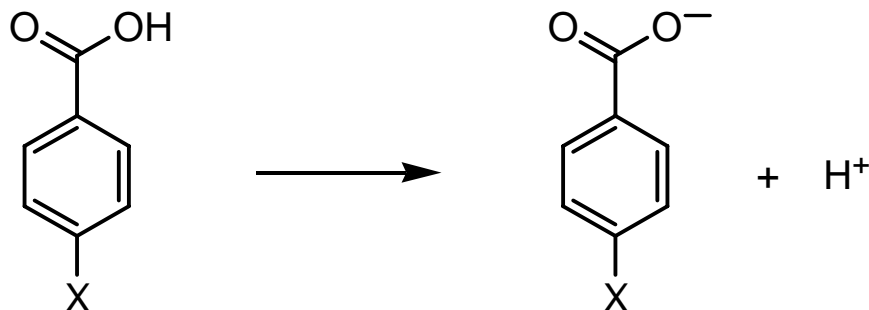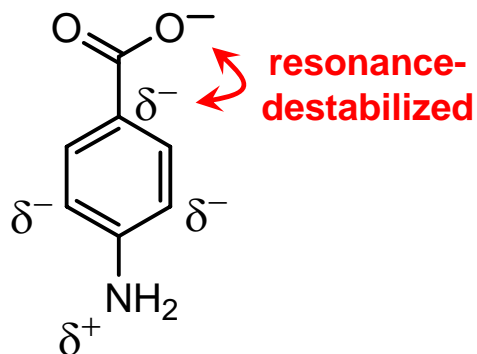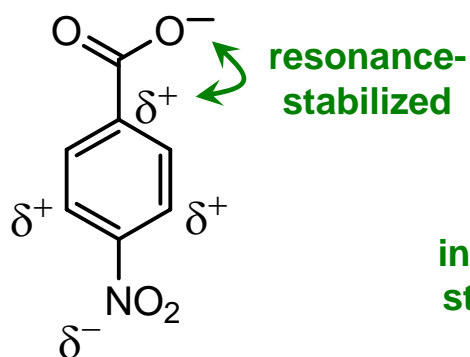# Linear Free-Energy Relationships (Substituent Effects, LFERs, or Hammett Plots)

Qualitative question: How does substituent X affect acidity?
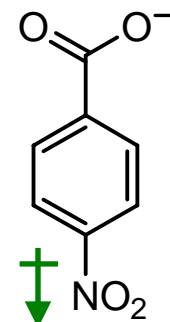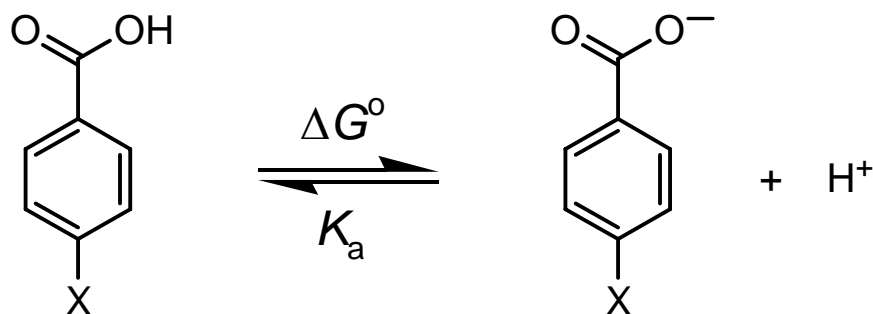As a reminder,

Electron-donating groups *decrease* **acidity.**

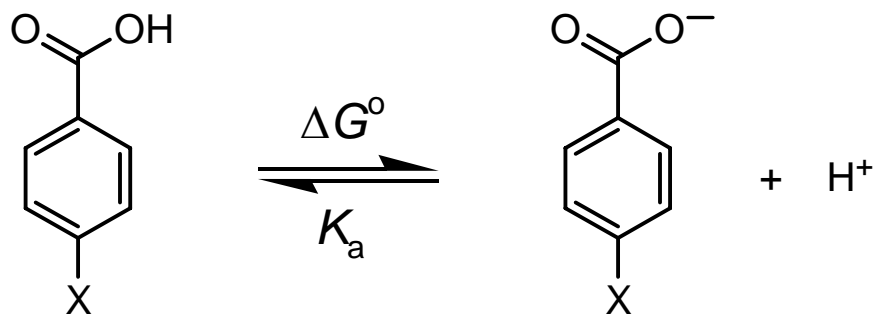**Electron-withdrawing groups** *increase* **acidity.**

Linear Free-Energy Relationships

$$\text{(ArCOOH)} \underset{K_a}{\overset{\Delta G^o}{\rightleftharpoons}} \text{(ArCOO}^-\text{)} + H^+$$

Qualitative question: How does substituent X affect acidity?

|			pK_a	K_a	ΔG^0
X =	**NH$_2$**	less acidic	4.86	1.4×10^{-5} M	6.7 kcal/mol
	CH$_3$				
	H		4.20	6.3×10^{-5} M	5.8 kcal/mol
	Br				
	CF$_3$				
	NO$_2$	more acidic	3.42	3.8×10^{-4} M	4.7 kcal/mol

Linear Free-Energy Relationships

Louis Hammett turned this into a quantitative question:

Can we construct a mathematical relationship between substituent X and acidity? (Can effect of substituent on ΔG^o and K_a be expressed mathematically?)

Is relationship for one reaction related to that for other reactions?

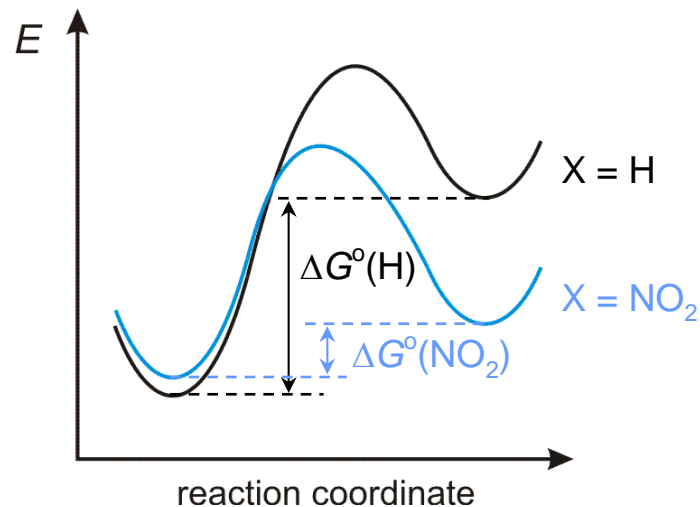# Linear Free-Energy Relationships
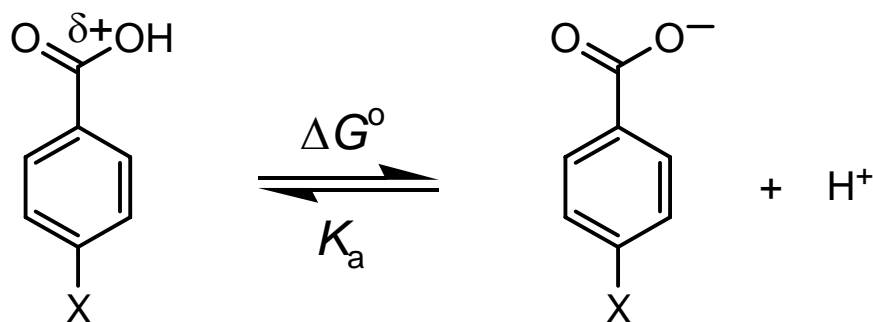
Hammett's Hypothesis, Part 1:

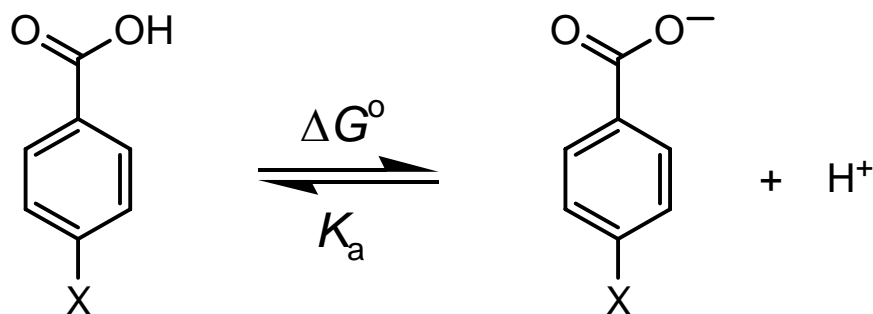For each substituent X, there is a characteristic free-energy difference

$$\log_{10} \frac{K_a(X)}{K_a(H)} = \frac{-\Delta\Delta G^o(X)}{2.303RT} = \sigma(X)$$

"Hammett parameter"

$$\Delta\Delta G^o(X) = \Delta G^o(X) - \Delta G^o(H)$$

Linear Free-Energy Relationships

$$\Delta G^o \quad K_a$$

(reaction scheme: para-X-substituted benzoic acid $\rightleftharpoons$ carboxylate anion $+$ H^+)

Hammett's Hypothesis, Part 1:

We can define a set of constants σ such that

$$\log_{10} \frac{K_a(X)}{K_a(H)} = \sigma(X)$$

X	**σ**	
NH$_2$	-0.66	$K_a(NH_2) < K_a(H)$
H	0	(by definition)
Br	0.23	
NO$_2$	0.78	$K_a(NO_2) > K_a(H)$

So far, this is just math.
Not a big deal.

Linear Free-Energy Relationships

Hammett's Hypothesis, Part 2:

These exact same constants σ apply to other (only somewhat related) reactions, such that

$$\log_{10} \frac{K_a(X)}{K_a(H)} = \rho\sigma(X)$$

Here, different reaction… but same general substituent effects!

$$\log_{10} \frac{K_a(X)}{K_a(H)}$$

This is a big deal.

$\rho = 0.489$

(ρ < 1 means less sensitive to substituents than benzoic acid K_a)
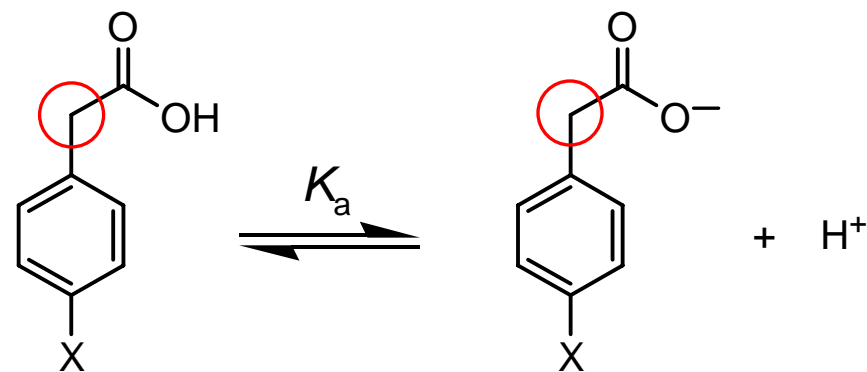
Linear Free-Energy Relationships

Hammett's Hypothesis, Part 2:

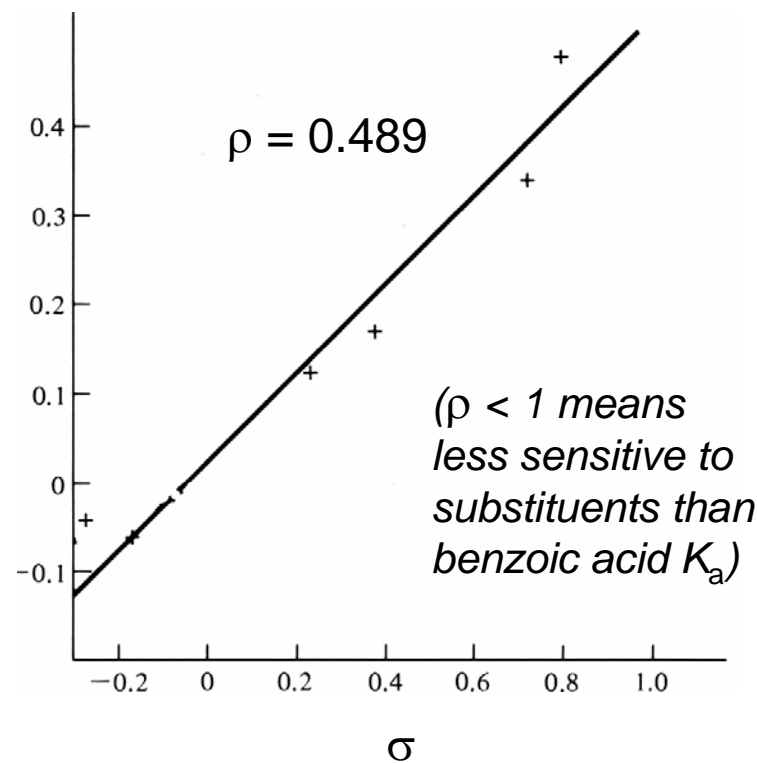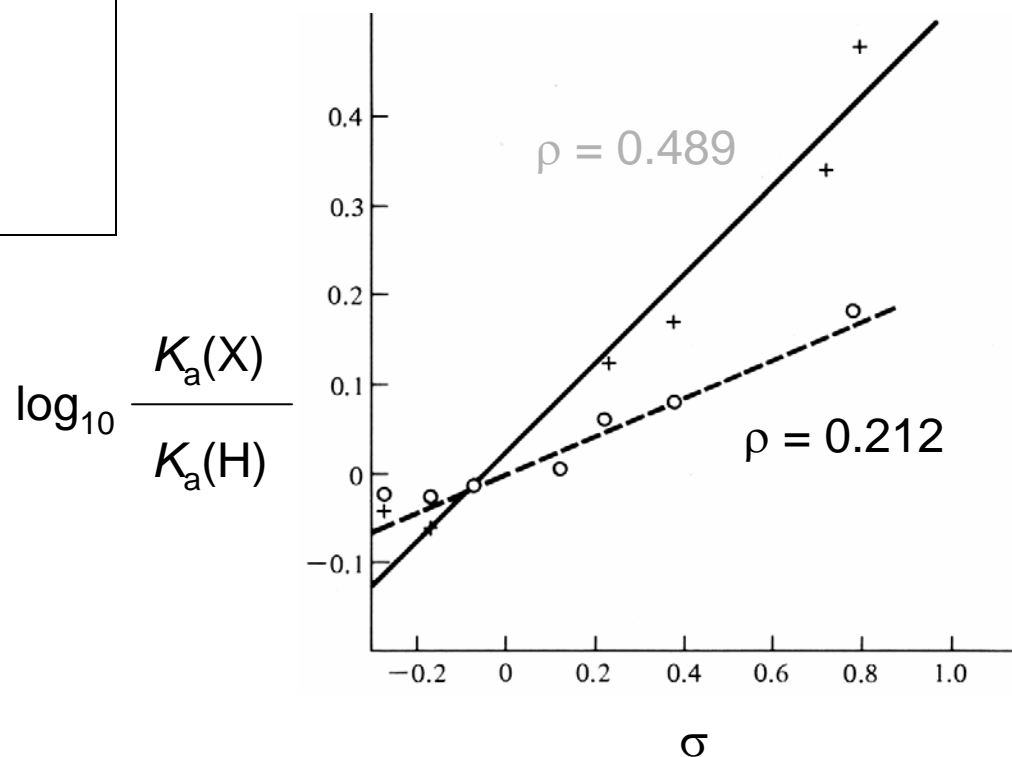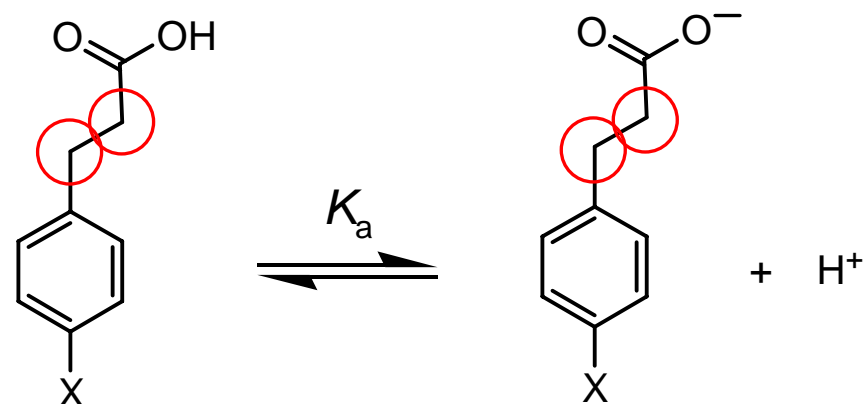These exact same constants σ apply to other (only somewhat related) reactions, such that

$$\log_{10} \frac{K_a(X)}{K_a(H)} = \rho\sigma(X)$$

(Denominator can actually be any constant.)

Remarkably, relationship between substituent σ and equilibrium stays linear.

$$\log_{10} \frac{K_a(X)}{K_a(H)}$$

$\rho = 0.489$

$\rho = 0.212$

Linear Free-Energy Relationships

Hammett's Hypothesis, Part 2:

$$\log_{10} \frac{K_a(X)}{K_0} = \rho\sigma(X)$$

(actually possible to use any constant in denominator)

Overall:

$\rho > 0$:   Equilibrium has ***same*** pattern as benzoic acid K_a's;
Electron-withdrawing substituents increase K_a,
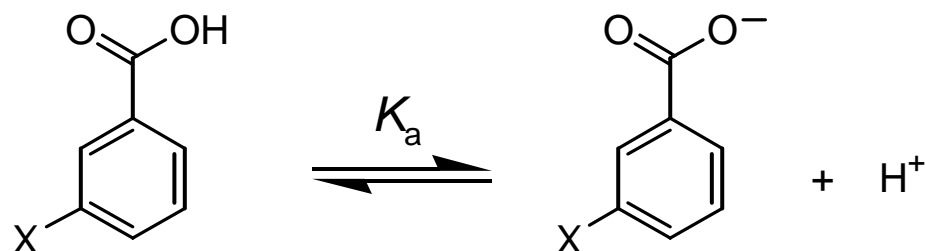Electron-donating substituents decrease K_a.

   $\rho > 1$:   **More** sensitive to substituents than benzoic acid K_a's.
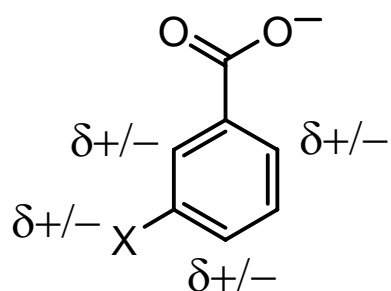 $0 > \rho > 1$: **Less** sensitive to substituents than benzoic acid K_a's.

$\rho < 0$:   Equilibrium has ***opposite*** pattern as benzoic acid K_a's;
Electron-withdrawing substituents decrease K_a,
Electron-donating substituents increase K_a.

Linear Free-Energy Relationships

If substituent effect is fundamentally different, then different set of σ values may be required.
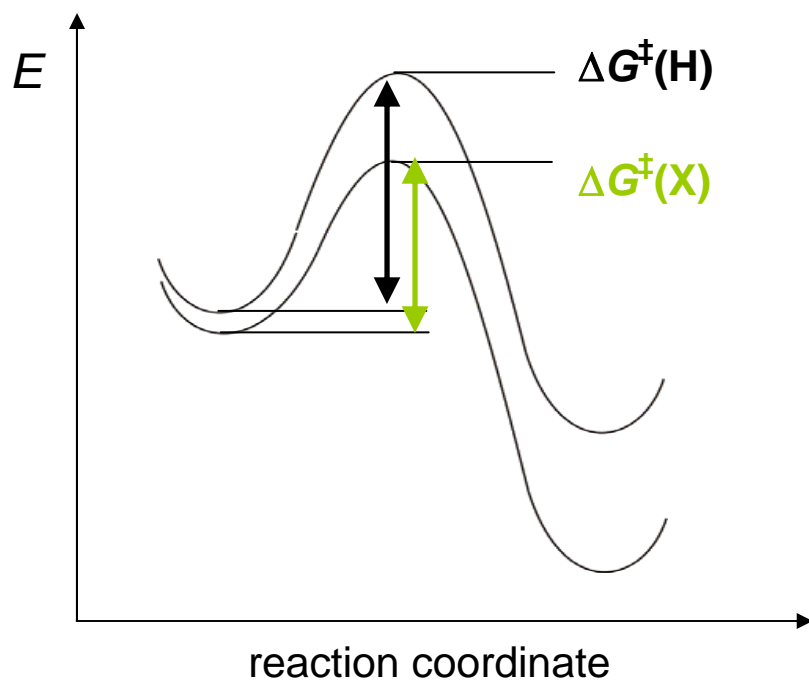

Pattern of stabilization/ destabilization is the same for σ_{meta};

Resonance less important,

Induction more important.

Substituent	$\sigma_{meta}^{a,c}$	$\sigma_{para}^{a,c}$
NH_2	−0.16	−0.66
CH_3	−0.07	−0.17
C_6H_5	0.06	−0.01
OH	0.12	−0.37
OCH_3	0.12	−0.27
F	0.34	0.06
I	0.35	0.18
CO_2H	0.37	0.45
Cl	0.37	0.23
$COCH_3$	0.38	0.50
Br	0.39	0.23
CO_2R	0.37	0.45
CF_3	0.43	0.54
CN	0.56	0.66
NO_2	0.71	0.78

Linear Free-Energy Relationships: Kinetics
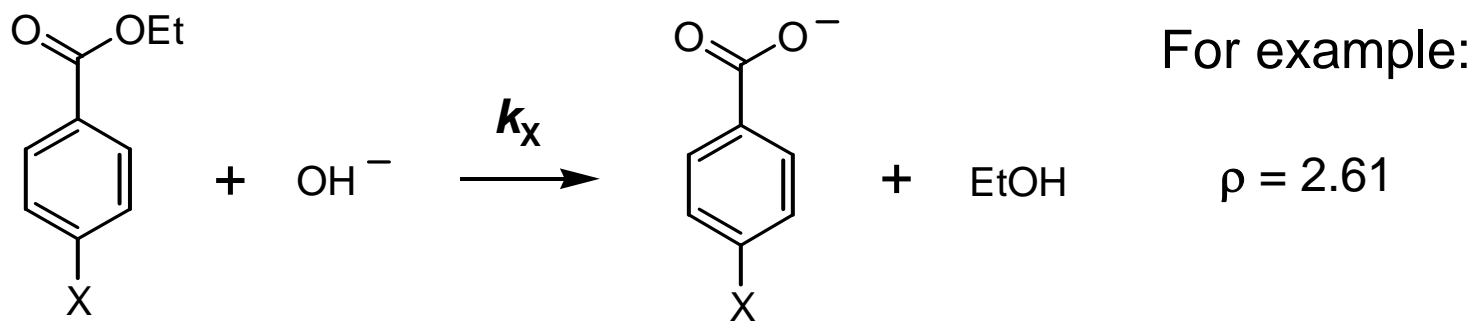

Remarkably, σ can be used for **rate constants** too.

$$\Delta\Delta G^{\ddagger}(X) = \Delta G^{\ddagger}(X) - \Delta G^{\ddagger}(H)$$

$$\log_{10} \frac{k_X}{k_H} = \frac{-\Delta\Delta G^{\ddagger}(X)}{2.303RT} = \rho\sigma(X)$$

rate constants!

Linear Free-Energy Relationships: Kinetics
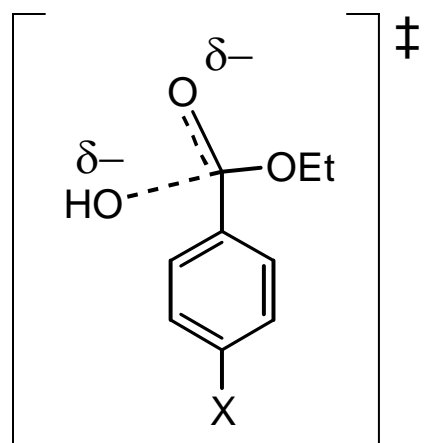

For example:

$$\rho = 2.61$$

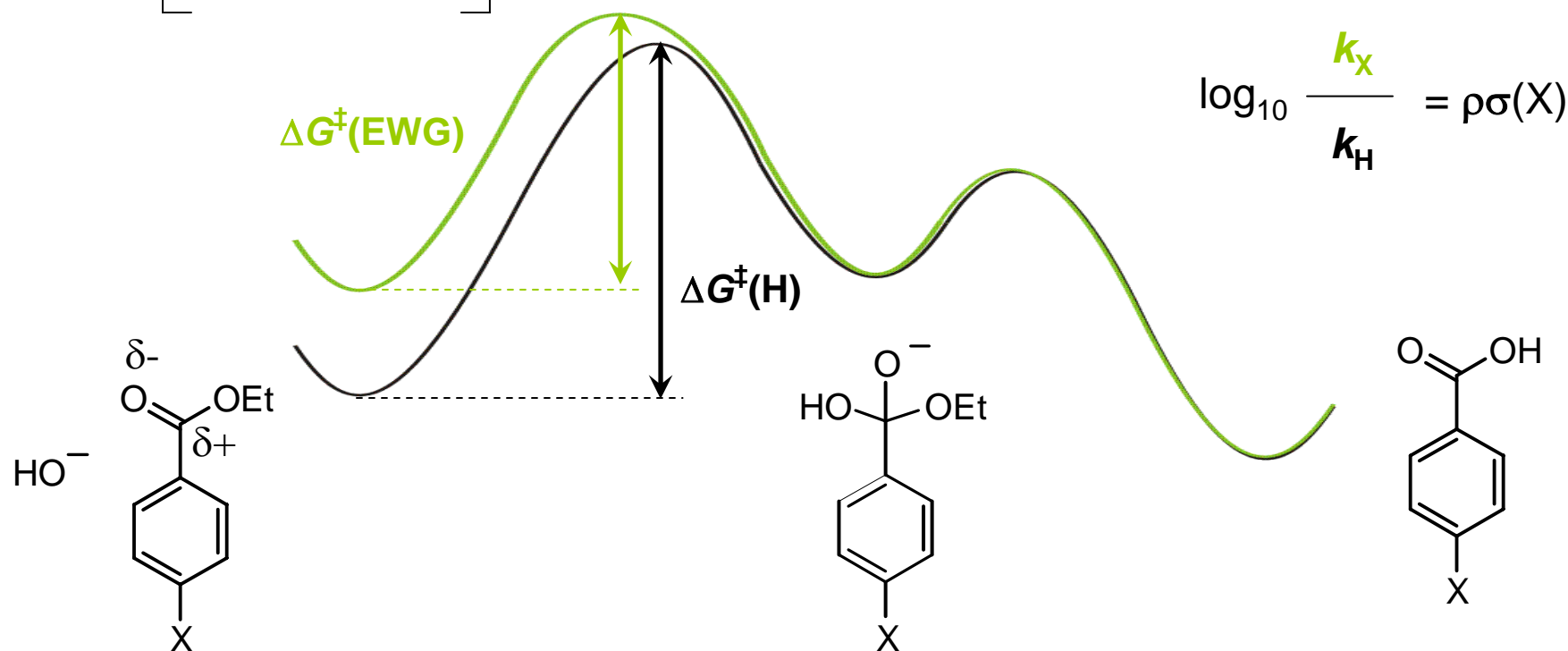$$\log_{10}\frac{k_X}{k_H} = \frac{-\Delta\Delta G^{\ddagger}(X)}{2.303RT} = \rho\sigma(X)$$

$\rho > 0$;

As with benzoic acid acidity,

EWGs increase rate constant,

EDGs decrease rate constant.

Linear Free-Energy Relationships

Electron-withdrawing X destabilizes $^{(\delta+)}C=O$.

Destabilizes C_{sp^3} in transition state less.
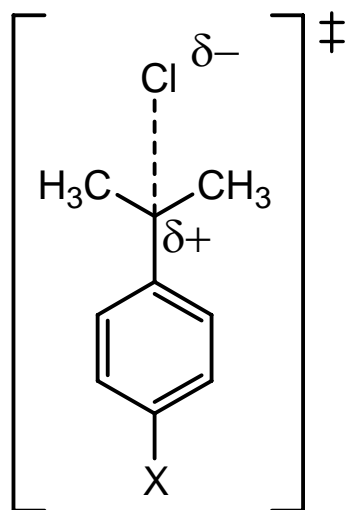
So, $k_{EWG} > k_H$.

Just like benzoic acid K_a's. So $\rho > 0$.

$$\log_{10} \frac{k_X}{k_H} = \rho\sigma(X)$$
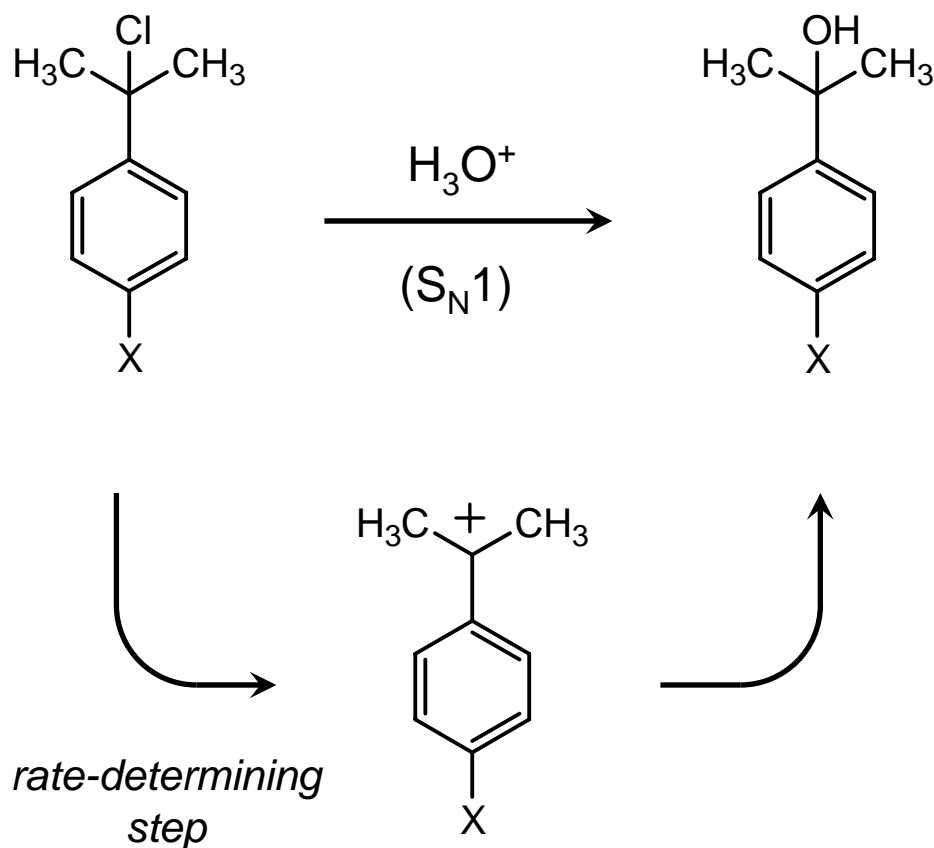
$\Delta G^\ddagger(EWG)$

$\Delta G^\ddagger(H)$

Linear Free-Energy Relationships

Direct resonance of changing charge in TS addressed by σ^+, σ^-.

Resonance stabilization particularly important in TS.
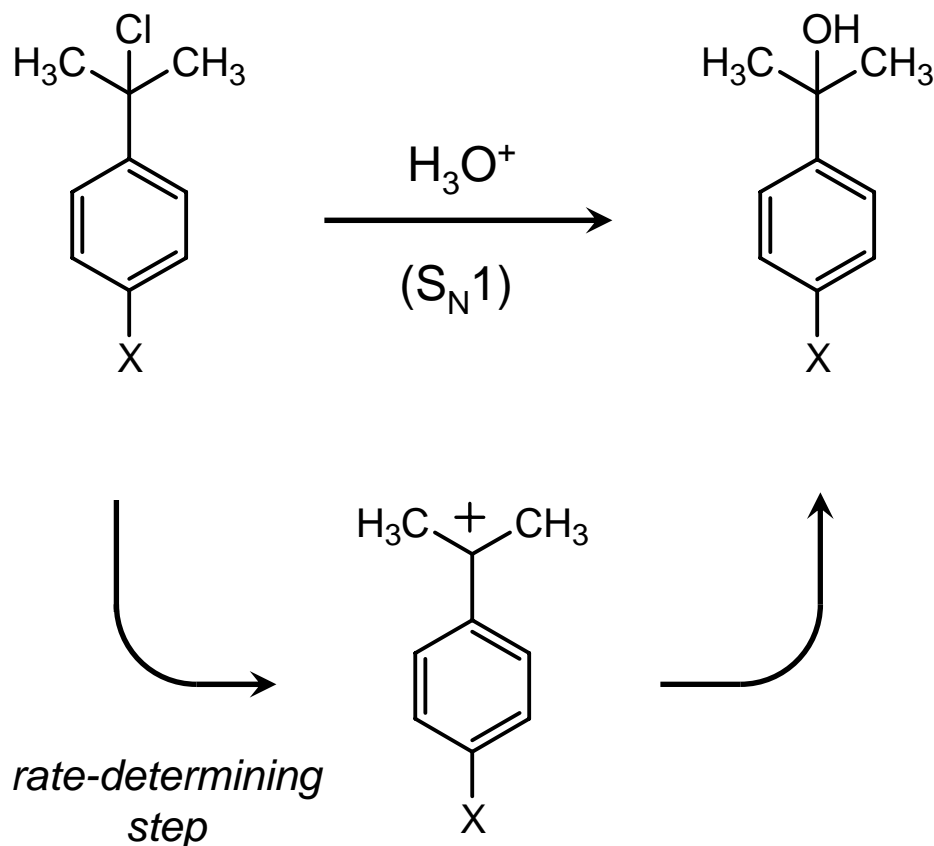

Resonant e^- donors stabilize TS, increase k.

H_3O^+

(S_N1)

rate-determining step

Linear Free-Energy Relationships

σ^+ accounts for direct resonance with phenyl substituents.

Substituent	$\sigma^{+a,d}$
NH_2	-1.3
CH_3	-0.31
C_6H_5	-0.17
OH	-0.92
OCH_3	-0.78
F	-0.07
I	0.13
CO_2H	0.42
Cl	0.11
$COCH_3$	—
Br	0.15
CO_2R	0.48
CF_3	—
CN	0.66
NO_2	0.79

Reference is cumyl chloride hydrolysis (this reaction).

H_3O^+

(S_N1)

rate-determining step

$$-\log_{10} \frac{k_X}{k_H} = \rho\sigma^+(X)$$

Negative sign (for σ+ only) means σ *values same direction as benzoic acids.*

Linear Free-Energy Relationships

$$\log_{10} \frac{K_a(X)}{K_a(H)} = \rho\sigma(X) \quad or \quad \log_{10} \frac{k_X}{k_H} = \rho\sigma(X)$$

Summary:

$\rho > 0$:   Process has ***same*** pattern as benzoic acid K_a's;
Electron-withdrawing substituents increase K_a or rate k,
Electron-donating substituents decrease K_a or rate k.

$\rho < 0$:   Process has ***opposite*** pattern as benzoic acid K_a's;
Electron-withdrawing substituents decrease K_a or rate k,
Electron-donating substituents increase K_a or rate k.

Linear Free-Energy Relationships

Keep in mind: For *multistep* kinetics,
Effect of substituent is between starting
material and rate-determining transition state.

$\Delta G^\ddagger$(H)

$\Delta G^\ddagger$(X)
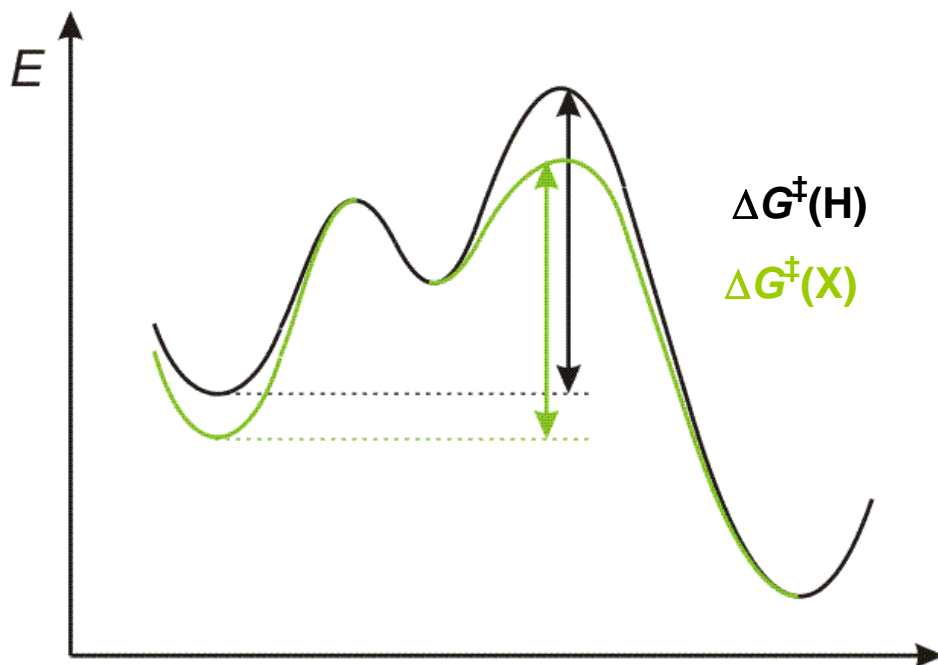
*Method is frequently used
to identify rate-determining
step/transition state.*

*Can also be used to
identify change in
rate-determining
transition state.*