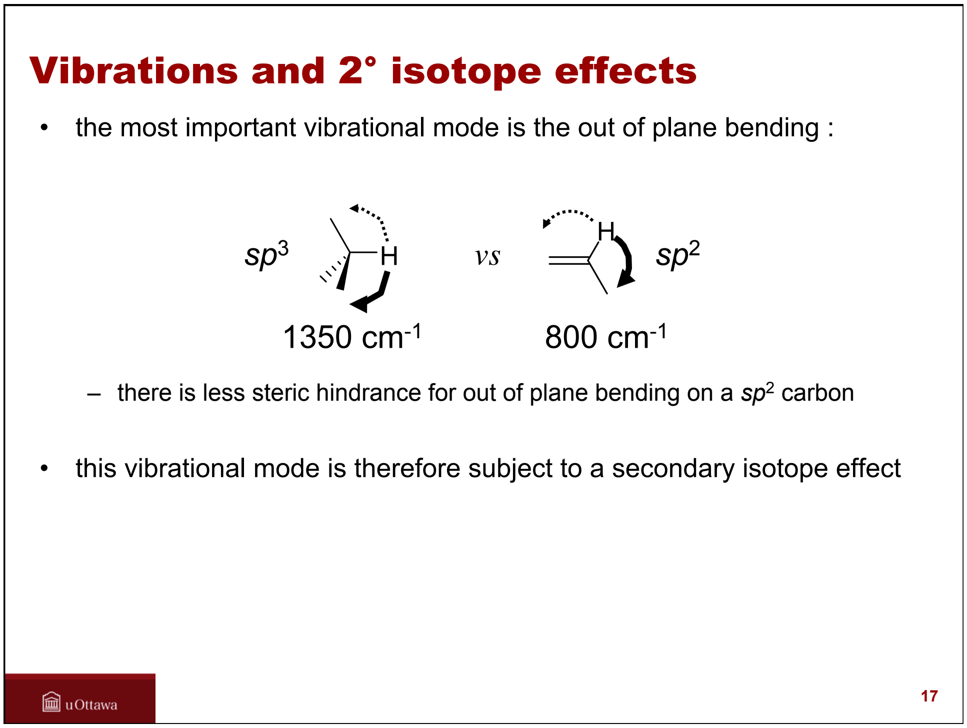
- for non-linear proton transfers, the bending vibrational modes are more important and even symmetrical stretching implies movement of H/D:



- therefore, there will be as much ΔZPE at the TS as in the reactant, and little $\Delta\Delta G^{\ddagger}_{CH/CD}$

Secondary isotope effects

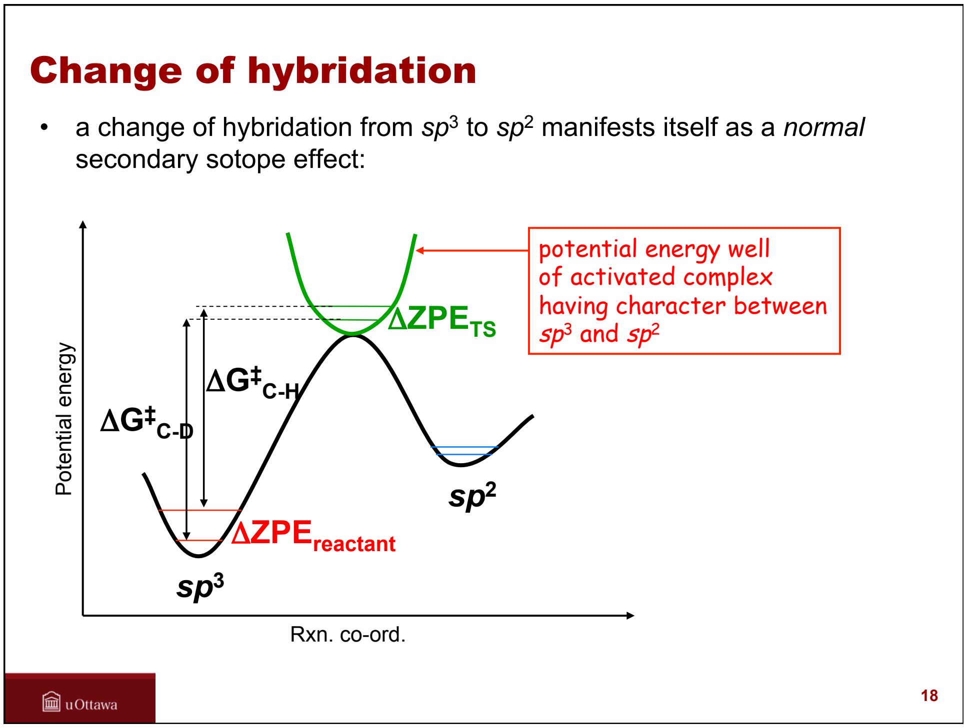
- result from the cleavage of bonds *adjacent* to the substituted atoms
- caused by a change in *hybridation* of the atom bearing the isotope, rather than the cleavage of its bond
  - the change of hybridation of carbon from *sp*^{3} to *sp*^{2} is 14 % slower for every deuterium it bears, compared to hydrogen



Vibrations and 2° isotope effects

- the most important vibrational mode is the out of plane bending :

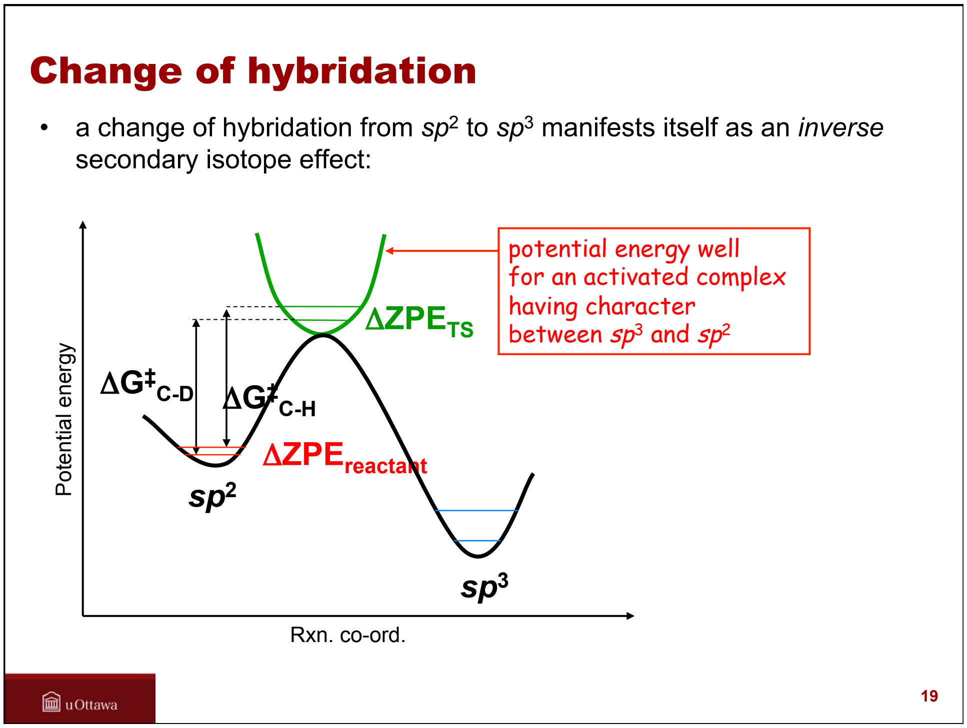
  - there is less steric hindrance for out of plane bending on a *sp*^{2} carbon
- this vibrational mode is therefore subject to a secondary isotope effect



Change of hybridation

- a change of hybridation from *sp*^{3} to *sp*^{2} manifests itself as a *normal* secondary sotope effect:

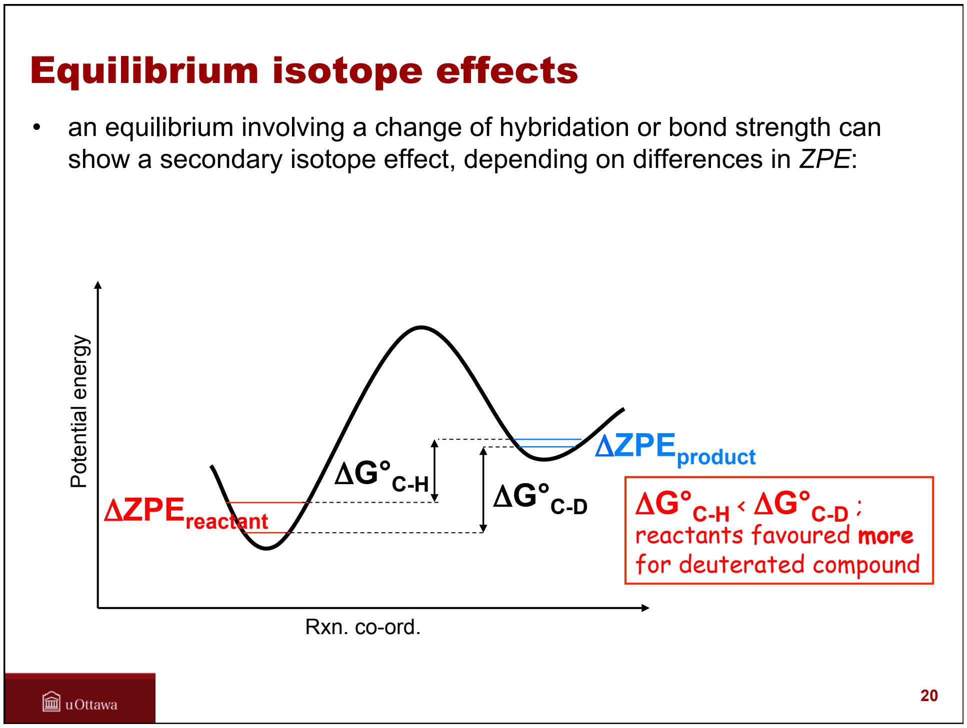
potential energy well of activated complex having character between *sp*^{3} and *sp*^{2}



Change of hybridation

- a change of hybridation from sp^2 to sp^3 manifests itself as an *inverse* secondary isotope effect:

potential energy well for an activated complex having character between sp^3 and sp^2



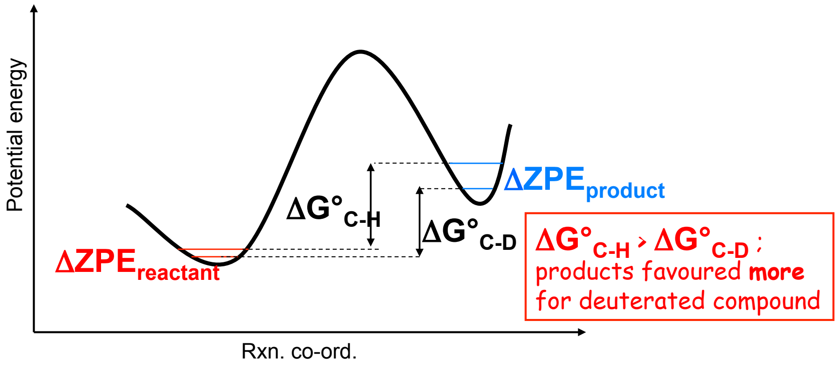
Equilibrium isotope effects

- an equilibrium involving a change of hybridation or bond strength can show a secondary isotope effect, depending on differences in *ZPE*:

$\Delta G°_{C\text{-}H} < \Delta G°_{C\text{-}D}$; reactants favoured **more** for deuterated compound

Equilibrium isotope effects

- an equilibrium involving a change of hybridation or bond strength can show a secondary isotope effect, depending on differences in *ZPE*:



$\Delta G°_{C\text{-}H} > \Delta G°_{C\text{-}D}$; products favoured **more** for deuterated compound

Solvent isotope effects

- measured by comparing the rate of a reaction in H_2O with that of the same reaction in D_2O
- result from proton transfers between electronegative atoms that *accompany* the formation and/or cleavage of bonds at the rds
  - especially if a water molecule is involved in the mechanism!
  - also include primary isotope effects of molecules that exchange protons

Fractionation factors

- the exchange of protons/deuterons can be subject to an equilibrium isotope effect
  - often observed when donor and acceptor atoms are different
  - e.g. N-H *vs* O-H
- a **fractionation factor, ϕ,** is measured to determine which atom prefers the H or D :
  - consider the solvent exchange equilibrium:

$$\boxed{X{-}H \;+\; S{-}D \rightleftharpoons X{-}D \;+\; S{-}H}$$

$$K_{eq} = \varphi = \frac{[S\text{-}H][X\text{-}D]}{[S\text{-}D][X\text{-}H]} = \frac{[X\text{-}D]/[X\text{-}H]}{[S\text{-}D]/[S\text{-}H]}$$

for ϕ>1, D prefers X

for ϕ<1, D prefers solvent

Values of ϕ

Bond	ϕ
RO-L	1.0
LO^-	0.5
$RO\text{-}L_2^+$	0.69
$R_3C\text{-}L$	0.69
$R_2N\text{-}L$	0.92
$R_3N\text{-}L^+$	0.97
RS-L	0.42

- note:
  - L = H or D
  - typically, alcohols do not have a preference for H or D
  - however, bonds with C, N and S prefer H
- fractionation factors can be used to predict solvent isotope effects…

…either equilibrium :

$$\frac{K_{eq,\,D2O}}{K_{eq,\,H2O}} = \frac{\prod_i^{prod}\phi_i^{prod}}{\prod_j^{react}\phi_j^{react}}$$

or kinetic :

$$\frac{k_{D2O}}{k_{H2O}} = \frac{\prod_i^{e.t.}\phi_i^{e.t.}}{\prod_i^{react}\phi_i^{react}}$$

Proton inventory

- if a rate constant is measured as a function of the molar fraction (*n*) of D_2O in H_2O, the number of protons “in flight” at the TS can be determined
  - i.e.: $k_n = k_{H2O}(1-n) + k_{D2O}(n) \;\; = k_{H2O}(1-n) + \phi k_{H2O}(n) \;\; = k_{H2O}(1-n+n\phi)$

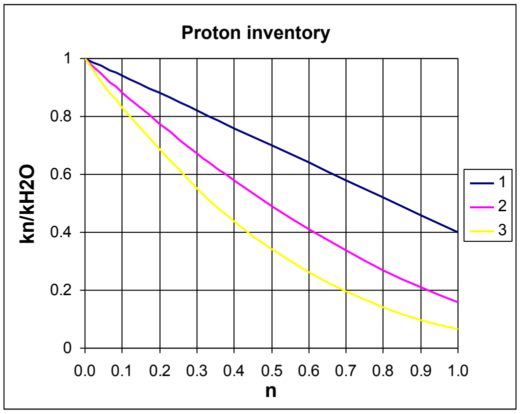
SO $$\frac{k_n}{k_{H2O}} = \frac{\prod_i^{e.t.}(1-n+n\phi_i^{e.t.})}{\prod_i^{react}(1-n+n\phi_i^{react})} \longleftarrow \boxed{\text{often } \phi\approx 1, \text{ for N-L and O-L}}$$

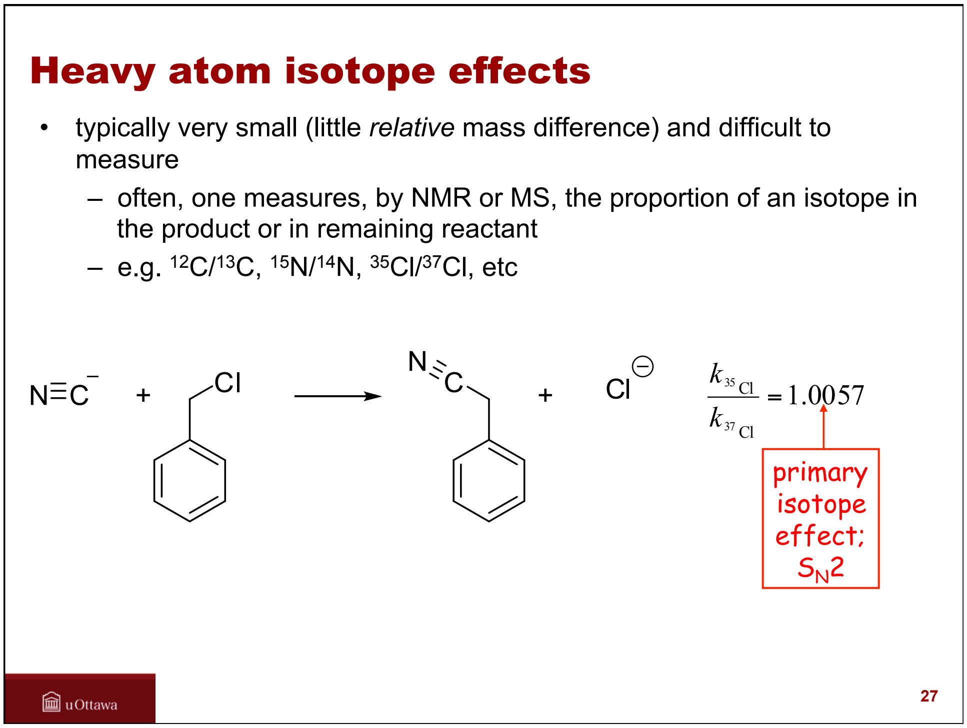
therefore $$\frac{k_n}{k_{H2O}} = (1-n+n\phi_1^{e.t.})(1-n+n\phi_2^{e.t.})(1-n+n\phi_3^{e.t.})\ldots$$

where each φ represents a fractionation factor for a proton in flight at the TS

Proton inventory

- the plot of k_n/k_{H2O} *vs* *n* reveals the number of protons in flight
  - i.e., 1 = linear, 2 = quadratic, 3 = cubic



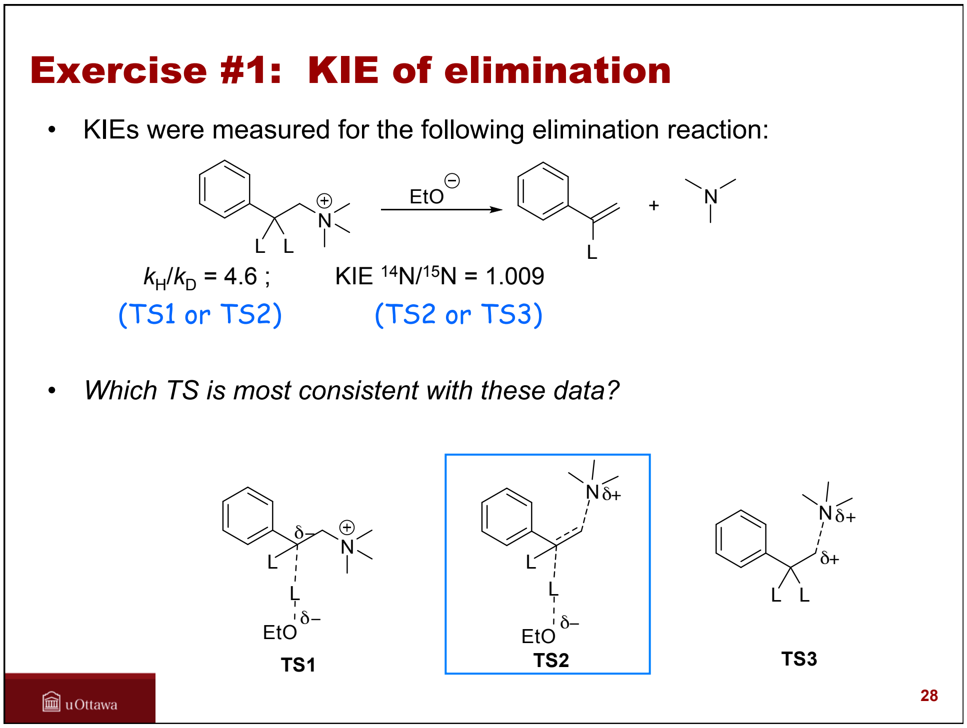


Heavy atom isotope effects

- typically very small (little *relative* mass difference) and difficult to measure
  - often, one measures, by NMR or MS, the proportion of an isotope in the product or in remaining reactant
  - e.g. $^{12}C/^{13}C$, $^{15}N/^{14}N$, $^{35}Cl/^{37}Cl$, etc

$$\frac{k_{^{35}Cl}}{k_{^{37}Cl}} = 1.0057$$

primary isotope effect; S_N2



Exercise #1: KIE of elimination

- KIEs were measured for the following elimination reaction:

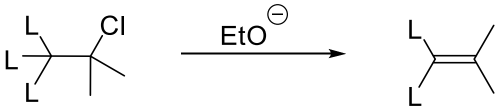
$k_H/k_D = 4.6$; KIE $^{14}N/^{15}N = 1.009$

(TS1 or TS2) (TS2 or TS3)

- *Which TS is most consistent with these data?*

Exerciee #2: KIE of elimination

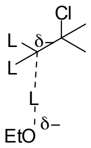
- KIE was measured for the following elimination reaction:



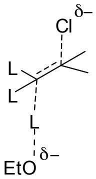
$k_H/k_D = 1.1$

(too small for TS1 or TS2)

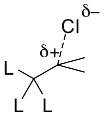
- *Which TS is most consistent with these data?*



TS1



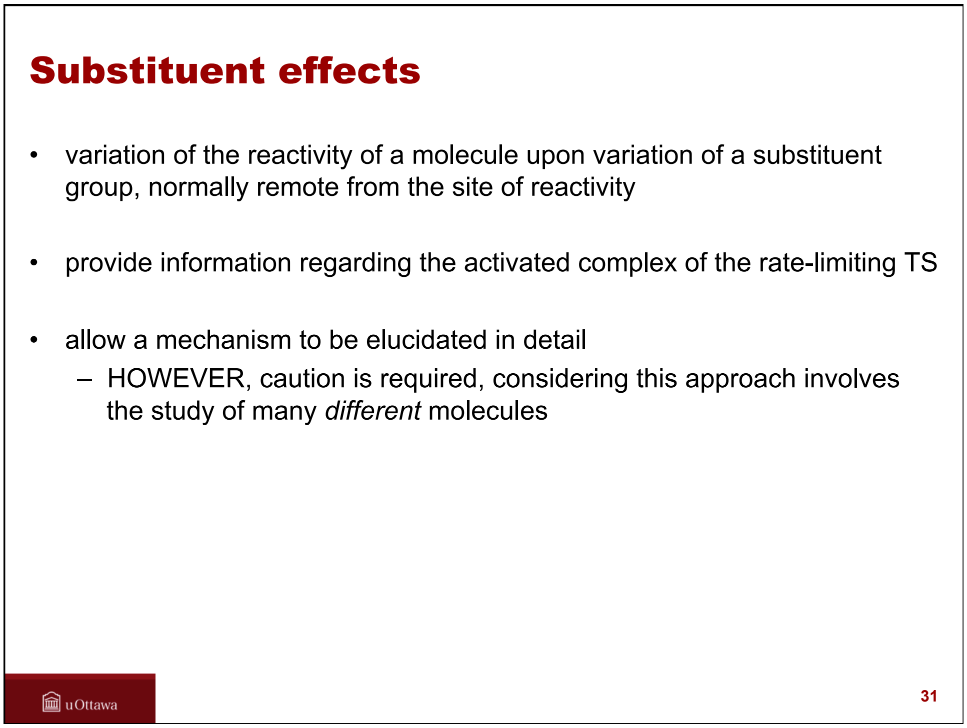
TS2



TS3

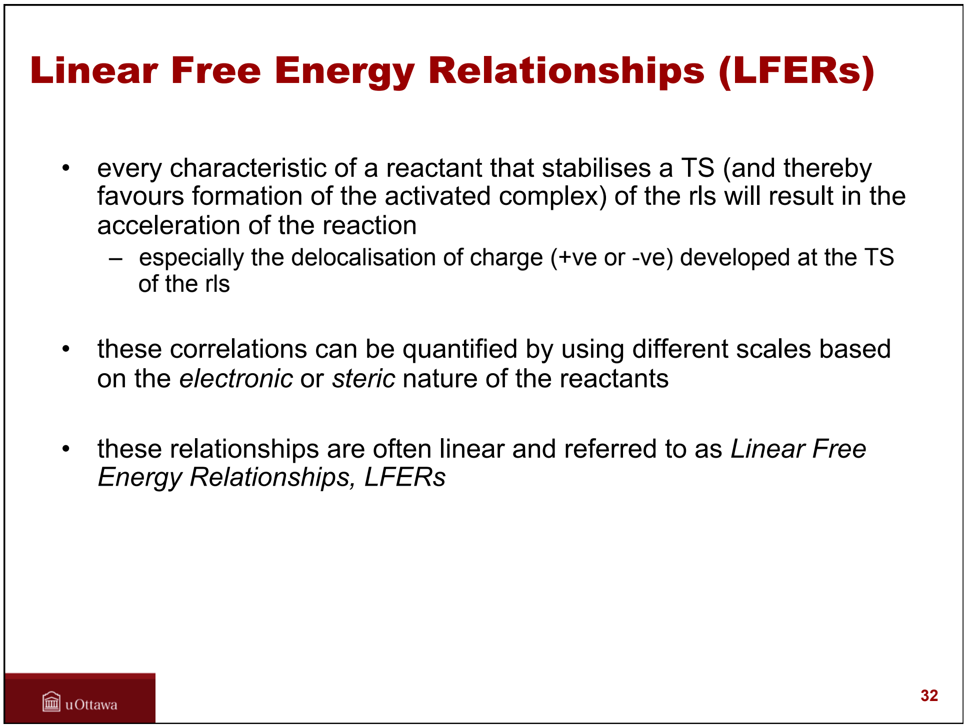
Outline: Origins of substituent effects

- see section 8.2 of A&D
  - field / dipole effects
  - inductive effects
  - resonance effects
  - polarisability effects
  - steric effects
  - solvation effects



Substituent effects

- variation of the reactivity of a molecule upon variation of a substituent group, normally remote from the site of reactivity
- provide information regarding the activated complex of the rate-limiting TS
- allow a mechanism to be elucidated in detail
  - HOWEVER, caution is required, considering this approach involves the study of many *different* molecules



Linear Free Energy Relationships (LFERs)

- every characteristic of a reactant that stabilises a TS (and thereby favours formation of the activated complex) of the rls will result in the acceleration of the reaction
  - especially the delocalisation of charge (+ve or -ve) developed at the TS of the rls
- these correlations can be quantified by using different scales based on the *electronic* or *steric* nature of the reactants
- these relationships are often linear and referred to as *Linear Free Energy Relationships, LFERs*

A useful approximation

- quantity of free energy necessary to change K by one order of magnitude:

$\Delta G = -RT \ln K$
$\Delta G = -2.303 \times RT \log K$
$\Delta G = 2.303 \times RT \times pK$
$\Delta G = 1.4$ kcal/mol $\times\ pK$ (at 298 K)

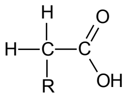
  - this is equally valid for ΔG_{rxn} (K_{eq}) as for $\Delta G^{‡}$ ($K^{‡}$, k_{obs})

Field effects

- the variation of a substituent can change the magnitude or even the direction of a dipole moment
- a field effect results from the effect of this change, transmitted *through space*, on the site of reactivity
- weaker than an inductive effect
- much weaker than a resonance effect

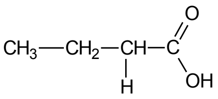
Inductive effect

- the electron donating or withdrawing ability of a given substituent, on the site of reactivity
  - depends on the electronegativity of the substituent

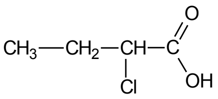

$\mathrm{H{-}CH(R){-}C(=O)OH}$

R =	pK_a
H	4,76
CH_3	4,87
Br	2,90
Cl	2,86
F	2,59

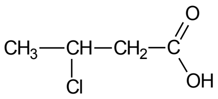
  - transmitted *via* the electron density of connecting σ *bonds*
  - decreases over distance


$\mathrm{CH_3{-}CH_2{-}CH(H){-}C(=O)OH}$

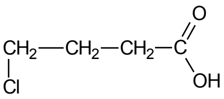
pK_a = 4,82


$\mathrm{CH_3{-}CH_2{-}CH(Cl){-}C(=O)OH}$

pK_a = 2,86


$\mathrm{CH_3{-}CH(Cl){-}CH_2{-}C(=O)OH}$

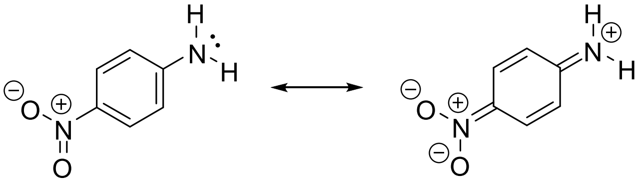
pK_a = 4,05

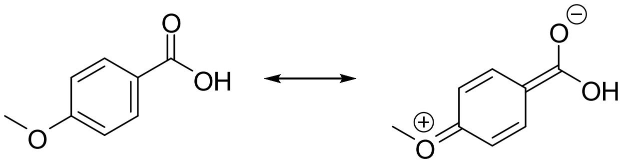

$\mathrm{CH_2(Cl){-}CH_2{-}CH_2{-}C(=O)OH}$

pK_a = 4,52

Resonance effect

- ability of a substituent to withdraw or donate electron density through π bonds
- important model for explanation of delocalisation of electron density in conjugated systems





Polarisability effect

- the ability of a cloud of electron density to *deform* can affect its reactivity
- a centre that strongly retains its electron density is said to be "hard" whereas a centre whose electron density is more diffuse is said to be "soft"
  - e.g. a thiolate (RS^-) of comparable basicity to an alkoxide ($R'O^-$) is nevertheless more nucleophilic AND a better leaving group, owing to its greater polarisability

Nucleophilicity

- nucleophilic substitution on a carbonyl or on a phosphate ester ("hard" centres) typically leads to formation of an intermediate
  - TS involves bond formation
  - rate depends simply on the strength (basicity) of the (hard) nucleophile
- nucleophilic substitution on a saturated carbon (a "soft" centre) does not involve an intermediate
  - rather, there are five bonds around the carbon at the TS
  - large, polarisable (soft) nucleophiles react more quickly

Nucleofugality

- the ease of expulsion of a leaving group (its *nucleofugality*) depends strongly on its electronic nature, affected by its protonation state and its basicity

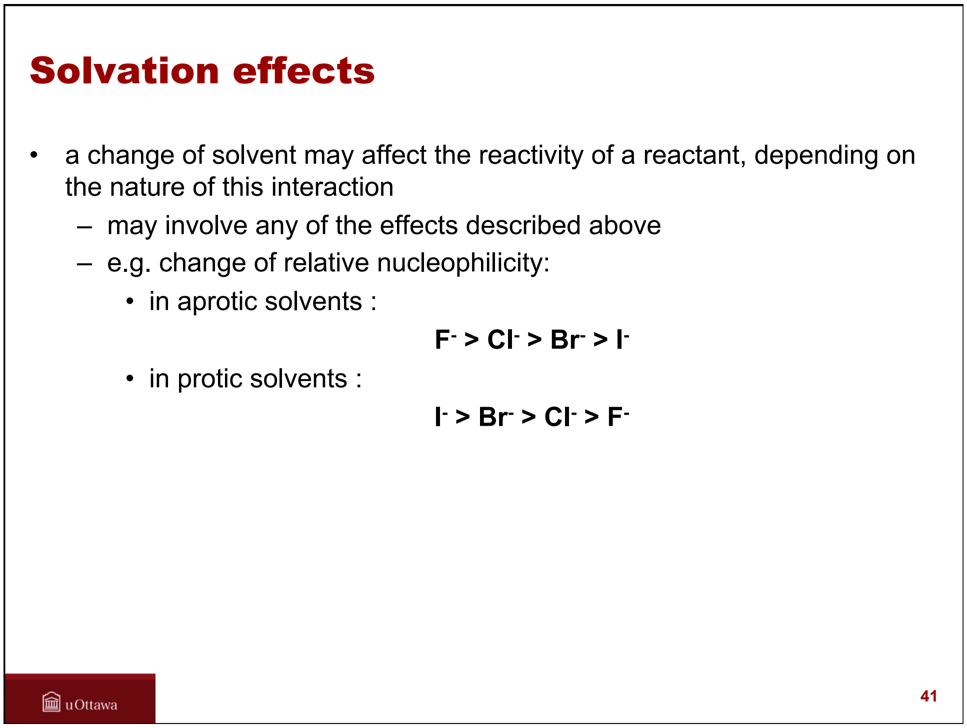
- weak bases (whose conjugate acids have pK_a values below ~8.0) are typically very easily expelled

Steric effects

- may strongly affect the probability, and therefore the rate, of a given reaction

- voluminous substituents may prevent a certain angle of a collision, rendering it non-productive

- note that even if steric effects are often treated separately from electronic effects, steric hindrance itself is also the result of the repulsion between clouds of *electron* density

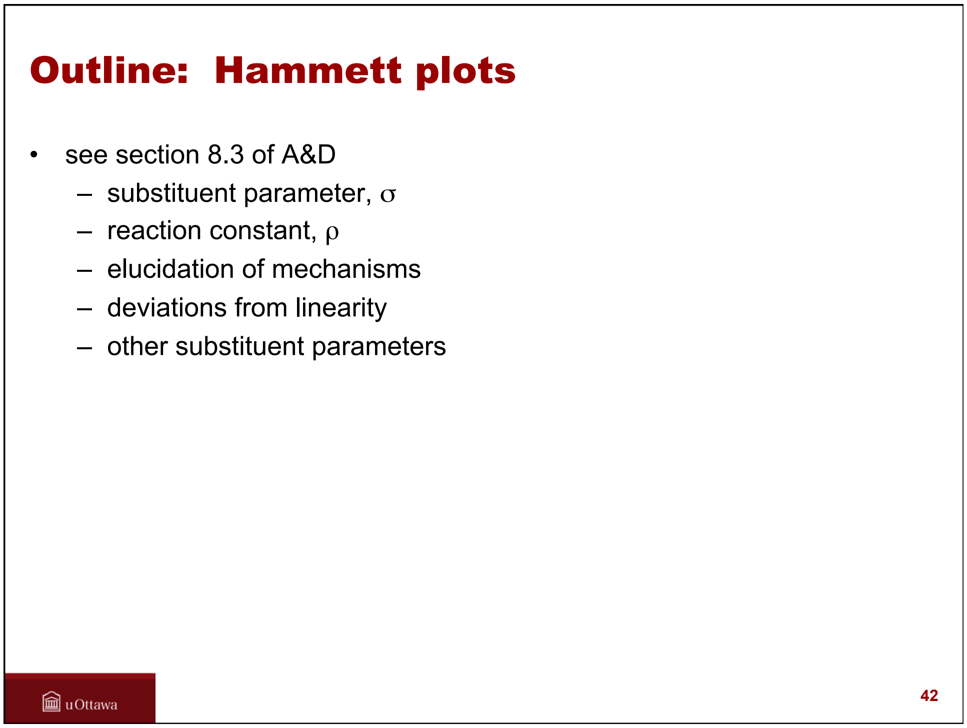


Solvation effects

- a change of solvent may affect the reactivity of a reactant, depending on the nature of this interaction
  - may involve any of the effects described above
  - e.g. change of relative nucleophilicity:
    - in aprotic solvents :

      $F^- > Cl^- > Br^- > I^-$
    - in protic solvents :

      $I^- > Br^- > Cl^- > F^-$



Outline: Hammett plots

- see section 8.3 of A&D
  - substituent parameter, σ
  - reaction constant, ρ
  - elucidation of mechanisms
  - deviations from linearity
  - other substituent parameters

Hammett

- **Louis Hammett** (1894-1987)
  - American physical chemist (Columbia)
  - studied the correlation of structure and function
  - credited with inventing the expression “physical organic chemistry”
  - laureate of awards from the National Academy of Science, *two* Norris Awards, Priestley Medal

Hammett Relation

- Hammett noted that the acidity constants of substituted benzoic acids varied according to the ability of the substituent to donate or withdraw electron density
  - he measured the empirical value corresponding to this capacity (*substituent constant*, σ)

$$(\mathrm{p}K_\mathrm{a})_\mathrm{X} = (\mathrm{p}K_\mathrm{a})_\mathrm{H} - \sigma_\mathrm{X}$$

- the rate constants of other reactions may be affected in the same way as the acidity reaction
  - a second parameter can therefore be used for each reaction (*reaction constant*, ρ)

$$\log k_\mathrm{X} = \log k_\mathrm{H} + \underset{\boxed{\text{reaction}}}{\rho}\,\underset{\boxed{\text{substituent}}}{\sigma_\mathrm{X}}$$

$$\boxed{\log\left(\frac{k_\mathrm{X}}{k_\mathrm{H}}\right) = \rho\sigma_\mathrm{X}}$$

Substituent constants, σ^0

- constants averaged over several different reactions give a better correlation than those originally observed by Hammett
- these constants can be determined even more distinctly for *meta vs para* substituents
  - for certain substituents, these values may vary significantly
    - e.g. for NO_2, σ^0_m = 0.71, whereas σ^0_p = 0.81
      for F, σ^0_m = 0.34, whereas σ^0_p = 0.15
      for OMe, σ^0_m = 0.1, whereas σ^0_p = -0.12

Table of substituent constants

EDG

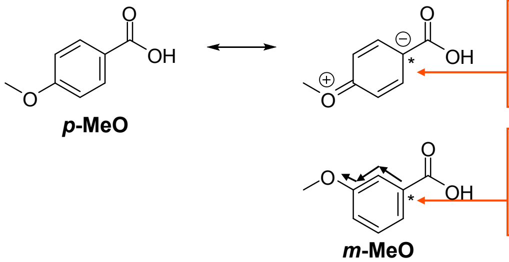
Substituent	σ_{meta}	σ_{para}
NMe_2	-0.10	-0.32
NH_2	-0.09	-0.30
OH	0.02	-0.22
OCH_3	0.1	-0.12
CH_3	-0.06	-0.14
H	**0**	**0**
Ph	0.05	0.05
F	0.34	0.15
Br	0.37	0.26
I	0.34	0.28
Cl	0.37	0.34
$OCOCH_3$	0.39	0.31
CO_2R	0.35	0.44
$COCH_3$	0.36	0.47
CF_3	0.46	0.53
CN	0.62	0.71
SO_2CH_3	0.64	0.73
NO_2	0.71	0.81

EWG

by definition

σ_{meta} *vs* σ_{para}

- from this table we note that $\sigma_{para} > \sigma_{meta}$ for several substituents
  - this tendency is especially pronounced for oxygenated substituents such as OH and OR
- in the *para* position, substituents can have very strong resonance effects
  - for oxygenated substituents these resonance effects are often in *competition* with inductive effects:



***p*-MeO**

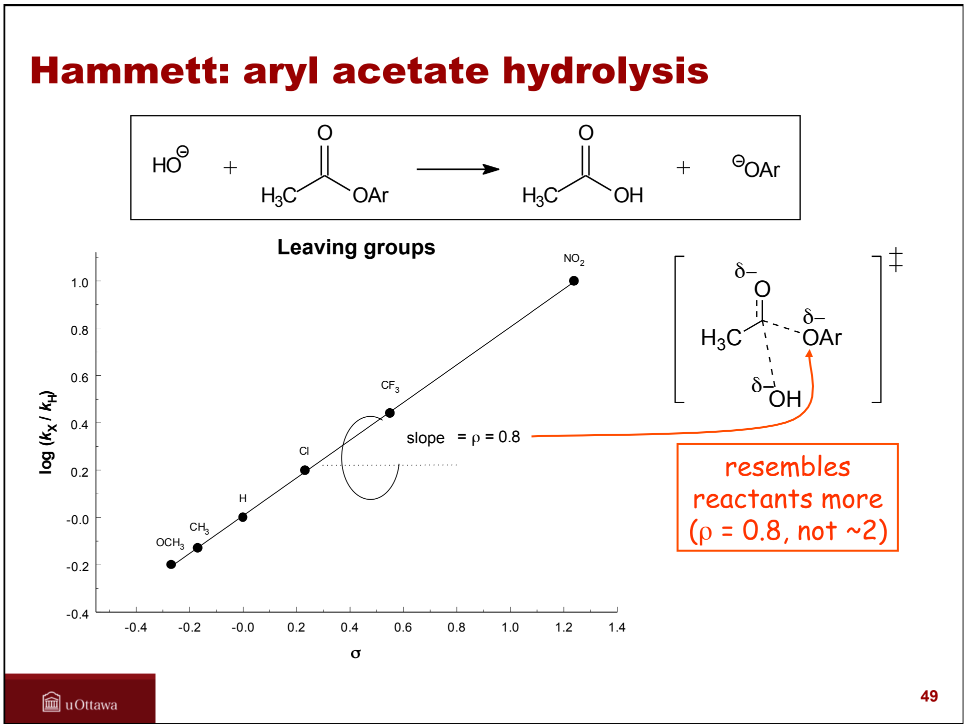
$\sigma_{para} < 0$; donator; resonance effect predominates

$\sigma_{meta} > 0$; withdrawer; inductive effect predominates

***m*-MeO**

Reaction constant, ρ

- measure of the sensitivity of a given reaction to electronic perturbation, on passing from reactants to the TS of the rls
  - $\rho = 1$ for the ionisation of benzoic acid, by definition
  - $\rho > 0$ for reactions accelerated by electron withdrawing groups
    - increase of negative charge at TS
  - $\rho < 0$ for reactions accelerated by electron donating groups
    - increase of positive charge at TS



Hammett: aryl acetate hydrolysis

slope = ρ = 0.8

resembles reactants more (ρ = 0.8, not ~2)

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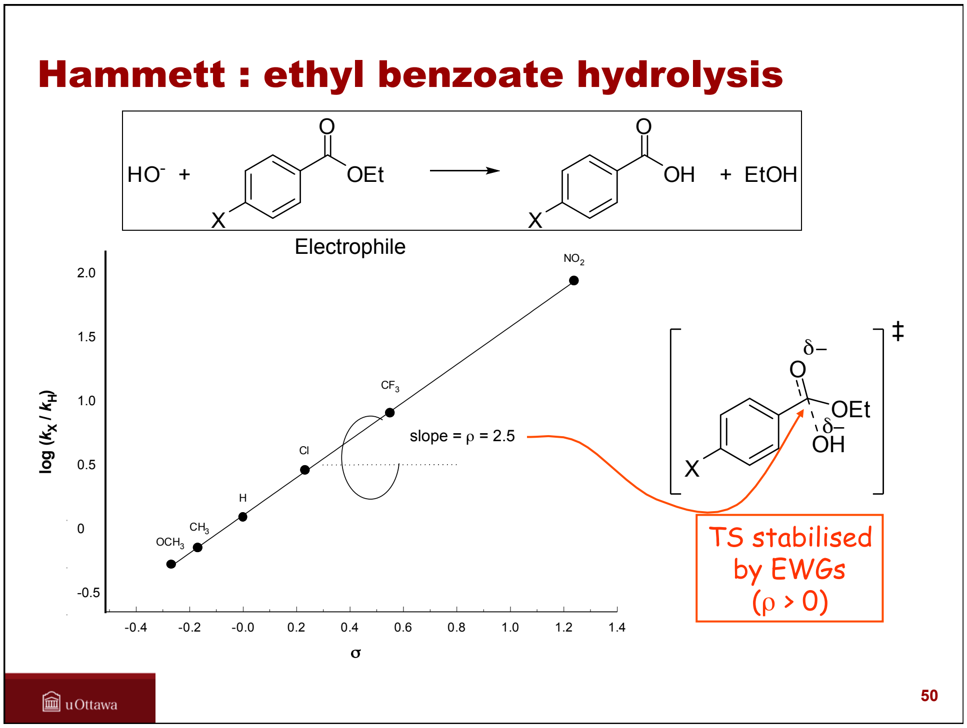

Hammett : ethyl benzoate hydrolysis

slope = ρ = 2.5

TS stabilised by EWGs (ρ > 0)

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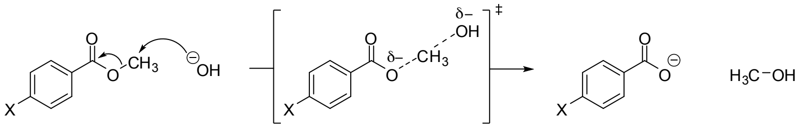
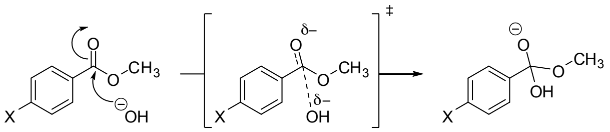
Hammett: methyl benzoate hydrolysis

- two mechanisms are consistent with the observed value of $\rho = 2.23$:
  - attack on the methyl group:



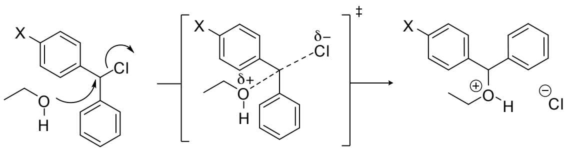
  - or attack on the acyl group:



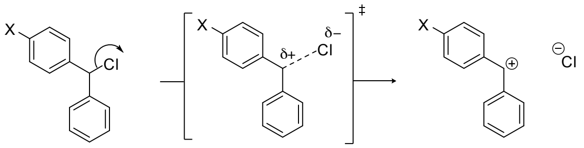
- **so the Hammett plot (alone) does not allow us to distinguish between these mechanisms**

Hammett: nucleophilic substitution

- only one mechanism is consistent with the observed value of $\rho = -5.09$:
  - consider attack on central carbon in rls (S_N2):



  - compared to departure of chloride in rls (first step of S_N1):

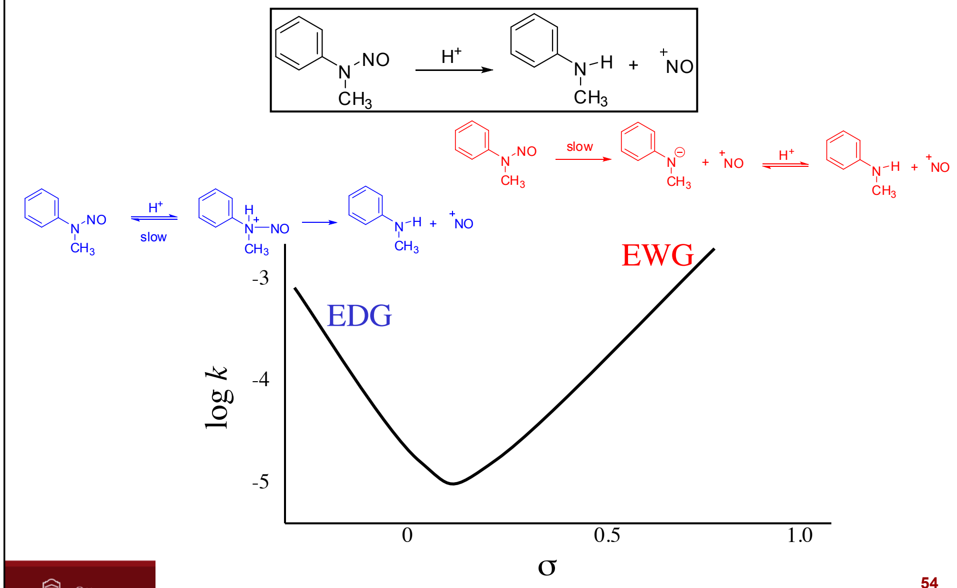


- **in this case, the Hammett plot allows the distinction between these two mechanisms**

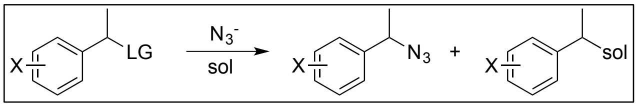
Deviation from linearity of Hammett eqn

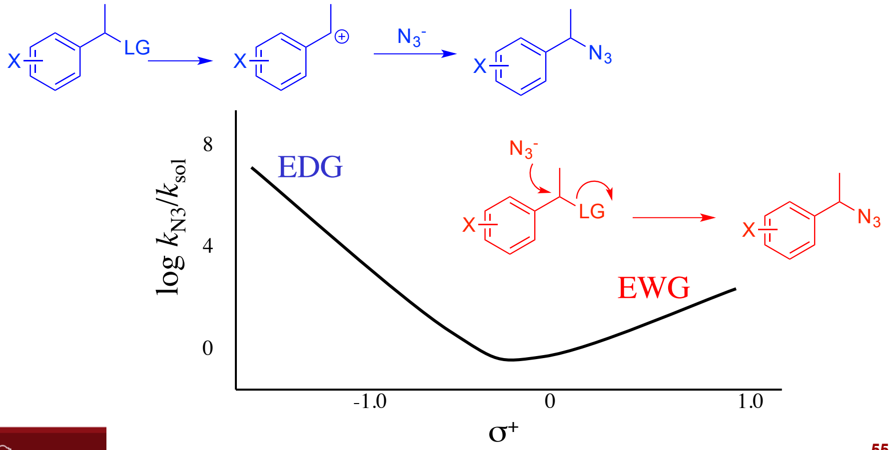
- for certain reactants, the lowest energy reaction pathway may *change* upon variation of the substituent
  - especially true if two pathways have similar *degrees* of electronic dependence, but in opposite *directions*
- this manifests itself as an *upward curvature* of the Hammett plot

Example: Upward curving Hammett plot



Example: Upward curving Hammett plot

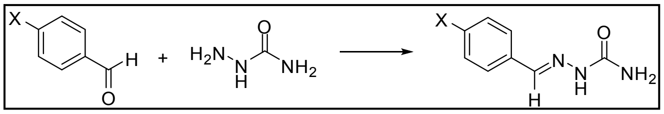


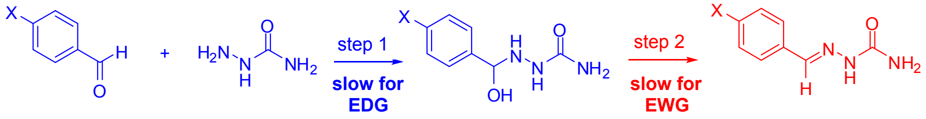


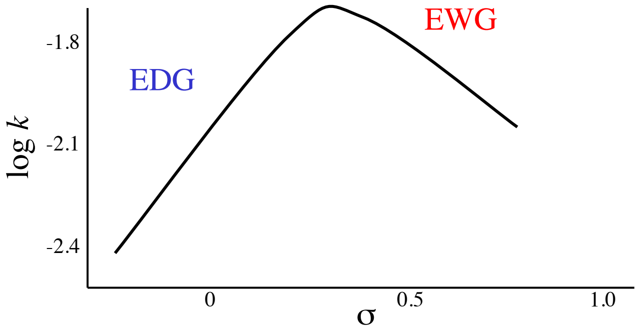
Deviation from linearity of Hammett eqn

- for certain other reactions, the *rate-limiting step* can change upon variation of the substituent
  - this is especially true if two reaction steps have TS that are similar in energy
- this manifests itself as a *downward curving* Hammett plot

Example: Downward curving Hammett plot







Other substituent parameters

- many other chemists have proposed other complementary substituent parameters
- some of these alternative parameters may be more appropriate for a certain kind of reaction of for a certain type of substituent
- for example:
  - σ_I for isolated inductive effects
  - σ_R isolated resonance effects
  - σ_- for reactions that involved the stabilisation of negative charge by resonance
    - based on the ionisation of phenols
  - σ_+ for reactions that involve the stabilisation of positive charge by resonance
    - based on the formation of a benzylic cation

Outline: Other “LFERs”

- see section 8.4 of A&D
    - Taft parameters
    - nucleophilicity and nucleofugality
    - Swain-Scott parameters

Taft

- **Robert W. Taft** (1922 – 1996)
    - American professor of physical organic chemistry
    - one of the founders of the University of California, Irvine (UCI) in 1965
    - studied substituent effects, acidity and basicity

Progress in
PHYSICAL
ORGANIC
CHEMISTRY

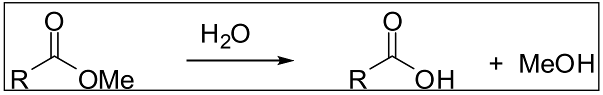
Taft Parameters

- the parameters developed by Hammett take account of:
  - field effects
  - inductive effects
  - resonance effects
  - **but NOT steric effects**

- in response, Taft developed different parameters that take account of the *polar* nature of a substituent (inductive effects and field effects) and of its *steric* nature
  - σ^* = Taft's polar substituent parameter
  - E_s = Taft's steric parameter

Taft Parameters

- *reference reaction* is the hydrolysis of methyl acetate de (R = CH_3) :



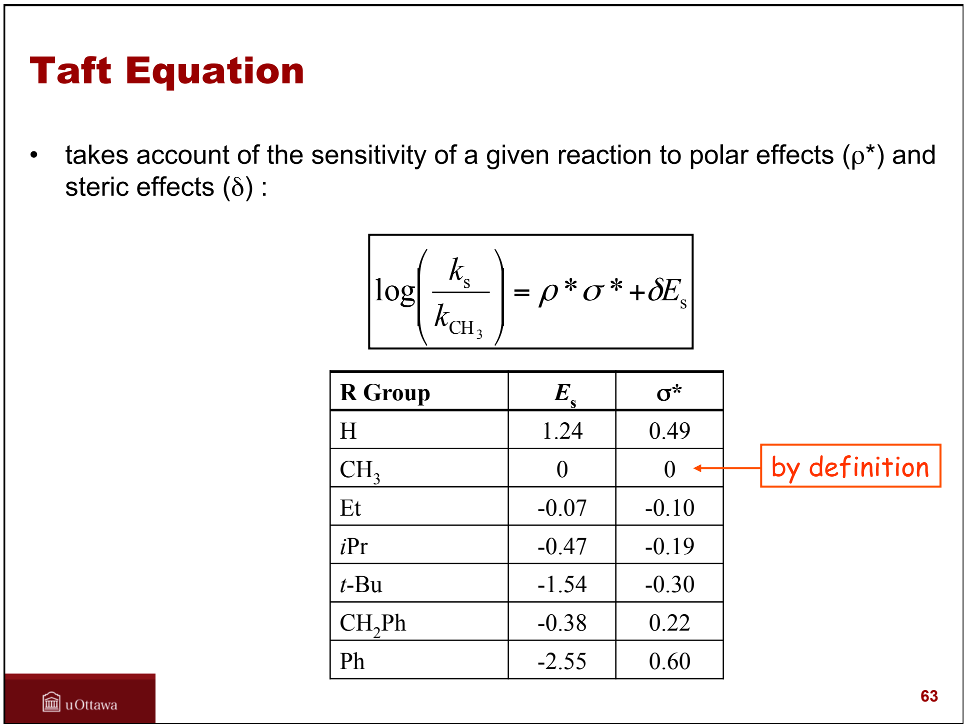
  - *steric parameter* is measured for the acid hydrolysis reaction, where the polarity of the substituent does not influence the rate

$$\log\left(\frac{k_s}{k_{CH_3}}\right) = E_s$$

  - *polarity parameter* is measured for the difference between the acid (A) and base (B) hydrolysis reactions

$$\sigma^* = \frac{1}{2.48}\left[\log\left(\frac{k}{k_0}\right)_B - \log\left(\frac{k}{k_0}\right)_A\right]$$

adjustment factor to make σ* the same magnitude as the Hammett σ value



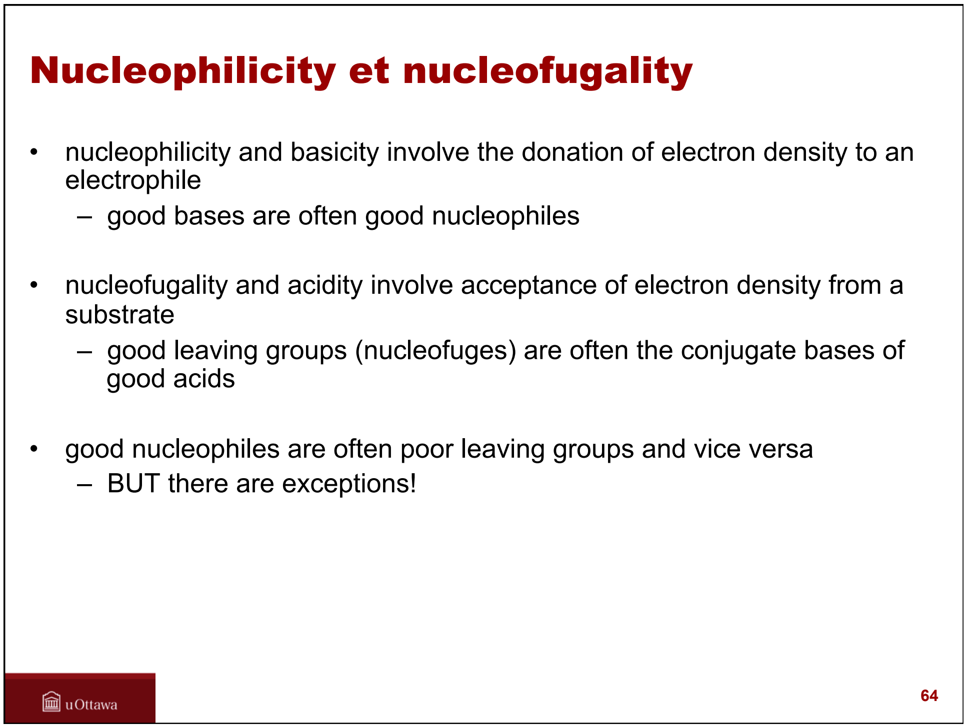
Taft Equation

- takes account of the sensitivity of a given reaction to polar effects (ρ*) and steric effects (δ) :

$$\boxed{\log\left(\frac{k_s}{k_{CH_3}}\right) = \rho^* \sigma^* + \delta E_s}$$

R Group	E_s	σ*
H	1.24	0.49
CH_3	0	0
Et	-0.07	-0.10
*i*Pr	-0.47	-0.19
t-Bu	-1.54	-0.30
CH_2Ph	-0.38	0.22
Ph	-2.55	0.60

by definition



Nucleophilicity et nucleofugality

- nucleophilicity and basicity involve the donation of electron density to an electrophile
  - good bases are often good nucleophiles
- nucleofugality and acidity involve acceptance of electron density from a substrate
  - good leaving groups (nucleofuges) are often the conjugate bases of good acids
- good nucleophiles are often poor leaving groups and vice versa
  - BUT there are exceptions!

Solvation

- solvation masks a nucleophile and decreases its reactivity
  - nucleophiles are typically more reactive in solvents that are polar, but *aprotic*
- nucleophiles having an adjacent electronegative atom can be orders of magnitude more reactive (known as the ***α effect***)
  - partially related to ground state destabilisation
  - partially related to a decrease in reactant solvation

Polarisability, basicity and solvation

- in general, nucleophilicity increases on descending a column of the periodic table
  - this tendency is due to polarisability
- HOWEVER, in polar *aprotic* solvents, anions are not well solvated, such that nucleophilicity increases with basicity on ascending a column of the periodic table

Shape of a nucleophile

- steric hindrance decreases nucleophilicity
- linear nucleophiles are typically better than expected on the basis of their basicity
  - e.g.: NC^-, N_3^-

Swain

- **C. Gardner Swain** (1917–1988)
  - Professor of Chemistry, MIT
  - studied physical organic chemistry and reactions mechanisms
  - focussed on nucleophilic reactivities, solvent effects, substituent effects, isotope effects
  - developed nucleophilicity scale (in 1953) with graduate student, Carleton Scott

Swain-Scott Parameters

- developed to create a LFER of nucelophilicity
- current reference reactions:

$$H_3C{-}I \quad + \quad Nuc_x \xrightarrow{k_{CH_3-I,\ Nuc_x}} H_3C{-}Nuc$$

$$H_3C{-}I \quad + \quad H_2O \xrightarrow{k_{CH_3-I,\ H_2O}} H_3C{-}OH$$

$$\boxed{\log\left(\frac{k_{CH_3-I,\ Nuc_x}}{k_{CH_3-I,\ H_2O}}\right) = n_x}$$

for each Nuc

- for a reaction of interest:

$$R{-}GP \quad + \quad Nuc_x \xrightarrow{k_{R\text{-}GP,\ Nuc_x}} R{-}Nuc$$

$$R{-}GP \quad + \quad H_2O \xrightarrow{k_{R\text{-}GP,\ H_2O}} R{-}OH$$

$$\boxed{\log\left(\frac{k_{R-GP,\ Nuc_x}}{k_{R-GP,\ H_2O}}\right) = sn_x}$$

for each rxn

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Values of n_x

- index of effective nucleophilicity, relative to water
  - NB: note *log* scale!

Nucleophile	n_x	**pK_a conj. acid**
PhS$^-$	9.92	6.52
I$^-$	7.42	-10.7
NC$^-$	6.70	9.3
Et$_3$N	6.66	10.7
CH$_3$O$^-$	6.29	15.7
Br$^-$	5.79	-7.77
N$_3^-$	5.78	4.74
PhO$^-$	5.75	9.89
Aniline	5.70	4.58
PhSH	5.70	-
Pyridine	5.23	5.23
Cl$^-$	4.37	-5.7
CH$_3$CO$_2^-$	4.3	4.75
F$^-$	2.7	3.45
H$_2$O	0.0	-1.7
CH$_3$OH	~0.0	-1.7

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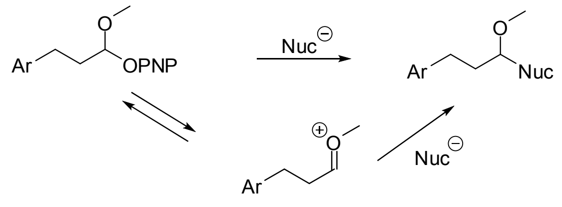
Example of Swain-Scott parameters

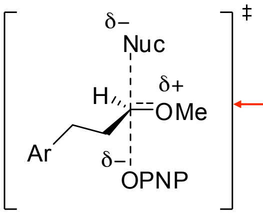
- the following reaction was studied for its dependence on nucleophilicity and nucleofugality:



first order in Nuc

significant departure of LG

- slope of Swain-Scott plot, *s* = 0.18



little dependence on Nuc

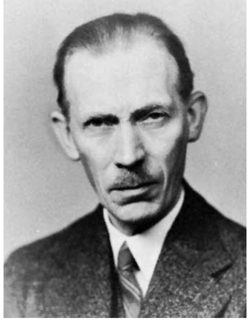
"pre-associated" TS

Outline: Brønsted Relationships

- see section 8.5 of A&D
  - β_{nuc}
  - β_{LG}
  - acid-base catalysis

Brønsted

- **Johannes Brønsted** (1879-1947)
  - Danish physical chemist (Copenhagen)
  - studied protonic theory of acid-base reactions (as did Lowry)
  - acid-base catalysis



Brønsted catalysis law

- Brønsted noted that the rate constants for reactions catalysed by a general acid (having a proton *in flight* in the rate limiting transition state) are proportional to the acidity constants of the general acids :

$$k_{\text{obs}} \propto K_{\text{a}}^{\alpha} \qquad \boxed{\log k_{\text{obs}} = \alpha \cdot \log K_{\text{a}} = -\alpha \cdot \text{p}K_{\text{a}}}$$

and for general bases :

$$k_{\text{obs}} \propto K_{\text{b}}^{\beta} \qquad \boxed{\log k_{\text{obs}} = \beta \cdot \log K_{\text{b}} = -\beta \cdot \text{p}K_{\text{b}}}$$

- Brønsted plots (log *k* vs p*K*) have slopes between 0 and 1:
  - slope of 0 : no proton transfer in rds
  - slope of 1 : proton already transferred before rds
  - intermediate slope: *proportional with charge developed at TS of rds*

Brønsted-type plots

- correlation of rate constants with the acidity of *parent compounds* of different fragments of reactants:
  - pK_a of conjugate acids of nucleophiles
    - slope β_{nuc}
  - pK_a of conjugate acids of leaving groups
    - slope β_{lg}

β_{nuc}

- for the reaction of a series of nucleophiles having similar electronic and steric structure, the rate constant can be related to the basicity of the nucleophile:

$$\log(k) = \beta_{\mathrm{Nuc}} \log(K_b) + \log(C)$$

$$\boxed{\log(k) = \beta_{\mathrm{Nuc}} \mathrm{p}K_a + \log(C')}$$

  - β_{nuc} is a measure of the sensitivity of the reaction to the basicity (nucleophilicity) of the nucleophile
  - β_{nuc} is thus related to the <u>charge developed on the nucleophile</u> at the TS and therefore to the <u>degree of bond formation</u>

β_{lg}

- for the reaction of a series of substrates having similar electronic and steric structure, the rate constant can be related to the acidity of the conjugate acid of the leaving group:

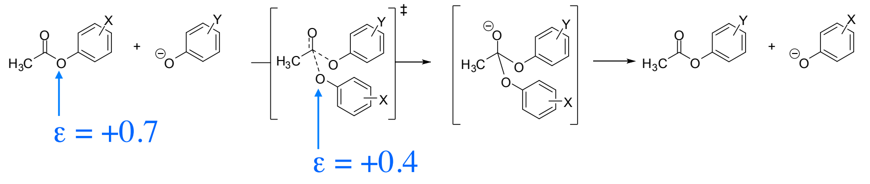
$$\boxed{\log(k) = \beta_{lg}\mathrm{p}K_a + \log(C)}$$

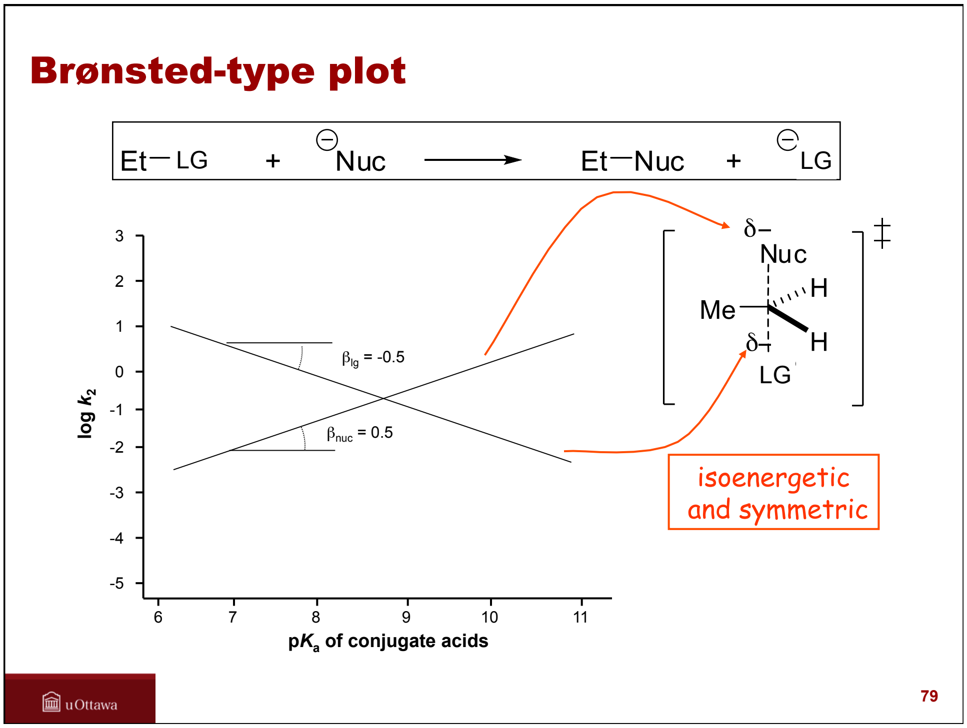
  - β_{lg} is a measure of the sensitivity of the reaction to the acidity of the conjugate acid (nucleofugality) of the leaving group
  - β_{lg} is thus related to the <u>charge developed on the leaving group</u> at the TS and therefore to the <u>degree of bond cleavage</u>

Slopes of Brønsted-type plots

- the value of the slope of a Brønsted-type plot can only very rarely be *directly* related to the degree of bond formation or cleavage
  - the slope β must also be known for the equilibrium constant of the reaction as well as for the rate constant
  - the *effective relative charge*, ε, must also be known for the reactants and the products

β_{lg} = -0.3 β_{nuc} = +0.6

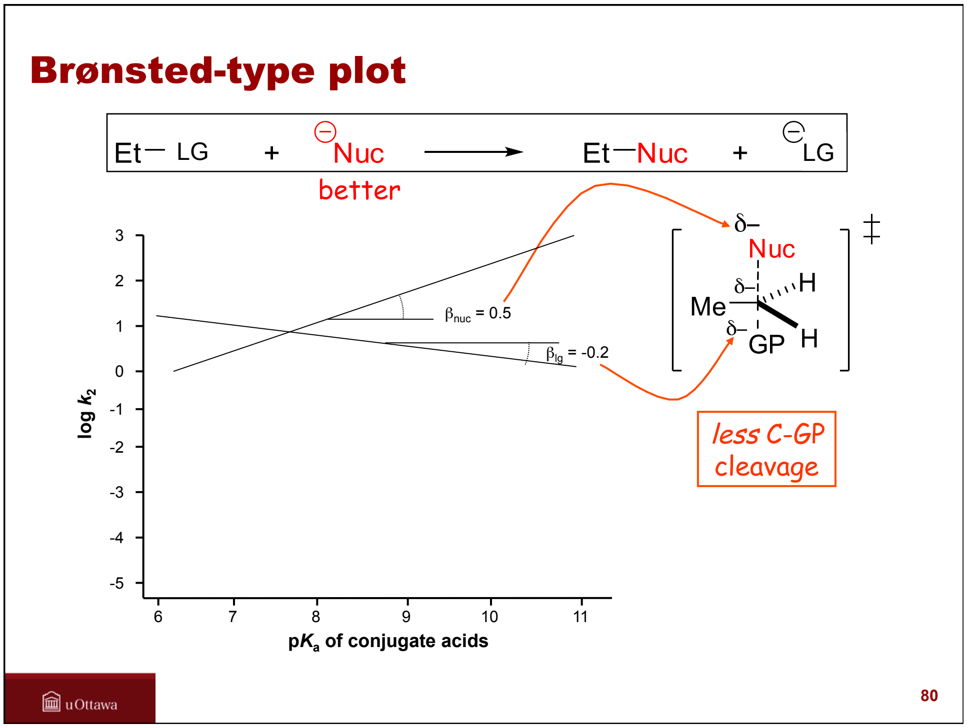




Brønsted-type plot

$$Et-LG + {}^{\ominus}Nuc \longrightarrow Et-Nuc + {}^{\ominus}LG$$

isoenergetic and symmetric

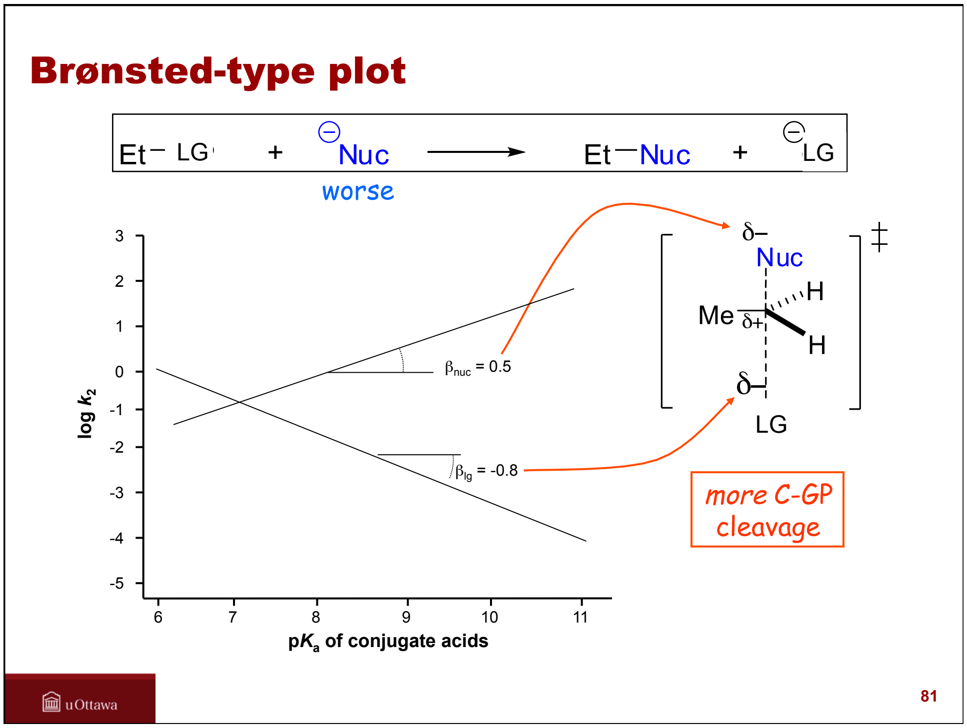


Brønsted-type plot

$$Et-LG + {}^{\ominus}Nuc \longrightarrow Et-Nuc + {}^{\ominus}LG$$

better

less C-GP cleavage

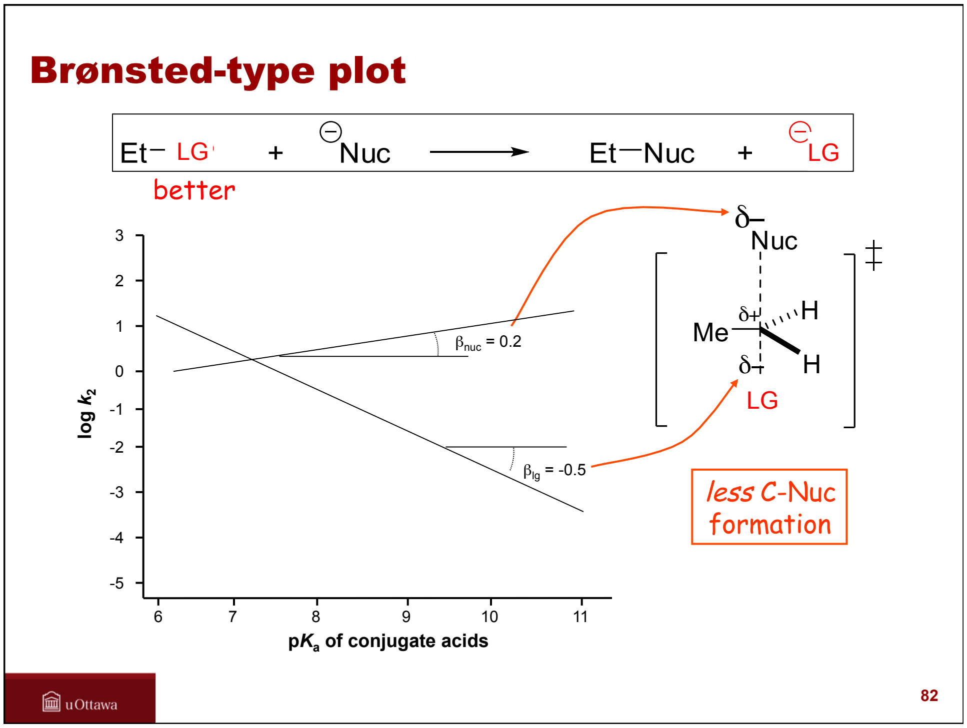


Brønsted-type plot

$\mathrm{Et{-}LG} + {}^{\ominus}\mathrm{Nuc} \longrightarrow \mathrm{Et{-}Nuc} + {}^{\ominus}\mathrm{LG}$

worse

more C-GP cleavage

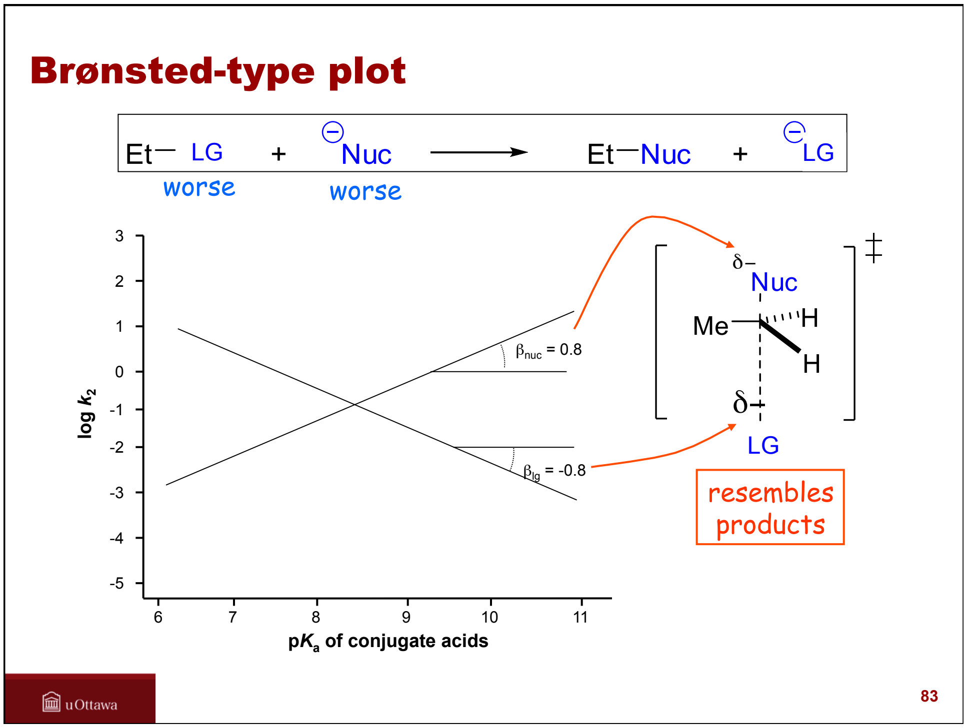


Brønsted-type plot

$\mathrm{Et{-}LG} + {}^{\ominus}\mathrm{Nuc} \longrightarrow \mathrm{Et{-}Nuc} + {}^{\ominus}\mathrm{LG}$

better

less C-Nuc formation

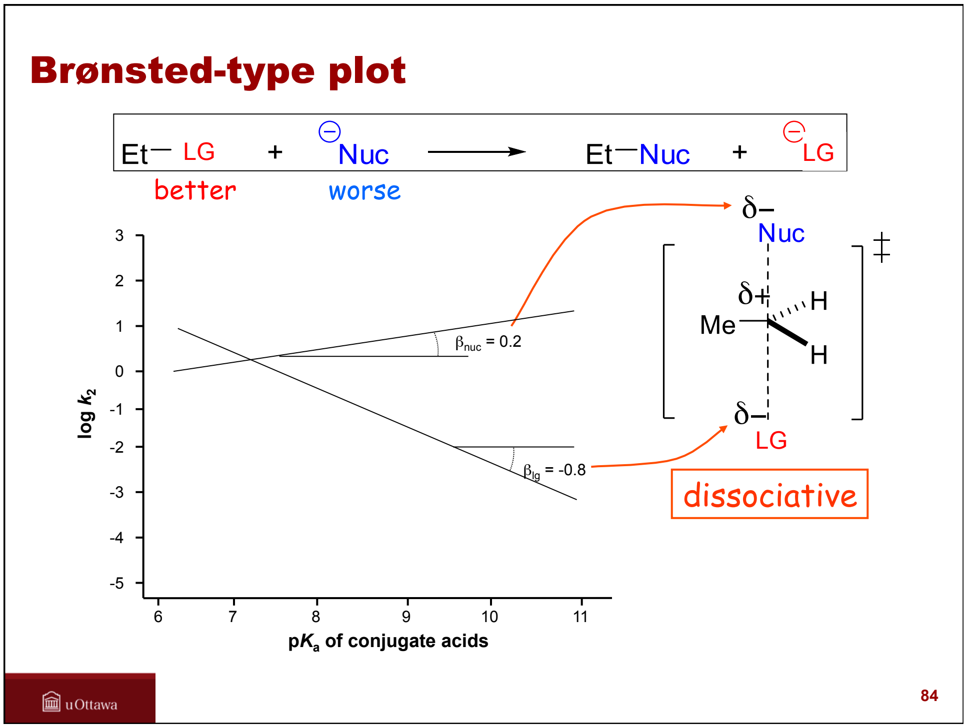


Brønsted-type plot

$\mathrm{Et{-}LG} + {}^{\ominus}\mathrm{Nuc} \longrightarrow \mathrm{Et{-}Nuc} + {}^{\ominus}\mathrm{LG}$

worse worse

resembles products



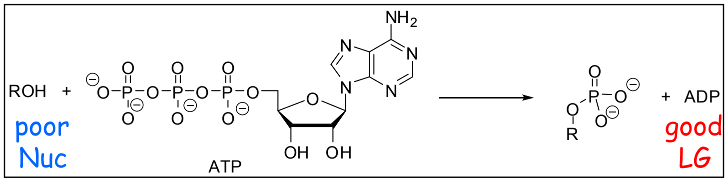
Brønsted-type plot

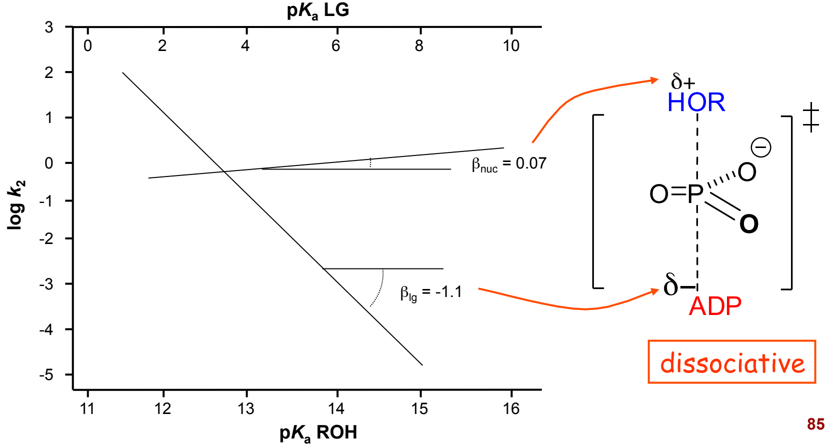
$\mathrm{Et{-}LG} + {}^{\ominus}\mathrm{Nuc} \longrightarrow \mathrm{Et{-}Nuc} + {}^{\ominus}\mathrm{LG}$

better worse

dissociative

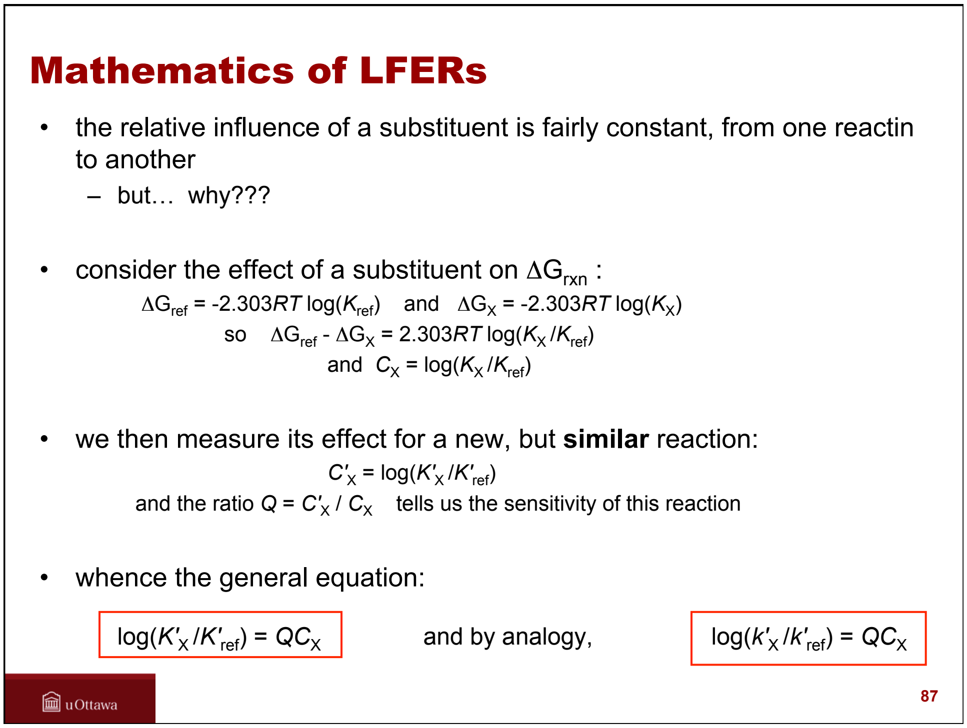
Brønsted-type plot





Outline: "LFERs"

- see section 8.6 of A&D
  - mathematical considerations
  - thermodynamic considerations
  - enthalpy/entropy compensation



Mathematics of LFERs

- the relative influence of a substituent is fairly constant, from one reactin to another
  - but… why???
- consider the effect of a substituent on ΔG_{rxn} :

$$\Delta G_{ref} = -2.303RT\log(K_{ref}) \quad \text{and} \quad \Delta G_X = -2.303RT\log(K_X)$$

$$\text{so} \quad \Delta G_{ref} - \Delta G_X = 2.303RT\log(K_X/K_{ref})$$

$$\text{and} \quad C_X = \log(K_X/K_{ref})$$

- we then measure its effect for a new, but **similar** reaction:

$$C'_X = \log(K'_X/K'_{ref})$$

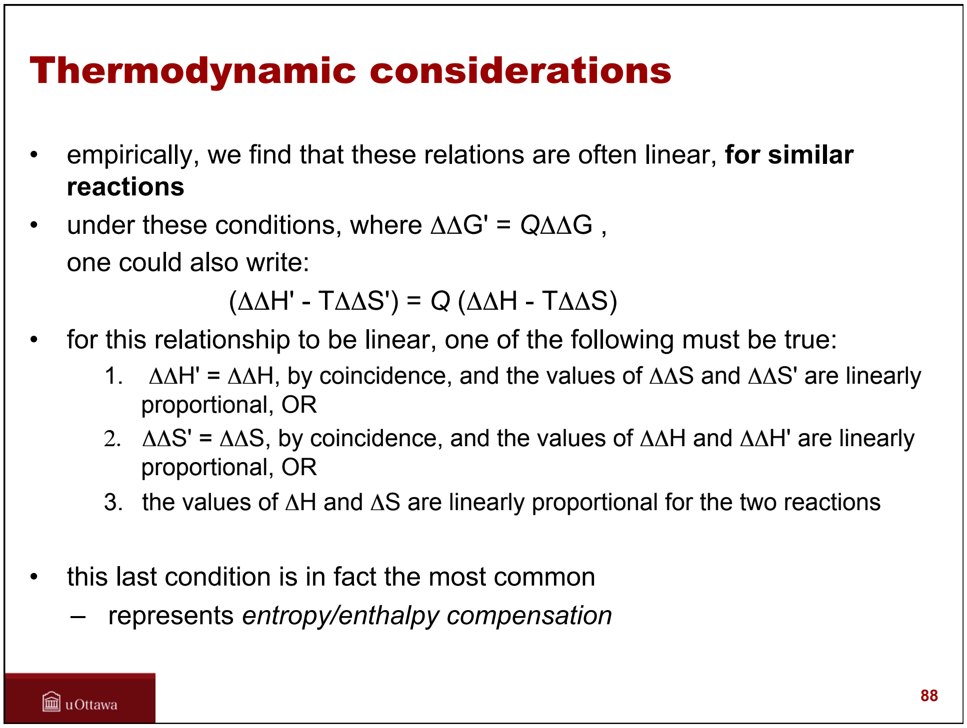
and the ratio $Q = C'_X / C_X$ tells us the sensitivity of this reaction

- whence the general equation:

$$\boxed{\log(K'_X/K'_{ref}) = QC_X}$$

and by analogy,

$$\boxed{\log(k'_X/k'_{ref}) = QC_X}$$



Thermodynamic considerations

- empirically, we find that these relations are often linear, **for similar reactions**
- under these conditions, where $\Delta\Delta G' = Q\Delta\Delta G$, one could also write:

$$(\Delta\Delta H' - T\Delta\Delta S') = Q\,(\Delta\Delta H - T\Delta\Delta S)$$

- for this relationship to be linear, one of the following must be true:
  1. $\Delta\Delta H' = \Delta\Delta H$, by coincidence, and the values of $\Delta\Delta S$ and $\Delta\Delta S'$ are linearly proportional, OR
  2. $\Delta\Delta S' = \Delta\Delta S$, by coincidence, and the values of $\Delta\Delta H$ and $\Delta\Delta H'$ are linearly proportional, OR
  3. the values of ΔH and ΔS are linearly proportional for the two reactions
- this last condition is in fact the most common
  - represents *entropy/enthalpy compensation*

Enthalpy/entropy compensation

- this phenomenon is easily explained on considering examples of steric effects and solvation effects:
  - steric effect:
    - for a reaction involving nucleophilic attack, a substrate having more steric hindrance at the TS will have a higher $\Delta H^\ddagger$
    - but since the nucleophile and solvent molecules will be more distant and bound less tightly at the transition state, $\Delta S^\ddagger$ will be less negative
  - solvation effect:
    - for an S_N2 reaction, the polar activated complex is stabilised in a polar solvent, so $\Delta H^\ddagger$ is smaller
    - but since the development of charge at the TS will lead to solvent molecules being bound more tightly, $\Delta S^\ddagger$ is equally more negative

Summary of LFERs

- Table 8.6, A&D

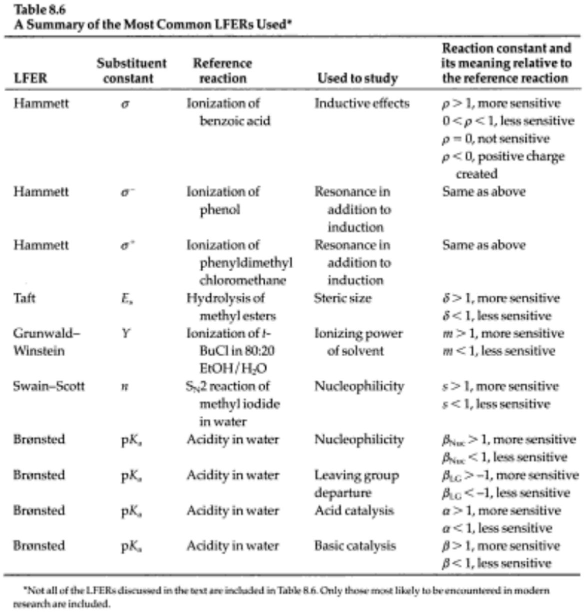


Table 8.6
A Summary of the Most Common LFERs Used*

LFER	Substituent constant	Reference reaction	Used to study	Reaction constant and its meaning relative to the reference reaction
Hammett	σ	Ionization of benzoic acid	Inductive effects	$\rho > 1$, more sensitive $0 < \rho < 1$, less sensitive $\rho = 0$, not sensitive $\rho < 0$, positive charge created
Hammett	σ^-	Ionization of phenol	Resonance in addition to induction	Same as above
Hammett	σ^+	Ionization of phenyldimethyl chloromethane	Resonance in addition to induction	Same as above
Taft	E_s	Hydrolysis of methyl esters	Steric size	$\delta > 1$, more sensitive $\delta < 1$, less sensitive
Grunwald–Winstein	Y	Ionization of *t*-BuCl in 80:20 EtOH/H_2O	Ionizing power of solvent	$m > 1$, more sensitive $m < 1$, less sensitive
Swain–Scott	n	S_N2 reaction of methyl iodide in water	Nucleophilicity	$s > 1$, more sensitive $s < 1$, less sensitive
Brønsted	pK_a	Acidity in water	Nucleophilicity	$\beta_{Nuc} > 1$, more sensitive $\beta_{Nuc} < 1$, less sensitive
Brønsted	pK_a	Acidity in water	Leaving group departure	$\beta_{LG} > -1$, more sensitive $\beta_{LG} < -1$, less sensitive
Brønsted	pK_a	Acidity in water	Acid catalysis	$\alpha > 1$, more sensitive $\alpha < 1$, less sensitive
Brønsted	pK_a	Acidity in water	Basic catalysis	$\beta > 1$, more sensitive $\beta < 1$, less sensitive

*Not all of the LFERs discussed in the text are included in Table 8.6. Only those most likely to be encountered in modern research are included.