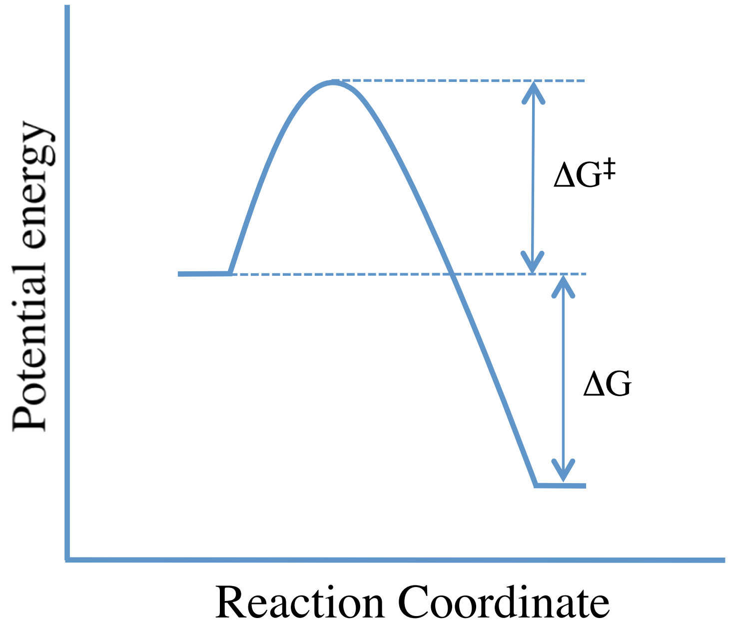
Linear Free Energy Relationship

Suppose overall free energy change for some reaction is ΔG
(or the barrier for the rate determining step is ΔG‡)



How does ΔG (or ΔG‡) change with changes in substituents or medium of reaction?

Need to integrate ΔG with respect to these changes
(whatever the changes might be but call them x, y, z, etc)

$$d\Delta G = (\delta\Delta G/\delta x)\ dx + (\delta\Delta G/\delta y)\ dy + \ldots..\ (\delta\Delta G/\delta z)\ dz$$

Linear Free Energy Relationship

Imagine instead of changing a number of variables (x, y, z),
only one variable is changed and everything else is kept the same

$$\Delta G_i - \Delta G_o = (\delta\Delta G/\delta x)(x_i - x_o)$$

Can also consider effect of changing the one variable (x) to the change in rate for the reaction

$$k = (\kappa T/h)\, e\, (-\Delta G^{\ddagger}/RT)$$

$$\Delta G^{\ddagger} = RT(\ln[\kappa T/h] - \ln k)$$

Thus the effect of rate change with change in x:

$$\Delta G^{\ddagger}_i - \Delta G^{\ddagger}_o = -RT \ln (k_i/k_o) = -2.303RT \log (k_i/k_o)$$

Therefore $\log (k_i/k_o) = -1/(2.303RT)\ (\delta\Delta G^{\ddagger}/\delta x)(x_i - x_0)$

This relationship describes how the rate changes for a given reaction by changing variable x
[rate k_i with x at one condition (x_i) to rate k_o with x at another condition (x_o)]

Linear Free Energy Relationship

* What if the change ($x_i – x_o$) is the same for two different reactions?

The energy change for a reaction may be linearly related to the energy change for a reference reaction

Consider a reaction B compared to a reference reaction A with the same change in x

$$\log (k_i/k_o)^B = \frac{(\delta\Delta G^{\ddagger}/\delta x)^B}{(\delta\Delta G^{\ddagger}/\delta x)^A} \log (k_i/k_o)^A$$

Can simplify equation:

$$\log (k_i/k_o)^B = G_i^{AB} \quad X_i$$

G_i^{AB}: describes the relative sensitivity of reactions A and B to the change from x_o to x_i

X_i: describes the effect of this change on a reference reaction A

All linear free energy relationships follow this same form, the effect of a change in one variable on a reference reaction is compared to the effect the same change has on another reaction

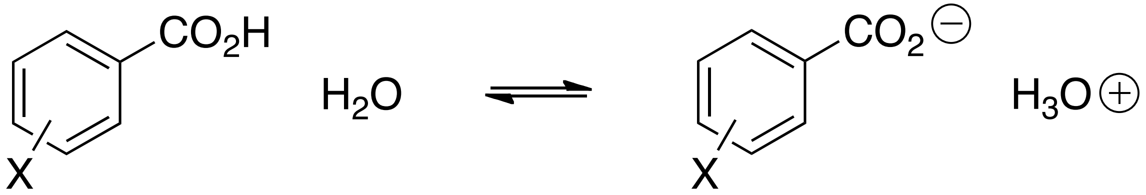
Hammett Equation

A Hammett equation is a linear free energy relationship that studies the effect of substituent changes on reactions

$$\log (k_i/k_o) = \rho \bullet \sigma$$

In any linear free energy relationship,
one of the first steps that need to be taken is to define *what is the reference reaction*

Hammett chose the dissociation constant for substituted benzoic acid as the model reaction



How is the equilibrium for this reaction affected by a substituent x either meta or para to the acid group (do not consider ortho due to steric effects where the acid might go out of planarity with the ring)?

Hammett originally studied equilibrium,
but relationship can also be applied to rate differences

Hammett Equation

The Hammett equation thus asks what influence does the electronic influence of substituent x have on the acid dissociation of benzoic acid

In addition to describing what is the reference reaction for a linear free energy relationship, also need to decide on which x is the reference substituent

Hammett decided that a hydrogen would be the reference substituent and he defined when X = H then $\sigma_H = 0$

The σ value for other substituents is thus determined by measuring the rate of benzoic acid dissociation with that substituent relative to when X = H

$\sigma = \log (k_x/k_H)$ (remember that ρ is defined as 1 for reference reaction)

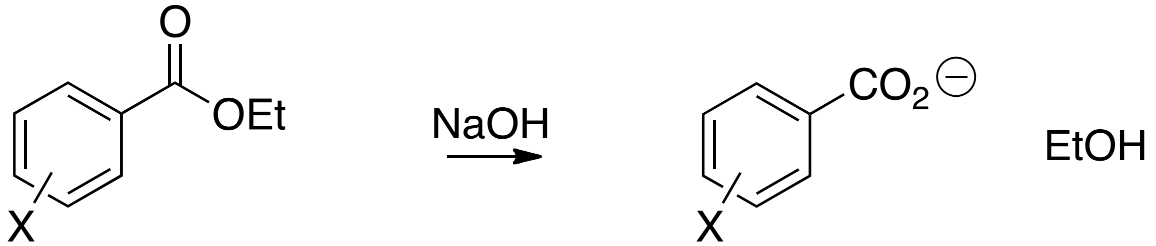
$\sigma > 0$, whenever substituents are more electron withdrawing than hydrogen (because with EWG the rate of benzoic acid dissociation is faster)

$\sigma < 0$, whenever substituents are more electron donating than hydrogen (because with EDG the rate of benzoic acid dissociation is slower)

Hammett Equation

Everything that has been done so far is studying the reference reaction and determining the substituent values (σ) with this reference reaction

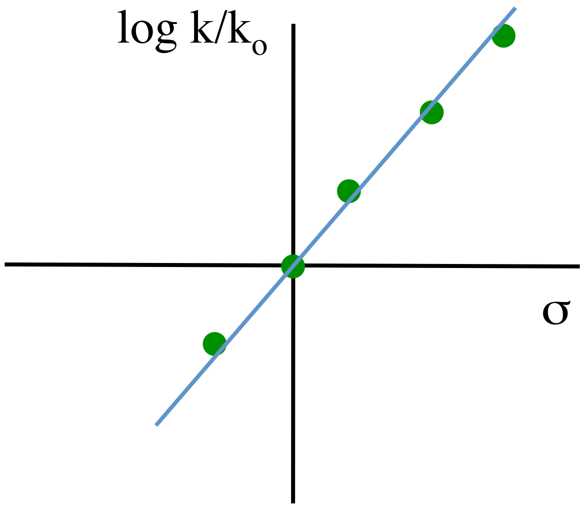
The key question with a LFER, however,
is what effect do these substituent changes have on another reaction?



When X = H,
$\sigma = 0$, $k = k_o$

When X = other substituents,
σ = value determine from reference,
then plot versus log k/k_o

Fit to a straight line where
slope = ρ



In the basic hydrolysis of ethyl benzoate, the slope was determined to be +2.2

What does the value of ρ tell us about the reaction mechanism?

$$\log (k_i/k_o) = \rho \bullet \sigma$$

Hammett Equation

Remember that the value of σ was determined with the reference reaction (dissociation of benzoic acid) by defining $\rho = 1$ and defining when X = H, $\sigma = 0$

When $\rho > 0$

The reaction is accelerated by electron withdrawing substituents, therefore aromatic ring has a higher electron density in the transition state than in the starting material

When $\rho < 0$

The reaction is accelerated by electron donating substituents, therefore aromatic ring has lower electron density in the transition state than in the starting material

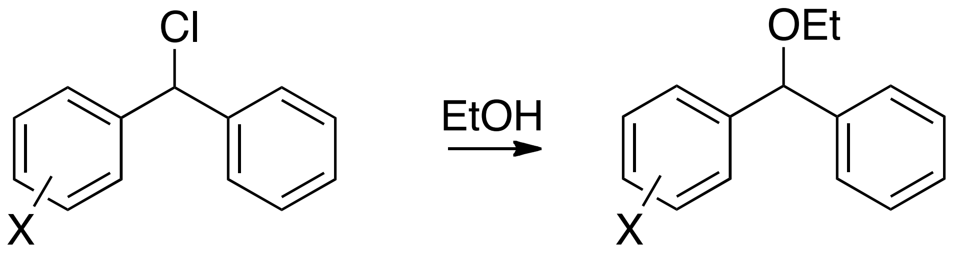
Also remember that scale was established with the reference reaction of benzoic acid where ρ was defined as +1

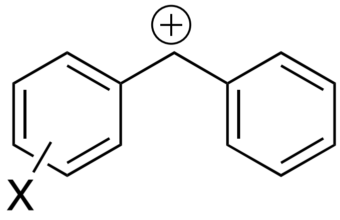
Can predict not only the type of charge in transition state versus the starting material (either more or less negative charge by the sign of ρ) the magnitude of charge is determined by the magnitude of ρ, if ρ is larger than +1 than the reaction under consideration has a greater amount of electron density in transition state than starting material relative to reference reaction

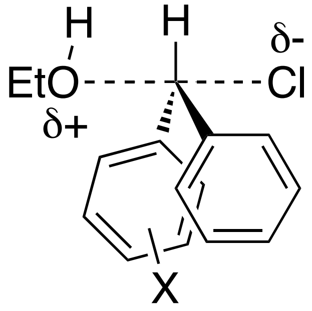
Hammett Equation

The Hammett equation is used often to determine type of charge being developed in transition state (can distinguish types of mechanisms) and the amount of charge

Consider the reaction of dibenzyl chloride with ethanol





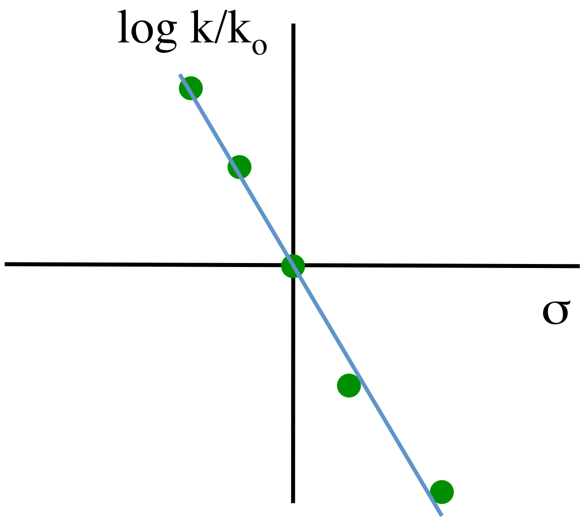


Does reaction occur with S_N1 or S_N2?

S_N1

S_N2

The amount (and type) of charge in TS relative to SM should be different for the S_N1 and S_N2 reactions



When a Hammett LFER is run, the ρ was determined to be -5.1, therefore a large amount of more positive charge in TS than SM

The data strongly indicates a S_N1 mechanism

Hammett Equation

In any linear free energy relationship there are a number of steps to properly perform the LFER and then being able to use the data to understand something about the mechanism

1) Determine what is the one aspect of the reaction that is going to be changed

2) Determine what is the reference reaction

3) Determine what is going to be the standard for the property that is being changed (in Hammett this was defined as when substituent was H)

4) Determine the values for the other possible changes by graphing log k_i/k_o and setting slope as equal to 1

5) Graph a new reaction being studied with log k_i/k_o versus the values for the property being changed

6) If the points of this graph are a straight line, then the new reaction is said to be "*linearly related*" to the reference reaction

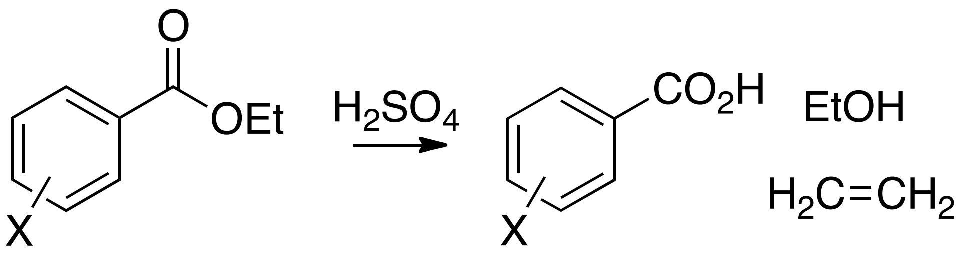
* What does it mean if a graph of log k_i/k_o versus standard values does not give a straight line?

Hammett Equation

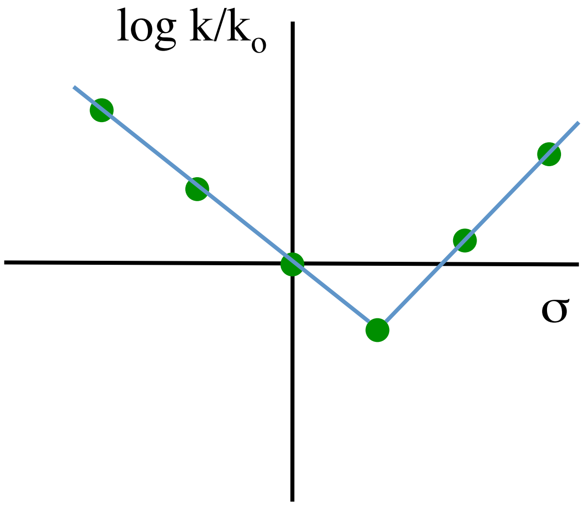
Possible explanations for a nonlinear fit:

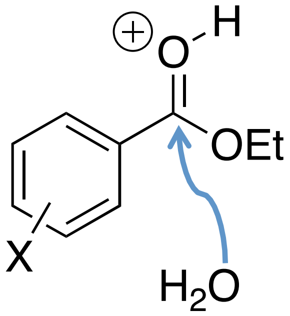
1) The mechanism changes with different substituents

Consider the acidic hydrolysis of an ester



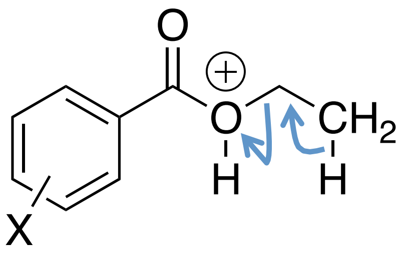
What is the mechanism?





Protonate carbonyl

EDG accelerate reaction



Protonate ester

EWG accelerate reaction

A Hammett LFER was run and it was determined that the slope of the graph changed at 0.7 σ, with more EWG the mechanism with the ester protonated was favored while with more EDG the carbonyl was protonated preferentially

Hammett Equation

2) Simply a nonlinear fit

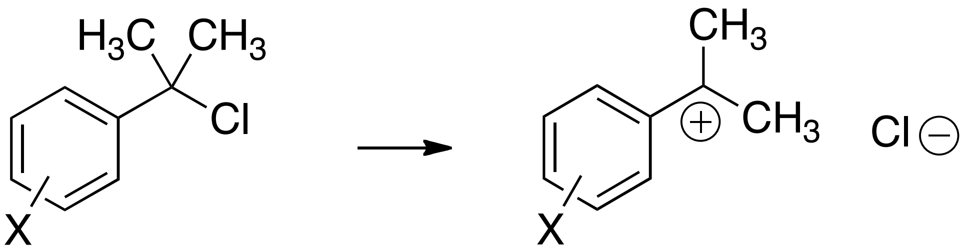
This result implies reaction being considered is not similar enough to the reference reaction (benzoic acid dissociation)

One possible reason for this observation is when reactions have a charge that is directly adjacent to the aromatic ring, in this case σ values do not correspond to a straight fit

The resonance effects dominate more than with the reference reaction

If this is the case,
then a new reference reaction is needed that corresponds to charge adjacent to ring

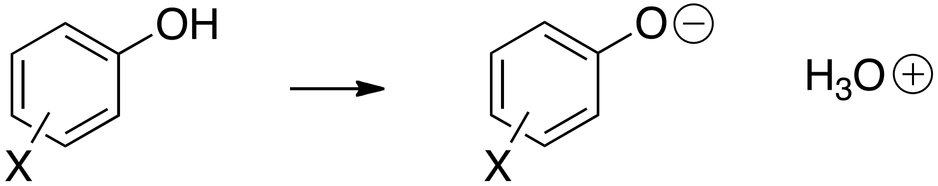
Reference reaction with a positive charge adjacent to ring:



This reference reaction is thus run with different substituents, x = H is still defined as σ+ = 0, but other substituents will get new standard values (called σ+)

Hammett Equation

Reference reaction with a negative charge adjacent to ring:



Substituted phenol derivatives will thus be measured and the graph of log k_i/k_o will be defined with a slope of 1 to determine the substituent values for this reaction (called σ- values)

If a new reaction being studied is not linearly related to the benzoic acid dissociation (thus not giving a straight line when log k_i/k_o is graphed versus σ), then the log k_i/k_o values will be graphed versus either σ+ or σ- to determine if the reaction is linearly related to either of these values

If the new reaction is linearly related when graphed versus σ- values, the reaction more than likely has a strong negative charge adjacent to the ring in the mechanism

If the new reaction is linearly related when graphed versus σ+ values, the reaction more than likely has a strong positive charge adjacent to the ring in the mechanism

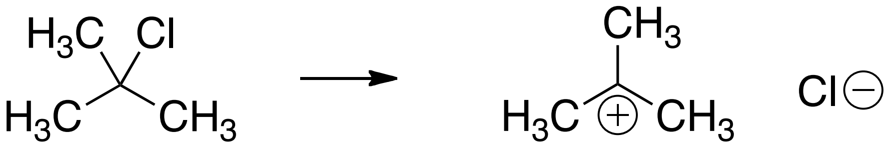
Grunwald-Winstein Equation

The Hammett equation is a LFER that studies the effect of substituents on reaction rate

The only criteria for a LFER is that only one change can be made to a reaction

Another common LFER is to study the effect solvent change has on reaction rate
(called a Grunwald-Winstein equation)

As seen in a number of reactions,
changing solvent can have a dramatic effect on reaction rate
(sometimes it can even change what mechanism is operating)

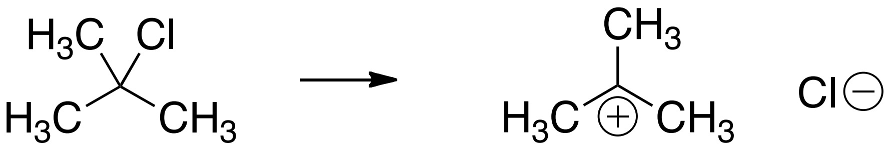


At 25˚C:
$\Delta H(g) = 150$ kcal/mol
$\Delta H(H_2O) = 20$ kcal/mol

→ The choice of solvent therefore has a dramatic effect on thermodynamics of reaction

Grunwald-Winstein Equation

The solvolysis of t-Butyl chloride is used as the reference reaction for this LFER



$$\log k/k_o = m \bullet Y$$

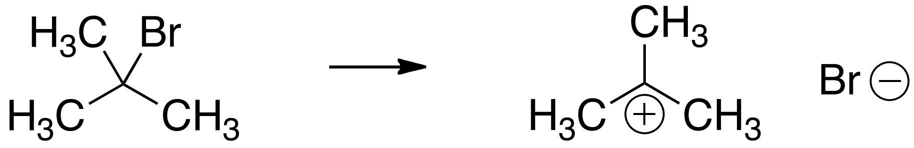
m = reaction parameter (similar to ρ in Hammett)

Y = solvent parameter (analogous to σ in Hammett for substituents)

The Y values for a solvent is thus determined by graphing log k/k_o for the solvolysis of t-Butyl chloride in the chosen solvent and setting the slope (m) equal to 1 with the standard solvent defined as 80% aqueous ethanol (therefore Y = 0 for this solvent)

A new reaction would then be tested by graphing log k/k_o versus Y and the slope of the straight line would be the m value, the magnitude of m would thus determine the amount of charge separation in the transition state for the new reaction relative to the reference reaction

Grunwald-Winstein Equation



m = 0.9 for the solvolysis of t-Butyl bromide

The solvolysis of t-Butyl bromide thus is less sensitive to changes in solvent than the reference reaction t-Butyl chloride, therefore the transition state has less carbocation character

The C-Cl bond is thus broken more in the transition state structure than the C-Br bond which results in more charge separation for t-Butyl chloride
(this should not be surprising since we would predict that the C-Br bond would break faster due to more polarizable leaving group which would imply an earlier transition state structure according to Hammond postulate)

Nucleophilicity

Another LFER that is commonly used is to measure the *nucleophilicity* of a nucleophile (called the Swain-Scott equation)

$$\log k/k_o = \eta \bullet S$$

η (eta) = nucleophilicity constant (analogous to σ in Hammett)

S = substrate sensitivity (dependent on reactivity of substrate, analogous to ρ in Hammett)

The reference reaction was determined to be a nucleophile reacting with methyl bromide in water solvent

$$CH_3Br \qquad NUC^{\ominus} \longrightarrow NUC{-}CH_3 \qquad Br^{\ominus}$$

The η value was set at 0 for water and then the η values for other nucleophiles were established by plotting $\log k/k_o$ versus η with a defined slope ($S = 1$)

(nucleophilicity values are thus defined as the S_N2 reactivity of the nucleophile with methyl bromide in *protic* solvent)

We will study more about nucleophilicity, and how to predict whether the η values increase or decrease, when we study nucleophilic reactions

Linear Free Energy Relationships

General form of LFER:

$$\log (k_i/k_o)^B \quad = \quad G_i^{AB} \quad X_i$$

Hammett Equation

$$\log (k_i/k_o)^B \quad = \quad \rho \quad \sigma$$

Effect of changing substituents on reaction rates,
reference reaction is dissociation of benzoic acid to define σ values,
how a new reaction is affected by the same change of substituents indicates the type and degree of charge in the transition state for the mechanism

Grunwald-Winstein Equation

$$\log (k_i/k_o)^B \quad = \quad m \quad Y$$

Effect of changing solvent on reaction rates,
reference reaction is solvolysis of t-Butyl chloride to define Y values,
how a new reaction is affected by the same change in solvent indicates degree of charge separation in transition state for the mechanism

Nucleophilicity (Swain-Scott)

$$\log (k_i/k_o)^B \quad = \quad S \quad \eta$$

Effect of changing nucleophile on reaction rates,
reference reaction is nucleophile reacting with methyl iodide in methanol solvent