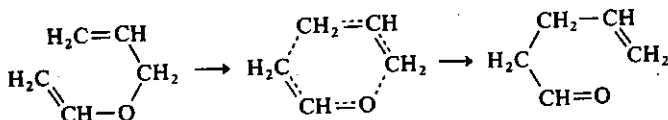


Unimolecular reactions that take place by way of cyclic transition states typically have negative entropies of activation because of the loss of rotational degrees of freedom associated with the highly ordered transition state. For example, thermal isomerization of allyl vinyl ether to 4-pentenal has $\Delta S^\ddagger = -8$ eu.¹⁴



It is important to remember that the enthalpy and entropy of activation reflect the response of the reacting system *as a whole* to formation of the activated complex. As a result, the interpretation of these parameters is more complicated for reactions taking place in solution than for gas phase reactions. This complexity is particularly true for processes involving formation or destruction of charged species. The solvolysis of *t*-butyl chloride in 80% aqueous ethanol, for example, has as its rate-determining step unimolecular ionization of the carbon-chlorine bond to form chloride ion and the *t*-butyl cation. One might guess that this ionization should lead to a positive entropy of activation, since two particles are being generated. In fact, the entropy of activation is -6.6 eu. Because of its polar character, the transition state requires a greater ordering of solvent molecules than the nonpolar reactant.¹⁵ It turns out to be generally true that reactions which generate charged species exhibit negative entropies of activation in solution. The reverse is true for reactions in which charged reactants lead to a neutral transition state.

4.3. Substituent Effects and Linear Free-Energy Relationships

In Chapter 1, Section 1.2 (p. 16), the effect of substituent groups on the acid strength of acetic acid derivatives was discussed qualitatively. It was noted in particular that the presence of groups more electronegative than hydrogen increased the acid strength relative to acetic acid. A number of important relationships between substituent groups and chemical properties have been developed. In many cases, such relationships can be expressed quantitatively and are useful both for interpretation of reaction mechanisms and for prediction of reaction rates and equilibria.

The most widely applied of these relationships is the *Hammett equation*, which relates rates and equilibria for many reactions of compounds containing substituted phenyl groups. It was noted in the 1930s that there is a relationship between the acid strengths of substituted benzoic acids and the rates of many other chemical reactions, for instance, the rates of hydrolysis of substituted ethyl benzoates. The correlation is illustrated graphically in Fig. 4.2, which shows $\log k/k_0$, where k_0 is the rate constant for hydrolysis of ethyl benzoate and k is the rate constant for the

14. F. W. Schuler and G. W. Murphy, *J. Am. Chem. Soc.* **72**, 3155 (1950).
15. E. Grunwald and S. Winstein, *J. Am. Chem. Soc.* **70**, 846 (1948).

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substituted esters, plotted against $\log K/K_0$, where K and K_0 are the corresponding acid dissociation constants. Analogous plots for many other reactions of aromatic compounds show a similar linear correlation with the acid dissociation constants of the corresponding benzoic acids. Neither the principles of thermodynamics nor theories of reaction rates predict or require that there should be such linear relationships. There are, in fact, numerous reaction series that fail to show such correlations. Some insight into the origin of the correlation can be gained by considering the relationship between the correlation equation and the free-energy changes involved in the two processes. The line in Fig. 4.2 defines the following equation, in which m is the slope of the line:

$$m \log \frac{K}{K_0} = \log \frac{k}{k_0} \tag{4.12}$$

Substituting for K and k with the appropriate free energy or free energy of activation:

$$\begin{aligned} m(\log K - \log K_0) &= \log k - \log k_0 \\ m(-\Delta G/2.3RT + \Delta G_0/2.3RT) &= -\Delta G^*/2.3RT + \Delta G_0^*/2.3RT \\ m(-\Delta G + \Delta G_0) &= -\Delta G^* + \Delta G_0^* \\ m\Delta\Delta G &= \Delta\Delta G^* \end{aligned} \tag{4.13}$$

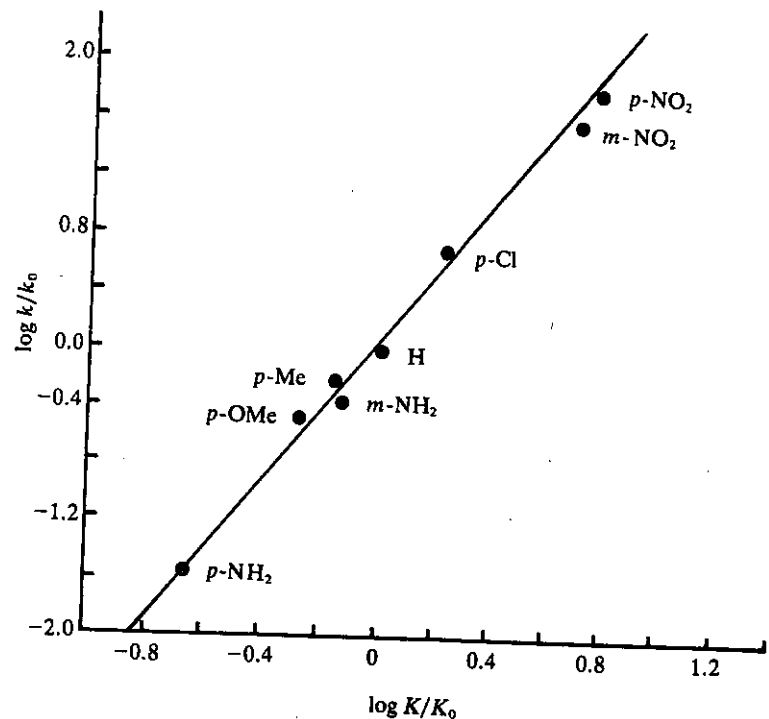
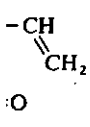


Fig. 4.2. Correlation of acid dissociation constants of benzoic acids with rates of alkaline hydrolysis of ethyl benzoates. [From L. P. Hammett, *J. Am. Chem. Soc.* 59, 96 (1937).]

sition states typically rotational degrees of freedom or example, thermal energy.¹⁴



of activation reflect the activated complex. It is indicated for reactions where the reactivity is particularly high for substituted species. The example, has as its characteristic bond to form the transition state should lead to a lower energy state. In fact, the transition state is more polar than the reactant.¹⁵ Substituted species exhibit reactions in which

groups on the acid. It was noted in many cases, that there are relationships between the rates of hydrolysis and equilibria. The Hammett equation, which relates the rate of hydrolysis to the Hammett constant of the substituent, is $\log k/k_0 = \rho \sigma$, where k_0 is the rate constant for the

The linear correlation therefore indicates that the change in the free energy of activation for hydrolysis of ethyl benzoate on introduction of a series of substituent groups is *directly proportional* to the change in the free energy of ionization that is caused by the same series of substituents on benzoic acid. The various correlations arising from such directly proportional changes in free energies are called *linear free-energy relationships*.

Since ΔG and ΔG^\ddagger are combinations of enthalpy and entropy terms, a linear free-energy relationship between two reaction series can result from one of three circumstances: (1) ΔH is constant and the ΔS terms are proportional for the two series, (2) ΔS is constant and the ΔH terms are proportional, or (3) ΔH and ΔS are linearly related. Dissection of the free-energy changes into enthalpy and entropy components has often shown the third case to be true.¹⁶

The Hammett free-energy relationship is expressed in the following equations for equilibria and for rate data, respectively:

$$\log \frac{K}{K_0} = \sigma\rho \quad (4.14)$$

$$\log \frac{k}{k_0} = \sigma\rho \quad (4.15)$$

The numerical values of the terms σ and ρ are defined by selection of the reference reaction, the ionization of benzoic acids. This reaction is arbitrarily assigned a value of the *reaction constant*, ρ , of 1. The *substituent constant*, σ , can then be determined for a series of substituent groups by measurement of the acid dissociation constant of the substituted benzoic acids. The σ values so defined are used in the correlation of other reaction series, and the ρ values of the reactions are thus determined.

The relationship between Eqs. (4.12) and (4.14) is evident when the Hammett equation is expressed in terms of free energy. For the standard reaction, $\log [K/K_0] = \sigma\rho$:

$$-\Delta G/2.3RT + \Delta G_0/2.3RT = \sigma\rho = \sigma$$

since $\rho = 1$ for the standard reaction. Substituting into Eq. (4.12):

$$m\sigma = -\Delta G^\ddagger/2.3RT + \Delta G_0^\ddagger/2.3RT$$

$$m\sigma = \log k - \log k_0$$

(4.16)

$$m\sigma = \log \frac{k}{k_0}$$

$$m = \rho$$

The value of σ reflects the effect the substituent group has on the free energy of ionization of the substituted benzoic acid. The effect of the substituent is believed to represent a combination of factors. A substituent group can cause a polarization

16. P. D. Bolton, K. A. Fleming, and F. M. Hall, *J. Am. Chem. Soc.* **94**, 1033 (1972); J. E. Leffler, *J. Org. Chem.* **20**, 1202 (1955).

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of charge density around the ring through the π system in both the reactant and the product. This will affect the position of the equilibrium. In the case of a reaction rate, the relative effects on the reactant and the transition state will determine the effect on the energy of activation. One mechanism for polarization and charge redistribution is the *resonance effect*, which is illustrated in Fig. 4.3a for several substituents. There is also an effect that originates with the bond dipoles between groups of differing electronegativity. Substituents with electronegativity greater than an aromatic carbon will place a net positive charge on the substituted carbon atom, whereas atoms less electronegative than an aromatic carbon will have the opposite effect. The resulting dipoles can perturb the electronic situation at the reaction site in two ways. The presence of the charge separation will influence the energy associated with development of charge elsewhere in the molecule. This is the result of through-space electrostatic interaction and is called a *field effect*. Depending on

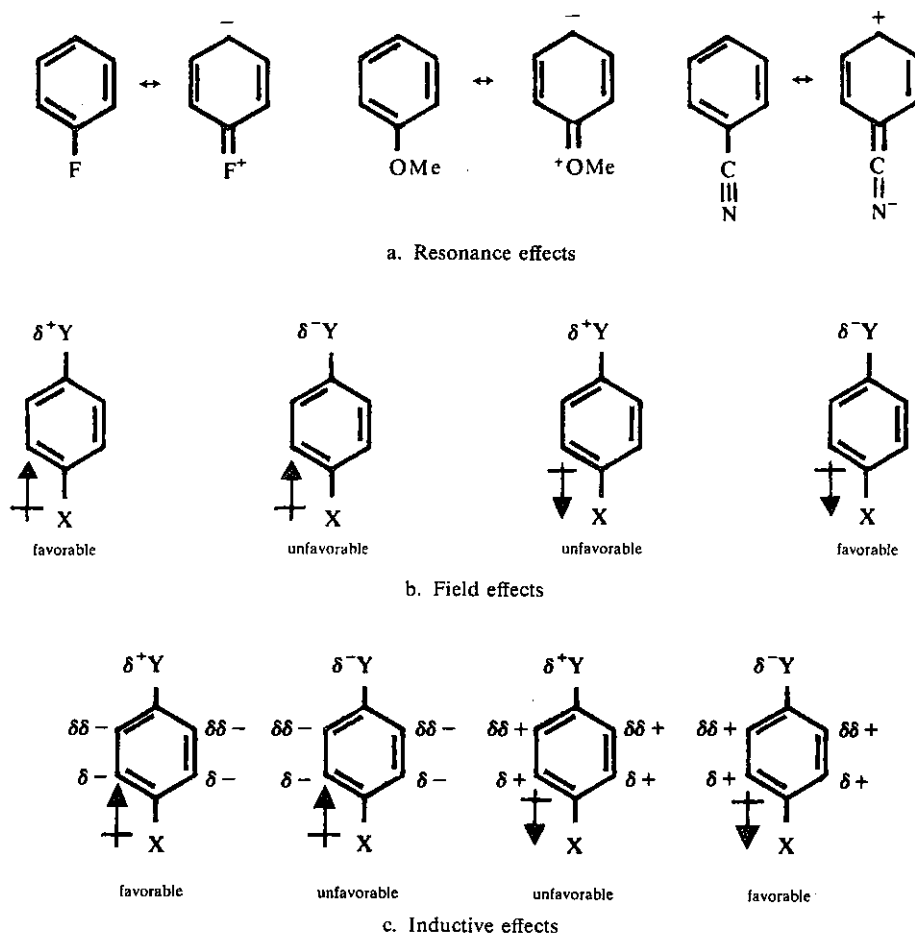


Fig. 4.3. Resonance, field, and inductive components of substituent effects in substituted benzenes.

the orientation of the dipole and of the charge developing at the reaction site, a substituent can either favor or disfavor the reaction, as illustrated in Fig. 4.3b. Another possible means of interaction of a substituent and the reaction site is called the *inductive effect*. This is transmission of bond dipoles through the intervening bonds by successive polarization of each bond. The experimental and theoretical results presently available indicate that the field effect outweighs the inductive effect as the primary means of transmission of the effect of bond dipoles.¹⁷

The Hammett equation in the form Eq. (4.14) or Eq. (4.15) is free of complications due to steric effects, since it is applied only to *meta* and *para* substituents. The geometry of the benzene ring ensures that groups in these positions cannot interact sterically with the site of reaction. Tables of σ values for many substituents have been collected; some values are shown in Table 4.3. The σ value for any substituent reflects the interaction of the substituent with the reacting site by a combination of resonance and field interactions. Table 4.4 shows a number of ρ values. The ρ value reflects the sensitivity of the particular reaction to substituent effects. The examples that follow illustrate some of the ways in which the Hammett equation can be used.

Example 4.2. The pK_a of *p*-chlorobenzoic acid is 3.98; that of benzoic acid is 4.19. Calculate σ for *p*-Cl.

$$\begin{aligned}\sigma &= \log \frac{K_{p\text{-Cl}}}{K_H} = \log K_{p\text{-Cl}} - \log K_H \\ &= -\log K_H - (-\log K_{p\text{-Cl}}) \\ &= pK_{aH} - pK_{a_{p\text{-Cl}}} \\ &= 4.19 - 3.98 = 0.21\end{aligned}$$

Example 4.3. If the ρ value for alkaline saponification of methyl esters of substituted benzoic acids is 2.38, and the rate constant for saponification of methyl benzoate under the conditions of interest is $2 \times 10^{-4} M^{-1} s^{-1}$, calculate the rate constant for hydrolysis of methyl *m*-nitrobenzoate.

$$\begin{aligned}\log \frac{k_{m\text{-NO}_2}}{k_H} &= \sigma_{m\text{-NO}_2}(\rho) = (0.70)(2.38) = 1.69 \\ \frac{k_{m\text{-NO}_2}}{k_H} &= 49 \\ k_{m\text{-NO}_2} &= 98 \times 10^{-4} M^{-1} s^{-1}\end{aligned}$$

17. M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.* **84**, 3548 (1962); M. J. S. Dewar and A. P. Marchand, *J. Am. Chem. Soc.* **88**, 354 (1966); H. D. Holtz and L. M. Stock, *J. Am. Chem. Soc.* **86**, 5188 (1964); C. L. Liotta, W. F. Fisher, G. H. Greene, Jr., and B. L. Joyner, *J. Am. Chem. Soc.* **94**, 4891 (1972); C. F. Wilcox and C. Leung, *J. Am. Chem. Soc.* **90**, 336 (1968); W. F. Reynolds, *Prog. Phys. Org. Chem.* **14**, 165 (1983).

Table 4.3. Substituent Constants^a

Substituent group	σ_m	σ_p	σ^+	σ^-	\mathcal{R}	σ_I	σ_R^0
Acetamido	0.14	0.0	-0.6	0.47	-0.27		
Acetoxy	0.39	0.31	0.18		0.68		0.16
Acetyl	0.36	0.47		0.82	0.53	0.20	-0.50
Amino	-0.09	-0.30	-1.3		0.04	0.44	-0.16
Bromo	0.37	0.26	0.15		0.72		
<i>t</i> -Butyl	-0.09	-0.15	-0.26		-0.10		
Carbomethoxy	0.35	0.44		0.74		0.20	0.16
Carboxy	0.35	0.44		0.73			
Chloro	0.37	0.24	0.11		0.55	0.46	-0.18
Cyano	0.62	0.70		0.99	0.69	0.56	0.08
Ethoxy	0.1	-0.14	-0.82		0.85		
Ethyl	-0.08	-0.13	-0.30		0.36		
Fluoro	0.34	0.15	-0.07		-0.07	0.50	-0.31
Hydrogen	0	0	0	0	0	0	0
Hydroxy	0.13	-0.38	-0.92		0.49		
Methanesulfonyl	0.64	0.73		1.05	0.90	0.60	0.12
Methoxy	0.10	-0.12	-0.78		0.41	0.27	-0.42
Methyl	-0.06	-0.14	-0.31		-0.05	-0.04	-0.13
Nitro	0.71	0.81		1.23	1.11	0.65	0.15
Phenyl	0.05	0.05	-0.18		0.14		
Trifluoromethyl	0.46	0.53		0.08	0.63	0.42	0.08
Trimethylammonio	0.99	0.96		0.74	1.46		
Trimethylsilyl	-0.04	-0.07			-0.05		

a. Values of σ_m , σ_p , σ^+ , and σ^- from O. Exner in *Correlation Analysis in Chemistry*, N. B. Chapman and I. Shorter (eds.), Plenum Press, New York, 1978, Chap. 10. \mathcal{R} and σ_I from C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.* **90**, 4328 (1968). 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.

Example 4.4. Using data in Tables 4.3 and 4.4, calculate how much faster *p*-bromobenzyl chloride will solvolyze in water than *p*-nitrobenzyl chloride.

$$\log \frac{k_{p\text{-Br}}}{k_{\text{H}}} = (-1.31)(0.26), \quad \log \frac{k_{p\text{-NO}_2}}{k_{\text{H}}} = (-1.31)(0.81)$$

$$\log k_{\text{Br}} - \log k_{\text{H}} = -0.34, \quad \log k_{\text{NO}_2} - \log k_{\text{H}} = -1.06$$

$$\log k_{\text{Br}} + 0.34 = \log k_{\text{H}}, \quad \log k_{\text{NO}_2} + 1.06 = \log k_{\text{H}}$$

$$\log k_{\text{Br}} + 0.34 = \log k_{\text{NO}_2} + 1.06$$

$$\log k_{\text{Br}} - \log k_{\text{NO}_2} = 0.72$$

$$\log \frac{k_{\text{Br}}}{k_{\text{NO}_2}} = 0.72$$

$$\frac{k_{\text{Br}}}{k_{\text{NO}_2}} = 5.25$$

Given in Table 4.3 in addition to the σ_m and σ_p values used with the classical Hammett equation are σ^+ and σ^- . These are substituent constant sets which reflect a recognition that the extent of resonance participation can vary for different reactions. The σ^+ values are used for reactions in which there is direct resonance interaction between an electron donor substituent and a cationic reaction center, whereas the σ^- set pertains to reactions in which there is a direct resonance interaction between the substituent and an electron-rich reaction site. These are cases where the resonance component of the substituent effect will be particularly important.

Table 4.4. Reaction Constants^a

Reaction	ρ
$\text{ArCO}_2\text{H} \rightleftharpoons \text{ArCO}_2^- + \text{H}^+$, water	1.00
$\text{ArCO}_2\text{H} \rightleftharpoons \text{ArCO}_2^- + \text{H}^+$, EtOH	1.57
$\text{ArCH}_2\text{CO}_2\text{H} \rightleftharpoons \text{ArCH}_2\text{CO}_2^- + \text{H}^+$, water	0.56
$\text{ArCH}_2\text{CH}_2\text{CO}_2\text{H} \rightleftharpoons \text{ArCH}_2\text{CH}_2\text{CO}_2^- + \text{H}^+$, water	0.24
$\text{ArOH} \rightleftharpoons \text{ArO}^- + \text{H}^+$, water	2.26
$\text{ArNH}_3^+ \rightleftharpoons \text{ArNH}_2 + \text{H}^+$, water	3.19
$\text{ArCH}_2\text{NH}_3^+ \rightleftharpoons \text{ArCH}_2\text{NH}_2 + \text{H}^+$, water	1.05
$\text{ArCO}_2\text{Et} + ^-\text{OH} \rightarrow \text{ArCO}_2^- + \text{EtOH}$	2.61
$\text{ArCH}_2\text{CO}_2\text{Et} + ^-\text{OH} \rightarrow \text{ArCH}_2\text{CO}_2^- + \text{EtOH}$	1.00
$\text{ArCH}_2\text{Cl} + \text{H}_2\text{O} \rightarrow \text{ArCH}_2\text{OH} + \text{HCl}$	-1.31
$\text{ArC}(\text{Me})_2\text{Cl} + \text{H}_2\text{O} \rightarrow \text{ArC}(\text{Me})_2\text{OH} + \text{HCl}$	-4.48
$\text{ArNH}_2 + \text{PhCOCl} \rightarrow \text{ArNHCOPh} + \text{HCl}$	-3.21

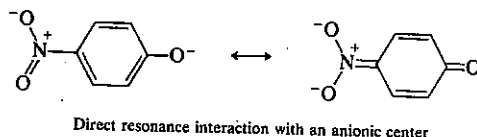
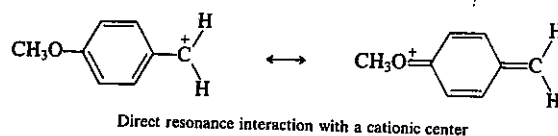
a. From P. R. Wells, *Linear Free Energy Relationships*, Academic Press, New York, 1968, pp. 12, 13.

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The underlying physical basis for the failure of Hammett σ_m and σ_p values to correlate certain reaction series is that all substituent interactions are some mixture of resonance and field effects. When direct resonance interaction is possible, the extent of the resonance increases and the substituent constants appropriate to a more "normal" mix of resonance and field effects then fail. There have been many attempts to develop sets of σ values that take into account extra resonance interactions.

One approach is to correct for the added resonance interaction. This is done in a modification of the Hammett equation known as the Yukawa-Tsuno equation¹⁸:

$$\log \frac{K}{K_0} = \rho\sigma + \rho(r)(\sigma^+ - \sigma) \quad (4.17)$$

The additional parameter r is adjusted from reaction to reaction; it reflects the extent of the additional resonance contribution. A large r corresponds to a reaction with a large resonance component, whereas when r goes to zero, the equation is identical to the original Hammett equation. When there is direct conjugation with an electron-rich reaction center, an equation analogous to Eq. (4.17) can be employed, but σ^- is used instead of σ^+ .

The Yukawa-Tsuno relationship expanded to include both the σ^+ and σ^- constants is called the LArSR equation¹⁹:

$$\log \frac{k}{k_0} = \rho(\sigma^0 + r^+\Delta\sigma_R^+ + r^-\Delta\sigma_R^-)$$

In this equation, the substituent parameters $\Delta\sigma_R^+$ and $\Delta\sigma_R^-$ reflect the incremental resonance interaction with electron-demanding and electron-releasing reaction centers, respectively. The variables r^+ and r^- are established for a reaction series by regression analysis and are measures of the extent of the extra resonance contribution: the larger their value, the greater the extra resonance contribution. Since both donor and acceptor capacity will not contribute in a single reaction process, either r^+ or r^- would be expected to be zero.

18. Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Jpn.* **32**, 971 (1959); J. Hine, *J. Am. Chem. Soc.* **82**, 4877 (1960); B. M. Wepster, *J. Am. Chem. Soc.* **95**, 102 (1973).
19. Y. Yukawa, Y. Tsuno, and M. Sawada, *Bull. Chem. Soc. Jpn.* **39**, 2274 (1966); Y. Yukawa, Y. Tsuno, and M. Sawada, *Bull. Chem. Soc. Jpn.* **45**, 1210 (1972).

Another approach to the treatment of the variability of resonance and field effects was devised by Swain and Lupton.²⁰ Their approach is to partition substituent effects into pure resonance and field contributions. The substituent constant would then be expressed as a sum of the field and resonance contributions.

$$\sigma = f\mathcal{F} + r\mathcal{R}$$

This treatment requires that *meta*- and *para*-substituted compounds be treated as separate reaction series, since they will have different relative resonance and field components, with resonance being stronger in the *para* series. Since the Swain-Lupton treatment uses four parameters, f , r , \mathcal{F} , and \mathcal{R} , in place of the single σ of the Hammett equation, the mathematical manipulations are somewhat more complex, but they can be easily handled with an appropriate calculator program. The result of the calculation is a "best-fit" correlation of the rate or equilibrium data with the terms f , r , \mathcal{F} , and \mathcal{R} . The computation also gives a "percent resonance" by comparing the magnitudes of f and r . The numerical reliability of both the substituent constants, \mathcal{F} and \mathcal{R} , and the question of whether complete separation of resonance and field effects is achieved is a matter of some dispute.²¹ The derived substituent constants are nevertheless qualitatively useful in comparing the properties of individual substituent groups and making at least a rough comparison of the interplay of resonance and field effects in different reactions. \mathcal{F} and \mathcal{R} values are included in Table 4.3 (p. 201). Certain substituents exhibit opposing resonance and field effects. Fluoro and methoxy groups are two examples (others can be located by examination of Table 4.3). This arises because these substituents act as electron donors by the resonance mechanism but the dipole associated with the substituent operates in the opposite direction.

The most elaborate and accurate treatment of substituent effects has been the development of a series of substituent constants, σ_R , chosen to reflect the resonance contribution of the substituent under various structural circumstances. This substituent constant is then used in conjunction with a second one σ_I , which reflects the inductive (and field) component of the overall substituent effect. The modified equation, called a *dual-substituent-parameter equation*, takes the form

$$\log \frac{K}{K_0} \quad \text{or} \quad \log \frac{k}{k_0} = \sigma_I \rho_I + \sigma_R \rho_R$$

where ρ_I and ρ_R are the reaction constants, which reflect the sensitivity of the system to inductive (and field) and resonance effects.²² The σ_I values have been defined from studies in aliphatic systems where no resonance component should be present.

20. C. G. Swain and E. C. Lupton, *J. Am. Chem. Soc.* **90**, 4328 (1968); C. G. Swain, S. H. Unger, N. R. Rosenquist, and M. S. Swain, *J. Am. Chem. Soc.* **105**, 492 (1983); C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, and E. J. Lien, *J. Med. Chem.* **16**, 1207 (1973).
21. W. F. Reynolds and R. D. Topsom, *J. Org. Chem.* **49**, 1989 (1984); A. J. Hoefnagel, W. Osterbeek, and B. M. Wepster, *J. Org. Chem.* **49**, 1993 (1984); M. Charton, *J. Org. Chem.* **49**, 1997 (1984); S. Marriott, W. F. Reynolds, and R. D. Topsom, *J. Org. Chem.* **50**, 741 (1985); C. G. Swain, *J. Org. Chem.* **49**, 2005 (1984).
22. S. Ehrenson, R. T. C. Brownlee, and R. W. Taft, *Prog. Phys. Org. Chem.* **10**, 1 (1973).

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By properly scaling the σ_I values with σ values from aromatic systems, it is possible to assign values such that

$$\sigma = \sigma_I + \sigma_R$$

Statistical analysis of data from many reaction series has shown that no single σ_R is applicable to the entire range of reactions. This again reflects the fact that the resonance component is variable and responds to the nature of the particular reaction. Therefore, a series of four σ_R values was established, each of which applies to various reaction types, ranging from direct conjugation with electron-deficient reaction centers to the other extreme. We will discuss only one of these, σ_R^0 , which applies in cases of minimal perturbation of the aromatic ring by charge development at the reaction site. The σ_R^0 values given in Table 4.3 are based on the use of ^{13}C chemical shifts as a measure of the sum of resonance and inductive effects. The chemical shift data of substituted benzenes were analyzed to provide the best correlation with the dual-substituent-parameter equation. In nonpolar solvents, which presumably best reflect the inherent molecular properties, $\rho_I = 3.74$ for cyclohexane and 3.38 for carbon tetrachloride. The corresponding values of ρ_R are 20.59 and 20.73. The relative magnitudes of ρ_I and ρ_R indicate that the ^{13}C chemical shift is more responsive to the resonance character of the substituent than to the inductive character.²³

In general, the dissection of substituent effects need not be limited to resonance and field components, which are of special prominence in reactions of aromatic compounds. Any type of substituent interaction with a reaction center could be characterized by a substituent constant characteristic of the particular type of interaction and a reaction parameter indicating the sensitivity of the reaction series to that particular type of interaction. For example, it has been suggested that electronegativity and polarizability can be treated as substituent effects separate from field and resonance effects. This gives rise to the equation

$$\log \frac{k}{k_0} = \sigma_F \rho_F + \sigma_R \rho_R + \sigma_X \rho_X + \sigma_\alpha \rho_\alpha$$

where σ_F is the field, σ_R is the resonance, σ_X is the electronegativity, and σ_α is the polarizability substituent constant.²⁴ We will, in general, emphasize the resonance and field components in our discussion of substituent effects.

The various multiparameter equations can usually improve the correlation of data that give poor correlations with the single-parameter Hammett equation. It must be recognized that this in part may be a direct consequence of the introduction of additional variable parameters. To derive solid mechanistic insight into the basis of improved correlation requires a critical appraisal of the results, and statistical analysis may be necessary. The details of critical statistical evaluation of free-energy

23. J. Bromilow, R. T. C. Brownlee, V. O. Lopez, and R. W. Taft, *J. Org. Chem.* **44**, 4766 (1979).

24. R. W. Taft and R. D. Topsom, *Prog. Phys. Org. Chem.* **16**, 1 (1987).

correlations have been extensively discussed, but this topic is beyond the scope of our coverage.²⁵

It should be recognized that all of the approaches to linear free-energy relationships have been developed on an empirical basis. The reaction constants, substituent constants, and other parameters involved are specified by the definitions of the correlation equation. The data are then treated by the equation, and the variable parameters arise from the best fit to the correlation equation. In the case of the Hammett equation, each reaction series gives rise to its characteristic ρ value. For the Swain-Lupton equation, the *meta* series and the *para* series would each give rise to f and r .

We might ask if insight into substituent effects can be obtained by analyzing the structural perturbations produced by substituents by molecular orbital calculations. This is a fundamentally challenging task because of the uncertainty of the structure at the transition state and also a large task because of the large number of calculations that would be involved. In one approach to the problem, the stabilizing (or destabilizing) effect of substituents as a positive charge (representing an electrophile) or a negative charge (representing a nucleophile) approaches a benzene ring was calculated.²⁶ The effect of the substituents, as reflected in the calculated stabilization or destabilization, was parallel to that indicated by linear free-energy correlations. The amino, hydroxy, and fluoro groups, for example, were found to provide extra stabilization for the approach of an electrophile in comparison with other substituents where a strong resonance interaction would not be expected. For the approach of a negative charge, these substituents were destabilizing, but extra stabilization was found for groups such as nitro, cyano, and sulfonyl. While detailed calculations have been undertaken for only a limited number of substituents, it appears that the MO calculations give rise to the same patterns as found on the basis of empirical correlation. The MO calculations support the idea that substituent effects in aromatic compounds are a combination of field effects and resonance effects.²⁷

* Let us now consider how linear free-energy relationships can provide insight into reaction mechanisms. The choice of benzoic acid ionization as the reference reaction for the Hammett equation leads to $\sigma > 0$ for electron-withdrawing groups and $\sigma < 0$ for electron-releasing groups, since electron-withdrawing groups favor the ionization of the acid and electron-releasing groups have the opposite effect. Further inspection of the Hammett equation shows that ρ will be positive for all reactions that are favored by electron-withdrawing groups and negative for all

25. For detailed discussion of analysis of substituent effects, see J. Shorter, in *Correlation Analysis in Chemistry*, Plenum Press, New York, 1978; M. Charton, *Prog. Phys. Org. Chem.* **13**, 119 (1981); W. F. Reynolds, *Prog. Phys. Org. Chem.* **13**, 119 (1981); W. F. Reynolds, *Prog. Phys. Org. Chem.* **14**, 165 (1983).
26. E. R. Vorpapel, A. Streitwieser, Jr., and S. D. Alexandratos, *J. Am. Chem. Soc.* **103**, 3777 (1981).
27. R. D. Topsom, *Prog. Phys. Org. Chem.* **16**, 125 (1987); H. Agren and P. S. Bagus, *J. Am. Chem. Soc.* **107**, 134 (1985); R. D. Topsom, *Acc. Chem. Res.* **16**, 292 (1983); W. J. Reynolds, P. Dais, D. W. MacIntyre, R. D. Topsom, S. Marriott, E. v. Nagy-Felsobuki, and R. W. Taft, *J. Am. Chem. Soc.* **105**, 378 (1983); A. Pross and L. Radom, *Prog. Phys. Org. Chem.* **13**, 1 (1980).

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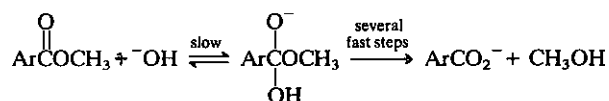
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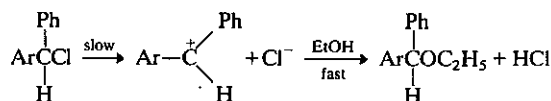
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reactions that are favored by electron-releasing groups. If the rates of a reaction series show a satisfactory correlation, both the sign and the magnitude of ρ provide information about the transition state for the reaction. In Example 4.3 (p. 200), the ρ value for saponification of substituted methyl benzoates is +2.38. This indicates that electron-withdrawing groups facilitate the reaction and that the reaction is somewhat more sensitive to substituent effects than the ionization of benzoic acids. The conclusion that the reaction is favored by electron-withdrawing substituents is in agreement with the accepted mechanism for ester saponification. The tetrahedral intermediate is negatively charged. Its formation should therefore be favored by substituents that can stabilize the developing charge.

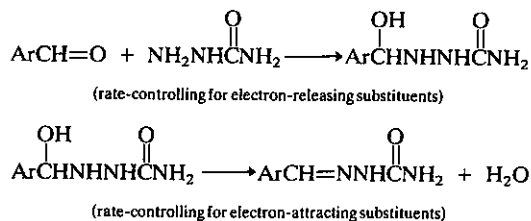


The solvolysis of diarylmethyl chlorides in ethanol shows a ρ value of -5.0 , indicating that electron-releasing groups strongly facilitate the reaction. This ρ value provides support for a mechanism involving ionization of the halides in the rate-determining step. Electron-releasing groups can facilitate the ionization by a stabilizing interaction with the electron-deficient carbon that develops as ionization proceeds.



The relatively large ρ shows that the reaction is very sensitive to substituent effects and implies that there is a relatively large redistribution of charge in the transition state.

Not all reactions can be fitted by the Hammett equation or the multiparameter variants. There can be several reasons for this. The most common is that there is a change in mechanism as substituents vary. In a multistep reaction, for example, one step may be rate-determining in the region of electron-withdrawing substituents, but a different step may become rate-limiting as the substituents become electron-releasing. The rate of the semicarbazone formation reaction of benzaldehydes, for example, shows a nonlinear Hammett plot with ρ of about 3.5 for electron-releasing groups, but with ρ near -0.25 for electron-withdrawing groups.²⁸ The change in ρ is believed to be the result of a change in the rate-limiting step.



28. D. S. Noyce, A. T. Bottini, and S. G. Smith, *J. Org. Chem.* **23**, 752 (1958).

Any reaction which shows a major shift in transition state structure over the substituent series would be expected to give a curved Hammett plot, since a variation in the extent of resonance participation would then be expected.

The substituent constants recorded in Table 4.3 (p. 201), provide valuable insight into the electronic nature of the various functional groups. By comparing σ with σ^+ , one gains a qualitative impression of the ability of a given substituent to act as an electron-donating group by resonance. The \mathcal{F} and σ_I values are indicators of the field and inductive characteristics of the various substituents. It should be noted that some groups, such as OMe and NH₂, that have strong electron-releasing capacity by resonance are electron-withdrawing when only field and inductive effects are considered. If \mathcal{F} and \mathcal{R} are taken as the best indicators of field versus resonance interactions, the substituents can be classified as in Table 4.5. By comparing σ_m values with σ_p values (Table 4.3), one can see that field effects usually dominate with *meta* substituents, while resonance effects are more important for *para* substituents. Thus σ_m constants of substituents such as hydroxy and methoxy have the positive signs while the σ_p constants are negative. This relationship is reasonable in terms of structure, since the *para* substituents are more favorably situated for resonance interaction.

There is a system for designating the electron-releasing or -attracting properties of substituents. This system is illustrated in Table 4.5. The symbols $+M$ and $-M$ have been used to designate resonance interactions (the M comes from "mesomerism," a synonym for resonance) and the symbols $+I$ and $-I$ for combined field and inductive effects (I for inductive because the importance of field effects was recognized only after the system was established).

The development of linear free-energy relationships in purely aliphatic molecules is complicated because steric and conformation factors come into play along with electronic effects. A number of successful treatments of aliphatic systems have been developed by separating polar effects from steric effects. We will not

Table 4.5. Classification of Substituent Groups

Resonance:		Electron-releasing ($-M$)		Electron-withdrawing ($+M$)
Field:		Electron-releasing ($-I$)	Electron-withdrawing ($+I$)	Electron-withdrawing ($+I$)
Me	AcNH	Br	OH	Ac
Et	AcO	Cl	MeO	CN
(Me) ₃ C	NH ₂	F	EtO	NO ₂
			Ph	CF ₃
				(Me) ₃ N ⁺

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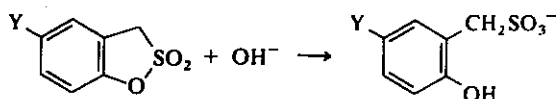
29. J. Hine, *Phy
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Practice Problems

5. Match the ρ values with the appropriate reactions. Explain your reasoning.
Reaction constants: +2.45, +0.75, -2.39, -7.29

Reactions:

- (a) nitration of substituted benzenes
 - (b) ionization of substituted benzenethiols
 - (c) ionization of substituted benzenephosphonic acids
 - (d) reaction of substituted *N,N*-dimethylanilines with methyl iodide.
6. (a) Determine the value of ρ for the reaction shown from the data given:



Y	$k(M^{-1} s^{-1})$
H	37.4
CH ₃ O	21.3
CH ₃	24.0
Br	95.1
NO ₂	1430

Answers

6a J. Am. Chem. Soc. 92, 860FF (1970)

5a-d "Linear Free Energy Relationships"
by P.R. Wells pp 12-13

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