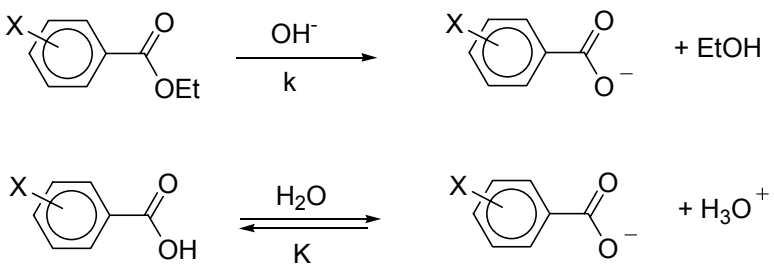
Handout: **Linear Free Energy Relationships (LFER)** (see also A.&D. p.445-453)

1. Correlations between rates and equilibria of reactions of compounds containing substituted phenyl groups was first noted by L. Hammett in 1937.
Hammett found that the following equation (1) applies for the rates of alkaline hydrolysis of substituted ethyl benzoates and the acidities (dissociation constants) of the corresponding benzoic acids.

Hammett equation (LFER)

$$m \log\left(\frac{K}{K_o}\right) = \log\left(\frac{k}{k_o}\right) \qquad (1)$$



K_o = K of benzoic acid X=H
K = K of subst. Benzoic acid X≠H
k_o = k of ethyl benzoate X=H
k = k of subst. Ethyl benzoat X≠H

Note: Bronsted equations are LFERs)

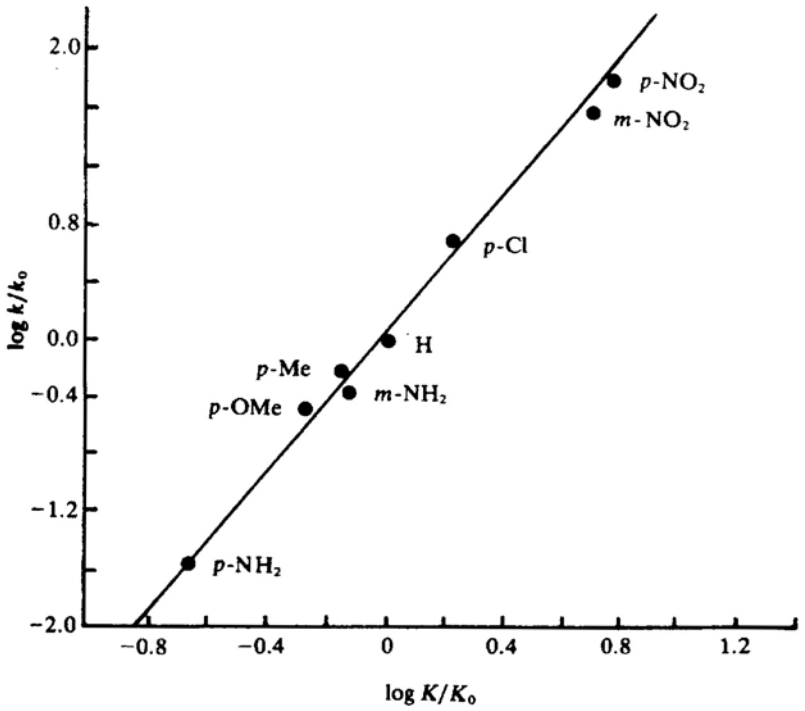


Fig. 4.2. Correlation of acid dissociation constants of benzoic acids with rates of alkaline hydrolysis of ethyl benzoates. [From L. P. Hammett, *J. Am. Chem. Soc.* **59**:96 (1937).]

2. From (1) : $m(\log K - \log K_o) = \log k - \log k_o$

and $m(-\Delta G/2.3RT + \Delta G_o/2.3RT) = -\Delta G^{\ddagger}/2.3RT + \Delta G_o^{\ddagger}/2.3RT$ (2)

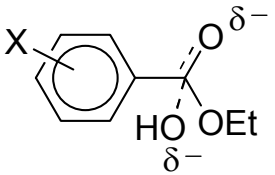
thus $m(-\Delta G + \Delta G_o) = -\Delta G^{\ddagger} + \Delta G_o^{\ddagger}$

and $m\,\Delta\Delta G = \Delta\Delta G^{\ddagger}$ (3)

In (2) we make use of definition of equilibrium constant $K = \exp(-\Delta G/RT)$ or $\log K = -\Delta G/2.3RT$ and transition state theory: $k = \kappa kT/h \times \exp(-\Delta G_o^{\ddagger}/RT)$ or $\log k = C - \Delta G_o^{\ddagger}/2.3RT$; $C = \log(\kappa kT/h)$

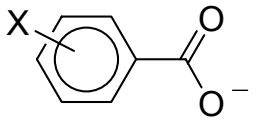
Equation (3) means that changes in $\Delta G^{\ddagger}$ on introducing a series of substituents are directly proportional to the changes in ΔG of ionization that is caused by the same series of substituents.

This makes sense:
r.d. step is addition of OH^- to benzoate with the following TS:



TS will decrease, the more X can aid in stabilizing δ^- charge at O

Dissociation constant largly depends on stability of conj. Base:



Acidity will increase, the more X can aid in stabilizing - charge at O

Thus, inductive and resonance effects that increase acidity of the subst. Benzoic acid will also have a stabilizing effect on the transition state for the hydroysis of the ester.

3. Hammett equation is typically expressed as follows:

$\text{Log}(k/k_o) = \sigma \times \rho$ (4) $\quad\quad$ $\text{Log}(K/K_o) = \sigma \times \rho$ (5)

ρ is the *reaction constant* $\quad\quad$ ρ = 1 for ionization of benzoic acid in water (standard reaction)

σ is the *substituent constant* $\quad\quad$ can be empirically determined from dissociation constants of substituted benzoic acids

It follows that σ = 0 for X = H.

Note: Swain-Scott Nucleophilicity constants are derived from a LFER of the type (4). k_o in (4) corresponds to the rate for the reference nucleophile (CH_3OH) and σ to the nucleophilicity constant n. The constant S in the Swain-Scott relationship corresponds to ρ above and allows application of the Swain-Scott relationship to other nucleophilic reactions. Again, S = 1 for the standard reaction ($Nu + CH_3I$)

4. Determination of ρ values
σ values defined for different X with standard reaction are used to determine empirically ρ for other reactions (e.g. hydrolysis of ethyl benzoate) see Table to the right

Table 4.6. Reaction Constants[a]

Reaction	ρ
$ArCO_2H \rightleftharpoons ArCO_2^- + H^+$, water	1.00
$ArCO_2H \rightleftharpoons ArCO_2^- + H^+$, EtOH	1.57
$ArCH_2CO_2H \rightleftharpoons ArCH_2CO_2^- + H^+$, water	0.56
$ArCH_2CH_2CO_2H \rightleftharpoons ArCH_2CH_2CO_2^- + H^+$, water	0.24
$ArOH \rightleftharpoons ArO^- + H^+$, water	2.26
$ArNH_3^+ \rightleftharpoons ArNH_2 + H^+$, water	3.19
$ArCH_2NH_3^+ \rightleftharpoons ArCH_2NH_2 + H^+$, water	1.05
$ArCO_2Et + {}^-OH \rightarrow ArCO_2^- + EtOH$	2.61
$ArCH_2CO_2Et + {}^-OH \rightarrow ArCH_2CO_2^- + EtOH$	1.00
$ArCH_2Cl + H_2O \rightarrow ArCH_2OH + HCl$	−1.31
$ArC(Me)_2Cl + H_2O \rightarrow ArC(Me)_2OH + HCl$	−4.48
$ArNH_2 + PhCOCl \rightarrow ArNHCOPh + HCl$	−3.21

a. From P. R. Wells, *Linear Free Energy Relationships*, Academic Press, New York, 1968, pp. 12, 13.

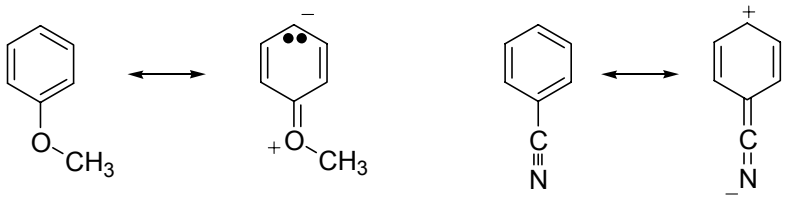
5. Meaning of ρ: The value of | ρ | is a measure of how sensitive the reaction is towards the nature of nearby substituents. E.g. in S_N1 reaction, | ρ | is related to the amount of δ+ in the TS, which is larger for a late TS.

ρ is positive, if substituents stabilize/destabilize a negative or partial negative charge.

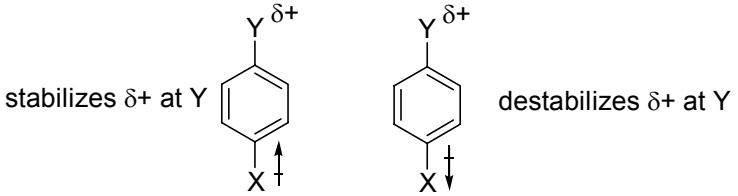
ρ is negative, if substituents stabilize/destabilize a positive or partial positive charge.

6. σ values are typically listed for *meta* and *para* substituents (σ_m, σ_p; see Table next page)
There are no σ values for *ortho* substituents, because the different steric interactions of an ortho substituent with the reaction center would prevent good Hammett relationships.

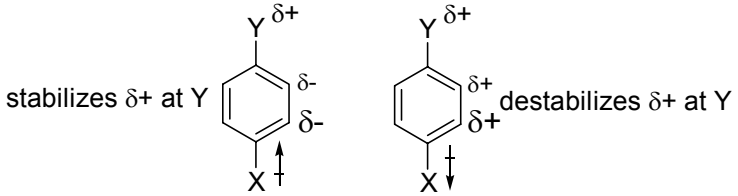
7. Different electronic effects contribution to the σ values:
Resonance Effects:



Field Effects: the dipole of the C-X bond will have an effect on a δ^+ elsewhere in the molecule. This effect is transmitted through space.



Inductive Effects: the dipole of the C-X bond is transmitted through polarization of the intervening sigma bonds.



8. Table of σ values for common organic substituents

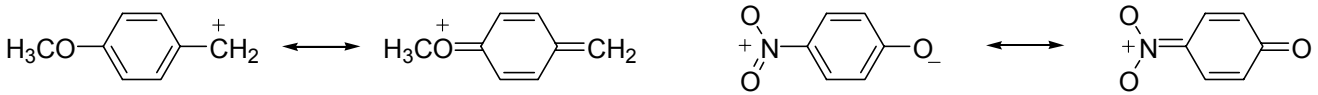
Table 4.5. Substituent Constants[a]

Substituent group		σ_m	σ_P	σ^+	σ^-	σ_I	σ_R^0
Acetamido	CH_3CONH	**0.14**	**0.0**	−0.6	0.47		
Acetoxy	CH_3CO_2	0.39	0.31	0.18			
Acetyl	CH_3CO	0.36	**0.47**		0.82	0.20	0.16
Amino	NH_2	**−0.09**	**−0.30**	−1.3		0.12	−0.50
Bromo	Br	0.37	**0.26**	0.15		0.44	−0.16
t-Butyl	$(CH_3)_3C$	**−0.09**	**−0.15**	−0.26			
Carbomethoxy	CH_3O_2C	0.35	**0.44**		0.74	0.20	0.16
Carboxy	HO_2C	**0.35**	**0.44**		0.73		
Chloro	Cl	**0.37**	**0.24**	0.11		0.46	−0.18
Cyano	CN	**0.62**	**0.70**		0.99	0.56	0.08
Ethoxy	C_2H_5O	0.1	−0.14	−0.82			
Ethyl	C_2H_5	**−0.08**	**−0.13**	−0.30			
Fluoro	F	**0.34**	**0.15**	−0.07		0.50	−0.31
Hydrogen	H	**0**	**0**	0	0	0	0
Hydroxy	OH	0.13	−0.38	−0.92			
Methanesulfonyl	CH_3SO_2	**0.64**	**0.73**		1.05	0.60	0.12
Methoxy	CH_3O	**0.10**	−0.12	−0.78		0.27	−0.42
Methyl	CH_3	**−0.06**	**−0.14**	−0.31		−0.04	−0.13
Nitro	NO_2	**0.71**	0.81		1.23	0.65	0.15
Phenyl	C_6H_5	**0.05**	**0.05**	−0.18	0.08		
Trifluoromethyl	CF_3	**0.46**	**0.53**		0.74	0.42	0.08
Trimethylammonio	$(CH_3)_3N^+$	0.99	0.96				
Trimethylsilyl	$(CH_3)_3Si$	−0.04	−0.07				

a. Values of σ_m, σ_p, σ^+, and σ^- from O. Exner, in *Correlation Analysis in Chemistry*, N. B. Chapman and J. Shorter, eds., Plenum Press, New York, 1978, Chapter 10. Values of σ_I and σ_R^0 from J. Bromilow, R. T. C. Brownlee, V. O. Lopez, and R. W. Taft, *J. Org. Chem.* **44**:4766 (1979). Values of σ_m and σ_p shown in boldface type are regarded as particularly reliable.

9. The *dual-substituent-parameter equation* (6), tries to separate resonance and inductive effects. σ_R and σ_I are the reaction constants, which refect the sensitivity of the system towards resonance and inductive effects.
The sum of σ_R and σ_I is approximately σ_p: $\sigma_p = \sigma_R + \sigma_I$

If there is direct resonance between the substituent and a cationic or anionic reaction center, the resonance component strongly increases and σ_p and σ_m fails to correlate the reaction series. In this case σ_+ and σ_- are used, which take into account the enhanced resonance component in these systems.
E.g.:



10. Application of Hammett Equation:

1. Calculate how much faster *p*-bromobenzyl chloride will solvolyze in water than will *p*-nitrobenzyl chloride.

Answer: $k_{Br}/k_{NO2} = 5.25$.

2. The r value for alkaline hydrolysis of substituted methyl benzoates is 2.38. The rate for saponification of methyl benzoate is 2×10^{-4} $M^{-1}s^{-1}$. Calculate the rate constant for methyl *m*-nitrobenzoate

Answer: 98×10^{-4} $M^{-1}s^{-1}$

3. The pKa of *p*-chlorobenzoic acid is 3.98, that of benzoic acid is 4.19. Calculate σ for *p*-Cl

Answer: 0.21