

# Medicinal Chemistry

## Chem 317

### Linear Free Energy Relationships The Hammett and Taft Equations

#### Correlation of Acidity of substituted benzoic and phenylacetic acids

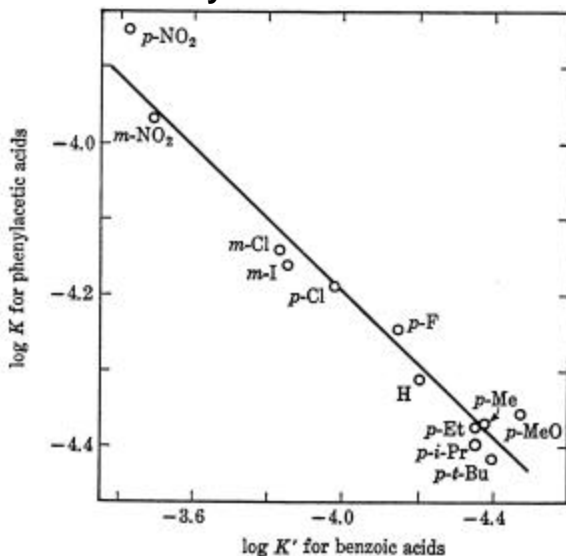


FIG. 4-1. Log-log plot of ionization constants of benzoic and phenylacetic acids in water at 25°.

#### The Hammett Equation

$$\text{Log} \left( \frac{k}{k_0} \right) = \rho r$$

$k$  and  $k_0$  are rate or equilibrium constants for a given transformation.

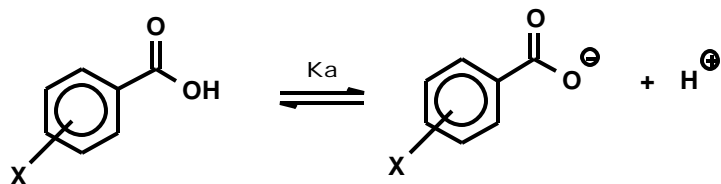
Where:

$k$  = value for substituted benzene derivative

$k_0$  = value for unsubstituted compound (substituent = H)

$\sigma$  = the substituent constant ( independent of reaction)

$\sigma$  is defined from the ionization constants of benzoic acids and by definition  $\sigma$  for H = 0



$\sigma$  is positive for electron withdrawing substituents

$\sigma$  is negative for electron donating substituents

$\rho$  = the reaction constant

If  $\rho$  is negative the transformation is facilitated by electron donating substituents

If  $\rho$  is positive, the transformation is facilitated by electron withdrawing substituents

Tables of Hammett  $\sigma$  valuesTable 2.2  $\sigma$  VALUES OF COMMON SUBSTITUENTS

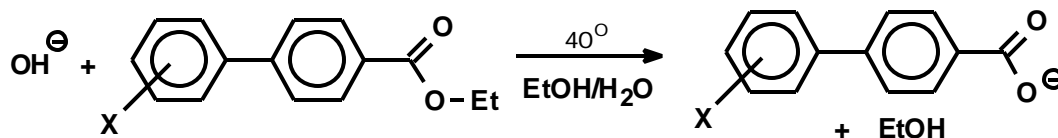
Substituent	$\sigma_{\text{meta}}^{a,c}$	$\sigma_{\text{para}}^{a,c}$
NH <sub>2</sub>	-0.16	-0.66
CH <sub>3</sub>	-0.07	-0.17
C <sub>6</sub> H <sub>5</sub>	0.06	-0.01
OH	0.12	-0.37
OCH <sub>3</sub>	0.12	-0.27
F	0.34	0.06
I	0.35	0.18
CO <sub>2</sub> H	0.37	0.45
Cl	0.37	0.23
COCH <sub>3</sub>	0.38	0.50
Br	0.39	0.23
CO <sub>2</sub> R	0.37	0.45
CF <sub>3</sub>	0.43	0.54
CN	0.56	0.66
NO <sub>2</sub>	0.71	0.78

TABLE 4-1. HAMMETT SUBSTITUENT CONSTANTS<sup>a</sup>

Substituent	$\sigma$		Substituent	$\sigma$	
	Meta	Para		Meta	Para
CH <sub>3</sub>	-0.069	-0.170	O <sup>-f</sup>	-0.708 <sup>c,e</sup>	-1.00 <sup>b,k</sup>
CH <sub>2</sub> CH <sub>3</sub>	-0.07	-0.151	OH	+0.121	-0.37
CH(CH <sub>3</sub> ) <sub>2</sub>	-0.068 <sup>b,c</sup>	-0.151	OCH <sub>3</sub>	+0.115	-0.268
C(CH <sub>3</sub> ) <sub>3</sub>	-0.10	-0.197	OC <sub>2</sub> H <sub>5</sub>	+0.1	-0.24
C <sub>6</sub> H <sub>5</sub>	+0.06	-0.01	OC <sub>4</sub> H <sub>9</sub>	+0.252	-0.320
C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> - <i>p</i>	.....	+0.26 <sup>d</sup>	OCOCH <sub>3</sub>	+0.39	+0.31
C <sub>6</sub> H <sub>4</sub> OCH <sub>3</sub> - <i>p</i>	.....	-0.10 <sup>d</sup>	F	+0.337	+0.062
CH <sub>2</sub> Si(CH <sub>3</sub> ) <sub>2</sub>	-0.16	-0.21	Si(CH <sub>3</sub> ) <sub>3</sub>	-0.04	-0.07
COCH <sub>3</sub>	+0.376	+0.502	PO <sub>3</sub> H <sup>-f</sup>	+0.2	+0.26
COC <sub>6</sub> H <sub>5</sub>	.....	+0.459 <sup>c,d</sup>	SH	+0.25	+0.15
CN	+0.56	+0.660	SCH <sub>3</sub>	+0.15	0.00
CO <sub>2</sub> <sup>-f</sup>	-0.1	0.0	SCOCH <sub>3</sub>	+0.39	+0.44
CO <sub>2</sub> H	+0.35 <sup>b,c</sup>	+0.406 <sup>b,c</sup>	SOCH <sub>3</sub>	+0.52	+0.49
CO <sub>2</sub> CH <sub>3</sub>	+0.321 <sup>b,c</sup>	+0.385 <sup>b,c</sup>	SO <sub>2</sub> CH <sub>3</sub>	+0.60	+0.72
CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	+0.37	+0.45	SO <sub>2</sub> NH <sub>2</sub>	+0.46	+0.57
CF <sub>3</sub>	+0.43	+0.54	SO <sub>3</sub> <sup>-f</sup>	+0.05	+0.09
NH <sub>2</sub>	-0.16	-0.66	S(CH <sub>3</sub> ) <sub>2</sub> <sup>+f</sup>	+1.00	+0.90
N(CH <sub>3</sub> ) <sub>2</sub>	-0.211 <sup>c,e</sup>	-0.83	Cl	+0.373	+0.227
NHCOCH <sub>3</sub>	+0.21	0.00	Br	+0.391	+0.232
N(CH <sub>3</sub> ) <sub>3</sub> <sup>+f</sup>	+0.88	+0.82	I	+0.352	+0.276 <sup>c,d</sup>
N <sub>3</sub> <sup>+f</sup>	+1.76 <sup>e</sup>	+1.91 <sup>e</sup>	IO <sub>2</sub>	+0.70	+0.76
NO <sub>2</sub>	+0.710	+0.778			

### A typical Hammett Plot

For the reaction:



$$\rho = +0.53$$

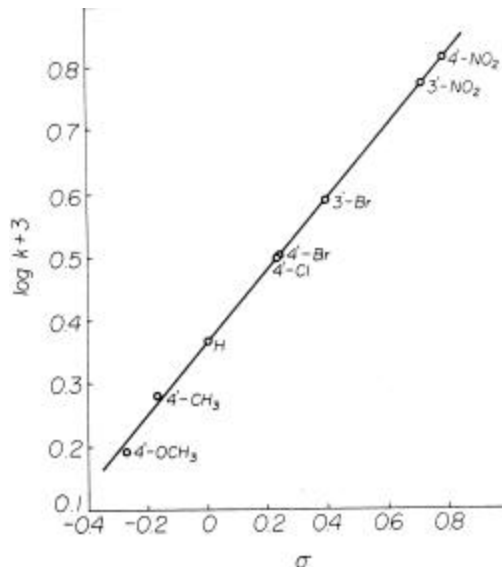


TABLE 7-2. Hammett  $\rho$  Values for Some Rate Processes<sup>a</sup>

No.	Reaction	Solvent	t/°C	$\rho$
1	ArCOOH + CH <sub>3</sub> OH + H <sup>+</sup> → ArCOOCH <sub>3</sub>	CH <sub>3</sub> OH	25	-0.229
2	ArCOOH + HN <sub>3</sub> → ArNH <sub>2</sub> + CO <sub>2</sub>	CHCl=CHCl	40	-1.415
3	ArCOOCH <sub>3</sub> + OH <sup>-</sup> → ArCOO <sup>-</sup>	60% Me <sub>2</sub> CO	25	2.229
4	ArCOOC <sub>2</sub> H <sub>5</sub> + OH <sup>-</sup> → ArCOO <sup>-</sup>	60% Me <sub>2</sub> CO	25	2.265
5	ArCOOC <sub>2</sub> H <sub>5</sub> + H <sup>+</sup> → ArCOOH	60% Me <sub>2</sub> CO	100	0.106
6	<i>p</i> -ArC <sub>6</sub> H <sub>4</sub> COOC <sub>2</sub> H <sub>5</sub> + OH <sup>-</sup> → <i>p</i> -ArC <sub>6</sub> H <sub>4</sub> COO <sup>-</sup>	88% C <sub>2</sub> H <sub>5</sub> OH	40	0.583
7	ArCH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub> + OH <sup>-</sup> → ArCH <sub>2</sub> COO <sup>-</sup>	87.83% C <sub>2</sub> H <sub>5</sub> OH	30	0.824
8	ArCH <sub>2</sub> CH <sub>2</sub> COOC <sub>2</sub> H <sub>5</sub> + OH <sup>-</sup> → ArCH <sub>2</sub> CH <sub>2</sub> COO <sup>-</sup>	87.83% C <sub>2</sub> H <sub>5</sub> OH	30	0.489
9	ArCH=CHCOOC <sub>2</sub> H <sub>5</sub> + OH <sup>-</sup> → ArCH=CHCOO <sup>-</sup>	87.83% C <sub>2</sub> H <sub>5</sub> OH	30	1.329
10	ArCOCl + H <sub>2</sub> O → ArCOOH	95% Me <sub>2</sub> CO	25	1.782
11	ArCONH <sub>2</sub> + OH <sup>-</sup> → ArCOO <sup>-</sup>	60% C <sub>2</sub> H <sub>5</sub> OH	100.1	1.100
12	ArCONH <sub>2</sub> + H <sup>+</sup> → ArCOOH	60% C <sub>2</sub> H <sub>5</sub> OH	99.6	-0.222
13	(ArCO) <sub>2</sub> O + H <sub>2</sub> O → ArCOOH	75% dioxane	58.25	1.568
14a	ArOCOC <sub>6</sub> H <sub>5</sub> + OH <sup>-</sup> → ArOH	60% Me <sub>2</sub> CO	-20	1.051
14b	ArOCOC <sub>6</sub> H <sub>5</sub> + OH <sup>-</sup> → ArOH	60% Me <sub>2</sub> CO	-10	1.034
14c	ArOCOC <sub>6</sub> H <sub>5</sub> + OH <sup>-</sup> → ArOH	60% Me <sub>2</sub> CO	0	0.976
14d	ArOCOC <sub>6</sub> H <sub>5</sub> + OH <sup>-</sup> → ArOH	60% Me <sub>2</sub> CO	15	0.930
15	ArNH <sub>2</sub> + C <sub>6</sub> H <sub>5</sub> COCl → ArNHCOC <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>6</sub>	25	-2.781

## The Taft Equation (Aliphatic systems)

$$\text{Log} \left( \frac{k}{k_0} \right) = \rho^* r$$

$\rho^*$  based on the ionization constants of substituted acetic acids. By definition  $\rho = 0$  for  $\text{CH}_3$

TABLE 4-3. TAFT POLAR SUBSTITUENT CONSTANTS<sup>5</sup>

Substituent	$\rho^*$	Substituent	$\rho^*$
$\text{Cl}_3\text{C}$	+2.65	$\text{C}_6\text{H}_5\text{CH}=\text{CH}$	+0.41
$\text{F}_2\text{CH}$	+2.05	$(\text{C}_6\text{H}_5)_2\text{CH}$	+0.40
$\text{CH}_3\text{OCO}$	+2.00	$\text{ClCH}_2\text{CH}_2$	+0.38
$\text{Cl}_2\text{CH}$	+1.94	$\text{CH}_3\text{CH}=\text{CH}$	+0.36
$\text{CH}_3\text{CO}$	+1.65	$\text{F}_3\text{CCH}_2\text{CH}_2$	+0.32
$\text{C}_6\text{H}_5\text{C}\equiv\text{C}$	+1.35	$\text{C}_6\text{H}_5\text{CH}_2$	+0.22
$\text{CH}_3\text{SO}_2\text{CH}_2$	+1.32	$\text{CH}_3\text{CH}=\text{CHCH}_2$	+0.13
$\text{NCCH}_2$	+1.30	$\text{F}_3\text{C}(\text{CH}_2)_3$	+0.12
$\text{FCH}_2$	+1.10	$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2$	+0.08
$\text{ClCH}_2$	+1.05	$\text{CH}_3$	0.000
$\text{BrCH}_2$	+1.00	$\text{C}_2\text{H}_5$	-0.10
$\text{F}_3\text{CCH}_2$	+0.92	<i>n</i> - $\text{C}_3\text{H}_7$	-0.12
$\text{ICH}_2$	+0.85	<i>n</i> - $\text{C}_4\text{H}_9$	-0.13
$\text{C}_6\text{H}_5\text{OCH}_2$	+0.85	Cyclohexyl	-0.15
$\text{CH}_2\text{OCH}_2$	+0.64 <sup>a</sup>	$(\text{CH}_3)_3\text{CCH}_2$	-0.16
$\text{CH}_3\text{COCH}_2$	+0.60	$(\text{CH}_3)_2\text{CH}$	-0.19
$\text{C}_6\text{H}_5$	+0.60	Cyclopentyl	-0.20
$\text{HOCH}_2$	+0.56	$(\text{C}_2\text{H}_5)_2\text{CH}$	-0.22
$\text{O}_2\text{NCH}_2\text{CH}_2$	+0.50	$(\text{CH}_3)_3\text{SiCH}_2$	-0.26
$\text{H}$	+0.49	$(\text{CH}_3)_3\text{C}$	-0.30

P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **82**, 795 (1960).