

9

EFFECTS OF STRUCTURE ON REACTIVITY

When the equation for a reaction of, say, carboxylic acids, is written, it is customary to use the formula RCOOH , which implies that all carboxylic acids undergo the reaction. Since most compounds with a given functional group do give more or less the same reactions, the custom is useful, and the practice is used in this book. It allows a large number of individual reactions to be classified together and serves as an aid both for memory and understanding. Organic chemistry would be a huge morass of unconnected facts without the symbol R. Nevertheless, it must be borne in mind that a given functional group does not always react the same way, regardless of what molecule it is a part of. The reaction at the functional group is influenced by the rest of the molecule. This influence may be great enough to stop the reaction completely or to make it take an entirely different course. Even when two compounds with the same functional group undergo the same reaction, the rates and/or the positions of equilibrium are usually different, sometimes slightly, sometimes greatly, depending on the structures of the compounds. The greatest variations may be expected when additional functional groups are present.

The effects of structure on reactivity can be divided into three major types: field, resonance (or mesomeric), and steric.¹ In most cases two or all three of these are operating, and it is usually not easy to tell how much of the rate enhancement (or decrease) is caused by each of the three effects.

Resonance and Field Effects

It is often particularly difficult to separate resonance and field effects; they are frequently grouped together under the heading of *electrical effects*.² Field effects were discussed on pp. 17-19. Table 1.3 contains a list of some $+I$ and $-I$ groups. As for resonance effects, on p. 36 it was shown how the electron density distribution in aniline is not the same as it would be if there were no resonance interaction between the ring and the NH_2 group. Most groups that contain an unshared pair on an atom connected to an unsaturated system display a similar effect; i.e., the electron density on the group is less than expected, and the density on the unsaturated system is greater. Such groups are said to be electron-donating by the resonance effect ($+M$ groups). Alkyl groups, which do not have an unshared pair, are also $+M$ groups, presumably because of hyperconjugation.

On the other hand, groups that have a multiple-bonded electronegative atom directly connected to an unsaturated system are $-M$ groups. In such cases we can draw canonical

¹For a monograph, see Klumpp *Reactivity in Organic Chemistry*; Wiley: New York, 1982. For a general theoretical approach to organic reactivity, see Pross *Adv. Phys. Org. Chem.* **1985**, *21*, 99-196.

²For reviews of the study of electrical effects by ab initio methods, see Topsom *Prog. Phys. Org. Chem.* **1987**, *16*, 125-191. *Mol. Struct. Energ.* **1987**, *4*, 235-269.

forms in which electrons have been taken from the unsaturated system into the group, e.g.,

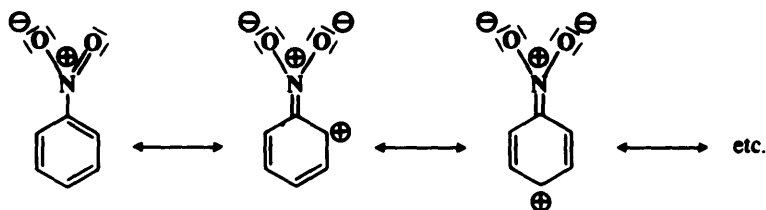
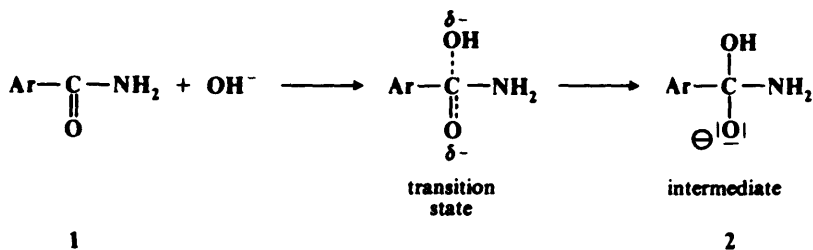


Table 9.1 contains a list of some $+M$ and $-M$ groups.

The resonance effect of a group, whether $+M$ or $-M$, operates only when the group is directly connected to an unsaturated system, so that, for example, in explaining the effect of the CH_3O group on the reactivity of the COOH in $\text{CH}_3\text{OCH}_2\text{CH}_2\text{COOH}$, only the field effect of the CH_3O need be considered. This is one way of separating the two effects. In *p*-methoxybenzoic acid both effects must be considered. The field effect operates through space, solvent molecules, or the σ bonds of a system, while the resonance effect operates through π electrons.

It must be emphasized once again that neither by the resonance nor by the field effect are any electrons actually being donated or withdrawn, though these terms are convenient (and we shall use them). As a result of both effects, the electron-density distribution is not the same as it would be without the effect (see pp. 18, 36). One thing that complicates the study of these effects on the reactivity of compounds is that a given group may have an effect in the transition state which is considerably more or less than it has in the unreacting molecule.

An example will show the nature of electrical effects (resonance and field) on reactivity. In the alkaline hydrolysis of aromatic amides (**0-11**), the rate-determining step is the attack of hydroxide ion at the carbonyl carbon:



In the transition state, which has a structure somewhere between that of the starting amide (**1**) and the intermediate (**2**), the electron density on the carbonyl carbon is increased. Therefore, electron-withdrawing groups ($-I$ or $-M$) on the aromatic ring will lower the free energy of the transition state (by spreading the negative charge). These groups have much less effect on the free energy of **1**. Since G is lowered for the transition state, but not substantially for **1**, ΔG^\ddagger is lowered and the reaction rate is increased (Chapter 6). Conversely, electron-donating groups ($+I$ or $+M$) should decrease the rate of this reaction. Of course, many groups are $-I$ and $+M$, and for these it is not always possible to predict which effect will predominate.

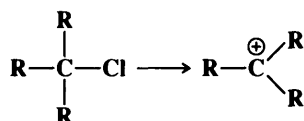
TABLE 9.1 Some groups with +M and -M effects, not listed in order of strength of effect
Ar appears in both lists because it is capable of both kinds of effect

+ M groups		-M groups	
O ⁻	SR	NO ₂	CHO
S ⁻	SH	CN	COR
NR ₂	Br	COOH	SO ₂ R
NHR	I	COOR	SO ₂ OR
NH ₂	Cl	CONH ₂	NO
NHCOR	F	CONHR	Ar
OR	R	CONR ₂	
OH	Ar		
OCOR			

Steric Effects

It occasionally happens that a reaction proceeds much faster or much slower than expected on the basis of electrical effects alone. In these cases it can often be shown that steric effects are influencing the rate. For example, Table 9.2 lists relative rates for the S_N2 ethanolysis of certain alkyl halides (see p. 294).³ All these compounds are primary bromides; the branching is on the second carbon, so that field-effect differences should be small. As Table 9.2 shows, the rate decreases with increasing β branching and reaches a very low value for neopentyl bromide. This reaction is known to involve an attack by the nucleophile from a position opposite to that of the bromine (see p. 294). The great decrease in rate can be attributed to *steric hindrance*, a sheer physical blockage to the attack of the nucleophile. Another example of steric hindrance is found in 2,6-disubstituted benzoic acids, which are difficult to esterify no matter what the resonance or field effects of the groups in the 2 or the 6 position. Similarly, once 2,6-disubstituted benzoic acids *are* esterified, the esters are difficult to hydrolyze.

Not all steric effects decrease reaction rates. In the hydrolysis of RCl by an S_N1 mechanism (see p. 298), the first step, which is rate-determining, involves ionization of the alkyl chloride to a carbocation:



The central carbon in the alkyl chloride is *sp*³-hybridized, with angles of about 109.5°, but

TABLE 9.2 Relative rates of reaction of RBr with ethanol³

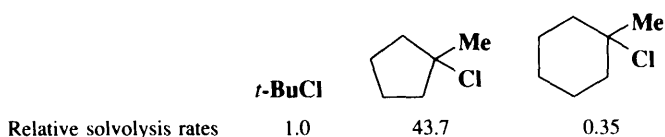
R	Relative rate
CH ₃	17.6
CH ₃ CH ₂	1
CH ₃ CH ₂ CH ₂	0.28
(CH ₃) ₂ CHCH ₂	0.030
(CH ₃) ₃ CCH ₂	4.2 × 10 ⁻⁶

³Hughes *Q. Rev., Chem. Soc.* **1948**, 2, 107-131.

when it is converted to the carbocation, the hybridization becomes sp^2 and the preferred angle is 120° . If the halide is tertiary and the three alkyl groups are large enough, they will be pushed together by the enforced tetrahedral angle, resulting in strain (see p. 163). This type of strain is called *B strain*⁴ (for back strain), and it can be relieved by ionization to the carbocation.⁵

The rate of ionization (and hence the solvolysis rate) of a molecule in which there is B strain is therefore expected to be larger than in cases where B strain is not present. Table 9.3 shows that this is so.⁶ Substitution of ethyl groups for the methyl groups of *t*-butyl chloride does not cause B strain; the increase in rate is relatively small, and the rate smoothly rises with the increasing number of ethyl groups. The rise is caused by normal field and resonance (hyperconjugation) effects. Substitution by one isopropyl group is not greatly different. But with the second isopropyl group the crowding is now great enough to cause B strain, and the rate is increased tenfold. Substitution of a third isopropyl group increases the rate still more. Another example where B strain increases solvolysis rates is found with the highly crowded molecules tri-*t*-butylcarbinol, di-*t*-butylneopentylcarbinol, *t*-butyldineopentylcarbinol, and trineopentylcarbinol, where rates of solvolysis of the *p*-nitrobenzoate esters are faster than that of *t*-butyl nitrobenzoate by factors of 13,000, 19,000, 68,000, and 560, respectively.⁷

Another type of strain, that can affect rates of cyclic compounds, is called *I strain* (internal strain).⁸ This type of strain results from changes in ring strain in going from a tetrahedral to a trigonal carbon or vice versa. For example, as mentioned above, S_N1 solvolysis of an alkyl halide involves a change in the bond angle of the central carbon from about 109.5° to about 120° . This change is highly favored in 1-chloro-1-methylcyclopentane because it relieves eclipsing strain (p. 156); thus this compound undergoes solvolysis in 80% ethanol at



25°C 43.7 times faster than the reference compound *t*-butyl chloride.⁹ In the corresponding cyclohexyl compound this factor is absent because the substrate does not have eclipsing

TABLE 9.3 Rates of hydrolysis of tertiary alkyl chlorides at 25°C in 80% aqueous ethanol⁶

Halide	Rate	Halide	Rate
Me₃CCl	0.033	Et₃CCl	0.099
Me₂EtCCl	0.055	Me₂(iso-Pr)CCl	0.029
MeEt₂CCl	0.086	Me(iso-Pr)₂CCl	0.45

⁴For a discussion, see Brown *Boranes in Organic Chemistry*, Cornell University Press: Ithaca, NY, 1972, pp. 114-121.

⁵For reviews of the effects of strain on reactivity, see Stirling *Tetrahedron* **1985**, *41*, 1613-1666. *Pure Appl. Chem.* **1984**, *56*, 1781-1796.

⁶Brown; Fletcher *J. Am. Chem. Soc.* **1949**, *71*, 1845.

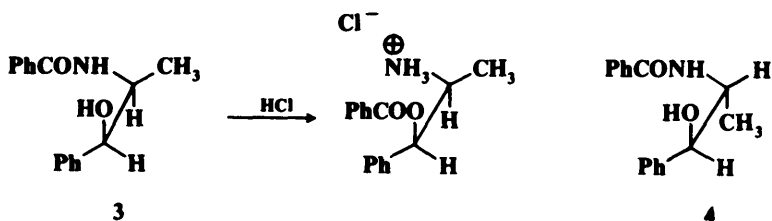
⁷Bartlett; Tidwell *J. Am. Chem. Soc.* **1968**, *90*, 4421.

⁸For a discussion, see Ref. 4, pp. 105-107, 126-128.

⁹Brown; Borkowski *J. Am. Chem. Soc.* **1952**, *74*, 1894. See also Brown; Ravindranathan; Peters; Rao; Rho *J. Am. Chem. Soc.* **1977**, *99*, 5373.

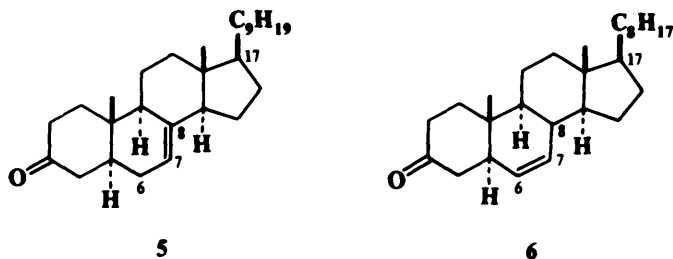
strain (p. 156), and this compound undergoes the reaction at about one-third the rate of *t*-butyl chloride. The reasons for this small decrease in rate are not clear. Corresponding behavior is found in the other direction, in changes from a trigonal to a tetrahedral carbon. Thus cyclohexanone undergoes addition reactions faster than cyclopentanone. Similar considerations apply to larger rings. Rings of 7 to 11 members exhibit eclipsing and transannular strain; and in these systems reactions in which a tetrahedral carbon becomes trigonal generally proceed faster than in open-chain systems.¹⁰

Conformational effects on reactivity can be considered under the heading of steric effects,¹¹ though in these cases we are considering not the effect of a group X and that of another group X' upon reactivity at a site Y but the effect of the conformation of the molecule. Many reactions fail entirely unless the molecules are able to assume the proper conformation. An example is the rearrangement of N-benzoylnorephedrine. The two dia-



stereomers of this compound behave very differently when treated with alcoholic HCl. In one of the isomers nitrogen-to-oxygen migration takes place, while the other does not react at all.¹² In order for the migration to take place, the nitrogen must be near the oxygen (*gauche* to it). When **3** assumes this conformation, the methyl and phenyl groups are anti to each other, which is a favorable position, but when **4** has the nitrogen *gauche* to the oxygen, the methyl must be *gauche* to the phenyl, which is so unfavorable that the reaction does not occur. Other examples are electrophilic additions to C=C double bonds (see p. 735) and E2 elimination reactions (see p. 983). Also, many examples are known where axial and equatorial groups behave differently.¹³

In steroids and other rigid systems, a functional group in one part of the molecule can strongly affect the rate of a reaction taking place at a remote part of the same molecule by altering the conformation of the whole skeleton. An example of this effect, called *conformational transmission*, is found in ergost-7-en-3-one (**5**) and cholest-6-en-3-one (**6**), where **6** condenses with benzaldehyde 15 times faster than **5**.¹⁴ The reaction site in both cases is



¹⁰See, for example, Schneider; Thomas *J. Am. Chem. Soc.* **1980**, *102*, 1424.

¹¹For reviews of conformational effects, see Green; Arad-Yellin; Cohen *Top. Stereochem.* **1986**, *16*, 131-218; Ōki *Acc. Chem. Res.* **1984**, *17*, 154-159; Seeman *Chem. Rev.* **1983**, *83*, 83-134. See also Ōki; Tsukahara; Moriyama; Nakamura *Bull. Chem. Soc. Jpn.* **1987**, *60*, 223, and other papers in this series.

¹²Fodor; Bruckner; Kiss; Ōhegyi *J. Org. Chem.* **1949**, *14*, 337.

¹³For a discussion, see Eliel *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962, pp. 219-234.

¹⁴Barton; McCapra; May; Thudium *J. Chem. Soc.* **1960**, 1297.

the carbonyl group, and the rate increases because moving the double bond from the 7 to the 6 position causes a change in conformation at the carbonyl group (the difference in the side chain at C-17 does not affect the rate).

Quantitative Treatments of the Effect of Structure on Reactivity¹⁵

Suppose a reaction is performed on a substrate molecule that can be represented as XGY, where Y is the site of the reaction, X a variable substituent, and G a skeleton group to which X and Y are attached, and we find that changing X from H to CH₃ results in a rate increase by a factor, say, 10. We would like to know just what part of the increase is due to each of the effects previously mentioned. The obvious way to approach such a problem is to try to find compounds in which one or two of the factors are absent or at least negligible. This is not easy to do acceptably because factors that seem negligible to one investigator do not always appear so to another. The first attempt to give numerical values was that of Hammett.¹⁶ For the cases of *m*- and *p*-XC₆H₄Y, Hammett set up the equation

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

where k_0 is the rate constant or equilibrium constant for X = H, k is the constant for the group X, ρ is a constant for a given reaction under a given set of conditions, and σ is a constant characteristic of the group X. The equation is called the *Hammett equation*.

The value of ρ was set at 1.00 for ionization of XC₆H₄COOH in water at 25°C. σ_m and σ_p values were then calculated for each group (for a group X, σ is different for the meta and para positions). Once a set of σ values was obtained, ρ values could be obtained for other reactions from the rates of just two X-substituted compounds, if the σ values of the X groups were known (in practice, at least four well-spaced values are used to calculate ρ because of experimental error and because the treatment is not exact). With the ρ value thus calculated and the known σ values for other groups, rates can be predicted for reactions that have not yet been run.

The σ values are numbers that sum up the total electrical effects (resonance plus field) of a group X when attached to a benzene ring. The treatment usually fails for the ortho position. The Hammett treatment has been applied to many reactions and to many functional groups and correlates quite well an enormous amount of data. Jaffé's review article¹⁶ lists ρ values for 204 reactions,¹⁷ many of which have different ρ values for different conditions.

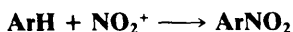
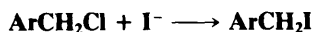
¹⁵For monographs, see Exner *Correlation Analysis of Chemical Data*; Plenum: New York, 1988; Johnson *The Hammett Equation*; Cambridge University Press: Cambridge, 1973; Shorter *Correlation Analysis of Organic Reactivity*; Wiley: New York, 1982; *Correlation Analysis in Organic Chemistry*; Clarendon Press: Oxford, 1973; Chapman: *Shorter Correlation Analysis in Chemistry: Recent Advances*; Plenum: New York, 1978; *Advances in Linear Free Energy Relationships*; Plenum: New York, 1972; Wells *Linear Free Energy Relationships*; Academic Press: New York, 1968. For reviews, see Connors *Chemical Kinetics*; VCH: New York, 1990, pp. 311-383; Lewis, in Bernasconi *Investigation of Rates and Mechanisms of Reactions* (vol. 6 of Weissberger *Techniques of Chemistry*), 4th ed.; Wiley: New York, 1986, pp. 871-901; Hammett, Ref. 2, pp. 347-390; Jones *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University Press: Cambridge, 1984, pp. 38-68; Charton, *CHEMTECH* **1974**, 502-511, **1975**, 245-255; Hine *Structural Effects in Organic Chemistry*; Wiley: New York, 1975, pp. 55-102; Afanas'ev *Russ. Chem. Rev.* **1971**, *40*, 216-232; Laurence; Wojtkowiak *Ann. Chim. (Paris)* **1970**, [14] *5*, 163-191. For a historical perspective, see Grunwald *CHEMTECH* **1984**, 698.

¹⁶For a review, see Jaffé *Chem. Rev.* **1953**, *53*, 191.

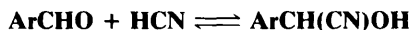
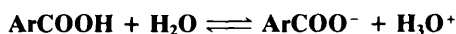
¹⁷Additional ρ values are given in Wells *Chem. Rev.* **1963**, *63*, 171-218 and van Bekkum; Verkade; Wepster *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 821-827.

Among them are reactions as disparate as the following:

Rate constants for



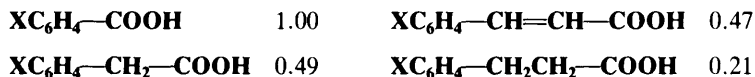
Equilibrium constants for



The Hammett equation has also been shown to apply to many physical measurements, including ir frequencies and nmr chemical shifts.¹⁸ The treatment is reasonably successful whether the substrates are attacked by electrophilic, nucleophilic, or free-radical reagents, the important thing being that the mechanism be the same *within* a given reaction series.

However, there are many reactions that do not fit the treatment. These are mostly reactions where the attack is directly on the ring and where the X group can enter into direct resonance interaction with the reaction site in the transition state (that is, the substrate is XY rather than XGY). For these cases, two new sets of σ values have been devised: σ^+ values (proposed by H. C. Brown) for cases in which an electron-donating group interacts with a developing positive charge in the transition state (this includes the important case of electrophilic aromatic substitutions; see Chapter 11), and σ^- values, where electron-withdrawing groups interact with a developing negative charge. Table 9.4 gives σ , σ^+ , and σ^- values for some common X groups.¹⁹ As shown in the table, σ is not very different from σ^+ for most electron-withdrawing groups. σ_m^- values are not shown in the table, since they are essentially the same as the σ_m values.

A positive value of σ indicates an electron-withdrawing group and a negative value an electron-donating group. The constant ρ measures the susceptibility of the reaction to electrical effects.²⁰ Reactions with a positive ρ are helped by electron-withdrawing groups and vice versa. The following ρ values for the ionization of some carboxylic acids illustrate this:²¹



¹⁸For a review of Hammett treatment of nmr chemical shifts, see Ewing, in Chapman; Shorter *Correlation Analysis in Chemistry: Recent Advances*; Plenum, New York, 1978, pp. 357-396.

¹⁹Unless otherwise noted, σ values are from Exner, in Chapman; Shorter, Ref. 18, pp. 439-540, and σ^+ values from Okamoto; Inukai; Brown *J. Am. Chem. Soc.* **1958**, *80*, 4969 and Brown; Okamoto *J. Am. Chem. Soc.* **1958**, *80*, 4979. σ^- values, except as noted, are from Jaffe. Ref. 16. Exner, pp. 439-540, has extensive tables giving values for more than 500 groups, as well as σ^+ , σ^- , σ_p , σ_m , and E_s values for many of these groups. Other large tables of the various sigma values are found in Hansch; Leo; Taft *Chem. Rev.* **1991**, *91*, 165-195. For tables of σ_p , σ_m , σ^+ , σ^- , and σ_R values of many groups containing Si, Ge, Sn, and Pb atoms, see Egorochkin; Razuvaev *Russ. Chem. Rev.* **1987**, *56*, 846-858. For values for heteroaromatic groups, see Mamaev; Shkurko; Baram *Adv. Heterocycl. Chem.* **1987**, *42*, 1-82.

²⁰For discussions of the precise significance of ρ , see Dubois; Ruasse; Argile *J. Am. Chem. Soc.* **1984**, *106*, 4840; Ruasse; Argile; Dubois *J. Am. Chem. Soc.* **1984**, *106*, 4846; Lee; Shim; Chung; Kim; Lee *J. Chem. Soc., Perkin Trans. 2* **1988**, 1919.

²¹Jones, Ref. 15, p. 42.

TABLE 9.4 σ , σ^+ , and σ^- values for some common groups¹⁹

Group	σ_p	σ_m	σ_p^+	σ_m^+	σ_p^-
O ⁻	-0.81 ³¹	-0.47 ³¹	-4.27 ³²	-1.15 ³²	
NMe ₂	-0.63	-0.10	-1.7		
NH ₂	-0.57	-0.09	-1.3	-0.16	
OH	-0.38 ²²	0.13 ²²	-0.92 ²³		
OMe	-0.28 ²²	0.10	-0.78	0.05	
CMe ₃	-0.15	-0.09	-0.26	-0.06	
Me	-0.14	-0.06	-0.31	-0.10 ²⁴	
H	0	0	0	0	0
Ph	0.05 ²⁵	0.05	-0.18	0 ²⁵	
COO ⁻	0.11 ³¹	0.02 ³¹	-0.41 ³²	-0.10 ³²	
F	0.15	0.34	-0.07	0.35	
Cl	0.24	0.37	0.11	0.40	
Br	0.26	0.37	0.15	0.41	
I	0.28 ²⁵	0.34	0.14	0.36	
N=NPh ²⁶	0.34	0.28	0.17		
COOH	0.44	0.35	0.42	0.32	0.73
COOR	0.44	0.35	0.48	0.37	0.68
COMe	0.47	0.36			0.87
CF ₃	0.53	0.46		0.57 ²⁴	
NH ₃ ⁺	0.60 ³¹	0.86 ³¹			
CN ²⁷	0.70	0.62	0.66	0.56	1.00
SO ₂ Me	0.73	0.64			
NO ₂	0.81	0.71	0.79	0.73 ²⁴	1.27
NMe ₃ ⁺	0.82 ²⁸	0.88 ²⁸	0.41	0.36	
N ₂ ⁺	1.93 ²⁹	1.65 ²⁹	1.88 ²⁹		3 ³⁰

This example shows that the insertion of a CH₂ or a CH=CH group diminishes electrical effects to about the same extent, while a CH₂CH₂ group diminishes them much more. A ρ greater than 1 would mean that the reaction is more sensitive to electrical effects than is the ionization of XC₆H₄COOH ($\rho = 1.00$).

Similar calculations have been made for compounds with two groups X and X' on one ring, where the σ values are sometimes additive and sometimes not,³³ for other ring systems such as naphthalene³⁴ and heterocyclic rings,³⁵ and for ethylenic and acetylenic systems.³⁶

²²Matsui; Ko; Hepler *Can. J. Chem.* **1974**, 52, 2906.

²³de la Mare; Newman *Tetrahedron Lett.* **1982**, 1305 give this value as -1.6.

²⁴Amin; Taylor *Tetrahedron Lett.* **1978**, 267.

²⁵Sjöström; Wold *Chem. Scr.* **1976**, 9, 200.

²⁶Byrne; Happer; Hartshorn; Powell *J. Chem. Soc., Perkin Trans. 2* **1987**, 1649.

²⁷For a review of directing and activating effects of C=O, C=C, C=N, and C=S groups, see Charton, in Patai *The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 1; Wiley: New York, 1989, pp. 239-298.

²⁸For a review of directing and activating effects of CN and C≡C groups, see Charton, in Patai: Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 1; Wiley: New York, 1983, pp. 269-323.

²⁹McDaniel; Brown *J. Org. Chem.* **1958**, 23, 420.

³⁰Ustyniuk; Subbotin; Buchneva; Gruzdnova; Kazitsyna *Doklad. Chem.* **1976**, 227, 175.

³¹Lewis; Johnson *J. Am. Chem. Soc.* **1959**, 81, 2070.

³²Hine *J. Am. Chem. Soc.* **1960**, 82, 4877.

³³Binev; Kuzmanova; Kaneti; Juchnovski *J. Chem. Soc., Perkin Trans. 2* **1982**, 1533.

³⁴Stone; Pearson *J. Org. Chem.* **1961**, 26, 257.

³⁵Berliner; Winikov *J. Am. Chem. Soc.* **1959**, 81, 1630; see also Wells; Ehrenson; Taft, Ref. 48.

³⁶For reviews, see Charton, in Chapman; Shorter, Ref. 18, pp. 175-268; Tomasik; Johnson *Adv. Heterocycl. Chem.* **1976**, 20, 1-64.

³⁷For reviews of the application of the Hammett treatment to unsaturated systems, see Ford; Katritzky; Topsom, in Chapman; Shorter, Ref. 18, pp. 269-311; Charton *Prog. Phys. Org. Chem.* **1973**, 10, 81-204.

The Hammett equation is a *linear free-energy relationship (LFER)*. This can be demonstrated as follows for the case of equilibrium constants (for rate constants a similar demonstration can be made with ΔG^\ddagger instead of ΔG). For each reaction, where X is any group,

$$\Delta G = -RT \ln K$$

For the unsubstituted case,

$$\Delta G_0 = -RT \ln K_0$$

The Hammett equation can be rewritten

$$\log K - \log K_0 = \sigma\rho$$

so that

$$\frac{-\Delta G}{2.3RT} + \frac{\Delta G_0}{2.3RT} = \sigma\rho$$

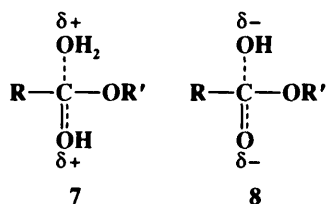
and

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

For a given reaction under a given set of conditions, σ , R , T , and ΔG_0 are all constant, so that σ is linear with ΔG .

The Hammett equation is not the only LFER.³⁷ Some, like the Hammett equation, correlate structural changes in reactants, but the Grunwald–Winstein relationship (see p. 360) correlates changes in solvent and the Brønsted relation (see p. 258) relates acidity to catalysis. The Taft equation is a structure–reactivity equation that correlates only field effects.³⁸

Taft, following Ingold,³⁹ assumed that for the hydrolysis of carboxylic esters, steric and resonance effects will be the same whether the hydrolysis is catalyzed by acid or base (see the discussion of ester–hydrolysis mechanisms, reaction 0-10). Rate differences would therefore be caused only by the field effects of R and R' in RCOOR'. This is presumably a good system to use for this purpose because the transition state for acid-catalyzed hydrolysis (7) has a greater positive charge (and is hence destabilized by $-I$ and stabilized by $+I$ substituents) than the starting ester, while the transition state for base-catalyzed hydrolysis (8)



³⁷For a discussion of physicochemical preconditions for LFERs, see Exner *Prog. Phys. Org. Chem.* **1990**, *18*, 129-161.

³⁸For reviews of the separation of resonance and field effects, see Charton *Prog. Phys. Org. Chem.* **1981**, *13*, 119-251; Shorter *Q. Rev., Chem. Soc.* **1970**, *24*, 433-453; *Chem. Br.* **1969**, *5*, 269-274. For a review of field and inductive effects, see Reynolds *Prog. Phys. Org. Chem.* **1983**, *14*, 165-203. For a review of field effects on reactivity, see Grob *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 569-575 [*Angew. Chem.* **88**, 621-627].

³⁹Ingold *J. Chem. Soc.* **1930**, 1032.

⁴⁰For another set of field-effect constants, based on a different premise, see Draffehn; Ponsold *J. Prakt. Chem.* **1978**, 320, 249.

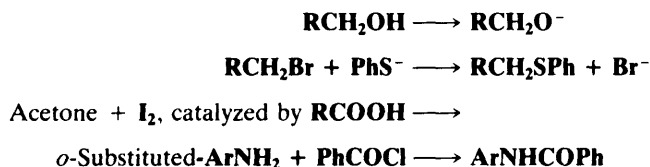
has a greater negative charge than the starting ester. Field effects of substituents X could therefore be determined by measuring the rates of acid- and base-catalyzed hydrolysis of a series XCH_2COOR' , where R' is held constant.³⁵ From these rate constants, a value σ_I could be determined by the equation⁴¹

$$\sigma_I \equiv 0.181 \left[\log \left(\frac{k}{k_0} \right)_B - \log \left(\frac{k}{k_0} \right)_A \right]$$

In this equation $(k/k_0)_B$ is the rate constant for basic hydrolysis of XCH_2COOR' divided by the rate constant for basic hydrolysis of CH_3COOR' , $(k/k_0)_A$ is the similar rate-constant ratio for acid catalysis, and 0.181 is an arbitrary constant. σ_I is a substituent constant for a group X, substituted at a saturated carbon, that reflects only field effects.⁴² Once a set of σ_I values was obtained, it was found that the equation

$$\log \frac{k}{k_0} = \rho_I \sigma_I$$

holds for a number of reactions, among them:⁴³



As with the Hammett equation, σ_I is constant for a given reaction under a given set of conditions. For very large groups the relationship may fail because of the presence of steric effects, which are not constant. The equation also fails when X enters into resonance with the reaction center to different extents in the initial and transition states. A list of some σ_I values is given in Table 9.5.⁴⁴ The σ_I values are about what we would expect for pure field-effect values (see p. 18) and are additive, as field effects (but not resonance or steric effects) would be expected to be. Thus, in moving a group one carbon down the chain, there is a decrease by a factor of 2.8 ± 0.5 (compare the values of R and RCH_2 in Table 9.5 for R = Ph and CH_3CO). An inspection of Table 9.5 shows that σ_I values for most groups are fairly close to the σ_m values (Table 9.4) for the same groups. This is not surprising, since σ_m values would be expected to arise almost entirely from field effects, with little contribution from resonance.

Since σ_p values represent the sum of resonance and field effects, these values can be divided into resonance and field contributions if σ_I is taken to represent the field-effect

⁴¹The symbol σ_f is also used in the literature; sometimes in place of σ_I , and sometimes to indicate only the field (not the inductive) portion of the total effect (p. 17).

⁴²There is another set of values (called σ^* values) that are also used to correlate field effects. These are related to σ_I values by $\sigma^* = \sigma_{f(X)} = 0.45\sigma_{f(XCH_2)}$. We discuss only σ_I , and not σ^* values.

⁴³Wells, Ref. 17, p. 196.

⁴⁴These values are from Bromilow; Brownlee; Lopez; Taft, Ref. 52, except that the values for NHAc, OH, and I are from Wells; Ehrenson; Taft, Ref. 48, the values for Ph and NMe_3^+ are from Ref. 51 and Taft; Deno; Skell, Ref. 47, and the value for CMe_3 is from Seth-Paul; de Meyer-van Duyse; Tollenaere *J. Mol. Struct.* **1973**, *19*, 811. The values for the CH_2Ph and CH_2COCH_3 groups were calculated from σ^* values by the formula given in footnote 42. For much larger tables of σ_I and σ_R values, see Charton, Ref. 38. See also Ref. 19 and Taylor; Wait *J. Chem. Soc., Perkin Trans. 2* **1986**, 1765.

TABLE 9.5 σ_I and σ_R° values for some groups⁴⁴

Group	σ_I	σ_R°	Group	σ_I	σ_R°
CMe ₃	-0.07	-0.17	OMe	0.27	-0.42
Me	-0.05	-0.13	OH	0.27	-0.44
H	0	0	I	0.39	-0.12
PhCH ₂	0.04		CF ₃	0.42	0.08
NMe ₂ ⁴⁵	0.06	-0.55	Br	0.44	-0.16
Ph	0.10	-0.10	Cl	0.46	-0.18
CH ₃ COCH ₂	0.10		F	0.50	-0.31
NH ₂	0.12	-0.50	CN	0.56	0.08
CH ₃ CO	0.20	0.16	SO ₂ Me	0.60	0.12
COOEt	0.20	0.16	NO ₂	0.65	0.15
NHAc	0.26	-0.22	NMe ₃ ⁺⁴⁶	0.86	

portion.⁴⁷ The resonance contribution σ_R^{48} is defined as

$$\sigma_R = \sigma_p - \sigma_I$$

As it stands, however, this equation is not very useful because the σ_R value for a given group, which should be constant if the equation is to have any meaning, is actually not constant but depends on the nature of the reaction.⁴⁹ In this respect, the σ_I values are much better. Although they vary with solvent in some cases, σ_I values are essentially invariant throughout a wide variety of reaction series. However, it is possible to overcome⁵⁰ the problem of varying σ_R values by using a special set of σ_R values, called σ_R° ,⁵¹ that measure the ability to delocalize π electrons into or out of an unperturbed or "neutral" benzene ring. Several σ_R° scales have been reported; the most satisfactory values are obtained from ¹³C chemical shifts of substituted benzenes.⁵² Table 9.5 lists some values of σ_R° , most of which were obtained in this way.⁵³

An equation such as

$$\log \frac{k}{k_0} = \rho_I \sigma_I + \rho_R \sigma_R^\circ$$

⁴⁴For σ_R° values for some other NR₂ groups, see Korzhenevskaya; Titov; Chotii; Chekhuta *J. Org. Chem. USSR* **1987**, 28, 1109.

⁴⁵Although we give a σ_I value for NMe₃⁺, (and F values for three charged groups in Table 9.6), it has been shown that charged groups (called polar substituents) cannot be included with uncharged groups (dipolar substituents) in one general scale of electrical substituent effects: Marriott; Reynolds; Topsom *J. Org. Chem.* **1985**, 50, 741.

⁴⁶Roberts; Moreland *J. Am. Chem. Soc.* **1953**, 75, 2167; Taft *J. Am. Chem. Soc.* **1957**, 79, 1045; *J. Phys. Chem.* **1960**, 64, 1805; Taft; Lewis *J. Am. Chem. Soc.* **1958**, 80, 2436; Taft; Deno; Skell *Annu. Rev. Phys. Chem.* **1958**, 9, 287-314, pp. 290-293.

⁴⁷For reviews of the σ_I and σ_R concept as applied to benzenes and naphthalenes, respectively, see Ehrenson; Brownlee; Taft *Prog. Phys. Org. Chem.* **1973**, 10, 1-80; Wells; Ehrenson; Taft *Prog. Phys. Org. Chem.* **1968**, 6, 147-322. See also Taft; Topsom *Prog. Phys. Org. Chem.* **1987**, 16, 1-83; Charton *Prog. Phys. Org. Chem.* **1987**, 16, 287-315.

⁴⁸Taft; Lewis *J. Am. Chem. Soc.* **1959**, 81, 5343; Reynolds; Dais; MacIntyre; Topsom; Marriott; von Nagy-Felsobuki; Taft *J. Am. Chem. Soc.* **1983**, 105, 378.

⁴⁹For a different way of overcoming this problem, see Happer; Wright *J. Chem. Soc., Perkin Trans. 2* **1979**, 694.

⁵⁰Taft; Ehrenson; Lewis; Glick *J. Am. Chem. Soc.* **1959**, 81, 5352.

⁵¹Bromilow; Brownlee; Lopez; Taft *J. Org. Chem.* **1979**, 44, 4766. See also Marriott; Topsom *J. Chem. Soc., Perkin Trans. 2* **1985**, 1045.

⁵²For a set of σ_R values for use in XY⁺ systems, see Charton *Mol. Struct. Energ.* **1987**, 4, 271-317.

which treats resonance and field effects separately, is known as a *dual substituent parameter equation*.⁵⁴

The only groups in Table 9.5 with negative values of σ_f are the alkyl groups methyl and *t*-butyl. There has been some controversy on this point.⁵⁵ One opinion is that σ_f values decrease in the series methyl, ethyl, isopropyl, *t*-butyl (respectively, -0.046 , -0.057 , -0.065 , -0.074).⁵⁶ Other evidence, however, has led to the belief that all alkyl groups have approximately the same field effect and that the σ_f values are invalid as a measure of the intrinsic field effects of alkyl groups.⁵⁷

Another attempt to divide σ values into resonance and field contributions⁵⁸ is that of Swain and Lupton, who have shown that the large number of sets of σ values (σ_m , σ_p , σ_p^- , σ_p^+ , σ_f , σ_R^+ , etc., as well as others we have not mentioned) are not entirely independent and that linear combinations of two sets of new values F (which expresses the field-effect contribution) and R (the resonance contribution) satisfactorily express 43 sets of values.⁵⁹ Each set is expressed as

$$\sigma = fF + rR$$

where f and r are weighting factors. Some F and R values for common groups are given in Table 9.6.⁶⁰ From the calculated values of f and r , Swain and Lupton calculated that the

TABLE 9.6 F and R values for some groups⁶⁰

Group	F	R	Group	F	R
COO ⁻	-0.27	0.40	OMe	0.54	-1.68
Me ₃ C	-0.11	-0.29	CF ₃	0.64	0.76
Et	-0.02	-0.44	I	0.65	-0.12
Me	-0.01	-0.41	Br	0.72	-0.18
H	0	0	Cl	0.72	-0.24
Ph	0.25	-0.37	F	0.74	-0.60
NH ₂	0.38	-2.52	NHCOCH ₃	0.77	-1.43
COOH	0.44	0.66	CN	0.90	0.71
OH	0.46	-1.89	NMe ₃ ⁺	1.54	
COOEt	0.47	0.67	N ₂ ⁺	2.36	2.81
COCH ₃	0.50	0.90			

⁵⁴There are also three-parameter equations. See, for example de Ligny and van Houwelingen *J. Chem. Soc., Perkin Trans. 2* **1987**, 559.

⁵⁵For a discussion, see Shorter, in Chapman; Shorter *Advances in Linear Free Energy Relationships*, Ref. 15, pp. 98-103.

⁵⁶For support for this point of view, see Levitt; Widing *Prog. Phys. Org. Chem.* **1976**, *12*, 119-157; Taft; Levitt *J. Org. Chem.* **1977**, *42*, 916; MacPhee; Dubois *Tetrahedron Lett.* **1978**, 2225; Screttas *J. Org. Chem.* **1979**, *44*, 3332; Hanson *J. Chem. Soc., Perkin Trans. 2* **1984**, 101.

⁵⁷For support for this point of view, see, for example, Ritchie *J. Phys. Chem.* **1961**, *65*, 2091; Bordwell; Drucker; McCollum *J. Org. Chem.* **1976**, *41*, 2786; Bordwell; Fried *Tetrahedron Lett.* **1977**, 1121; Charton *J. Am. Chem. Soc.* **1977**, *99*, 5687; *J. Org. Chem.* **1979**, *44*, 903; Adcock; Khor *J. Org. Chem.* **1978**, *43*, 1272; DeTar *J. Org. Chem.* **1980**, *45*, 5166; *J. Am. Chem. Soc.* **1980**, *102*, 7988.

⁵⁸Yukawa and Tsuno have still another approach, also involving dual parameters: Yukawa; Tsuno *Bull. Chem. Soc. Jpn.* **1959**, *32*, 971. For a review and critique of this method, see Shorter, in Chapman; Shorter, Ref. 18, pp. 119-173, pp. 126-144. This article also discusses the Swain-Lupton and Taft σ_f , σ_R approaches. For yet other approaches, see Afanas'ev *J. Org. Chem. USSR* **1981**, *17*, 373; *J. Chem. Soc., Perkin Trans. 2* **1984**, 1589; Ponec *Coll. Czech. Chem. Commun.* **1983**, *48*, 1564.

⁵⁹Swain; Lupton *J. Am. Chem. Soc.* **1968**, *90*, 4328; Swain; Unger; Rosenquist; Swain *J. Am. Chem. Soc.* **1983**, *105*, 492.

⁶⁰Taken from a much longer list in Swain; Unger; Rosenquist; Swain, Ref. 59. Long tables of R and F values are also given in Hansch; Leo; Taft, Ref. 19.

importance of resonance, % R , is 20% for σ_m , 38% for σ_p , and 62% for σ_p^+ .⁶¹ This is another dual substituent parameter approach.

Taft was also able to isolate steric effects.⁶² For the acid-catalyzed hydrolysis of esters in aqueous acetone, $\log(k/k_0)$ was shown to be insensitive to polar effects.⁶³ In cases where resonance interaction was absent, this value was proportional only to steric effects (and any others⁶⁴ that are not field or resonance). The equation is

$$\log \frac{k}{k_0} = E_s$$

Some E_s values are given in Table 9.7,⁶⁵ where hydrogen is taken as standard, with a value of 0.⁶⁶ This treatment is more restricted than those previously discussed, since it requires more assumptions, but the E_s values are approximately in order of the size of the groups. Charton has shown that E_s values for substituents of types CH_2X , CHX_2 , and CX_3 are linear functions of the van der Waals radii for these groups.⁶⁷

Two other steric parameters are independent of any kinetic data. Charton's ν values are derived from van der Waals radii,⁶⁸ and Meyer's V^a values from the volume of the portion of the substituent that is within 0.3 nm of the reaction center.⁶⁹ The V^a values are obtained by molecular mechanics calculations based on the structure of the molecule. Table 9.7 gives ν and V^a values for some groups.⁷⁰ As can be seen in the table, there is a fair, but not

TABLE 9.7 E_s , ν , and V^a values for some groups⁶⁵

Group	E_s	ν	$V^a \times 10^2$	Group	E_s	ν	$V^a \times 10^2$
H	0	0		Cyclohexyl	-2.03	0.87	6.25
F	-0.46	0.27	1.22	iso-Bu	-2.17	0.98	5.26
CN	-0.51			sec-Bu	-2.37	1.02	6.21
OH	-0.55			CF ₃	-2.4	0.91	3.54
OMe	-0.55		3.39	<i>t</i> -Bu	-2.78	1.24	7.16
NH ₂	-0.61			NMe ₃ ⁺	-2.84		
Cl	-0.97	0.55	2.54	Neopentyl	-2.98	1.34	5.75
Me	-1.24	0.52	2.84	CCl ₃	-3.3	1.38	6.43
Et	-1.31	0.56	4.31	CBr ₃	-3.67	1.56	7.29
I	-1.4	0.78	4.08	(Me ₃ CCH ₂) ₂ CH	-4.42	2.03	
Pr	-1.6	0.68	4.78	Et ₃ C	-5.04	2.38	
iso-Pr	-1.71	0.76	5.74	Ph ₃ C	-5.92	2.92	

⁶¹The Swain-Lupton treatment has been criticized by Reynolds; Topsom *J. Org. Chem.* **1984**, *49*, 1989; Hoefnagel; Oosterbeek; Wepster *J. Org. Chem.* **1984**, *49*, 1993; and Charton *J. Org. Chem.* **1984**, *49*, 1997. For a reply to these criticisms, see Swain *J. Org. Chem.* **1984**, *49*, 2005. A study of the rates of dediazonation reactions (3-23) was more in accord with the Taft and Charton (Ref. 38) σ_I and σ_R values than with the Swain-Lupton F and R values; Nakazumi; Kitao; Zollinger *J. Org. Chem.* **1987**, *52*, 2825.

⁶²For reviews of quantitative treatments of steric effects, see Gallo; Roussel; Berg *Adv. Heterocycl. Chem.* **1988**, *43*, 173-299; Gallo *Prog. Phys. Org. Chem.* **1983**, *14*, 115-163; Unger; Hansch *Prog. Phys. Org. Chem.* **1976**, *12*, 91-118.

⁶³Another reaction used for the quantitative measurement of steric effects is the aminolysis of esters (0-55); De Tar; Delahunty *J. Am. Chem. Soc.* **1983**, *105*, 2734.

⁶⁴It has been shown that E_s values include solvation effects; McClelland; Steenken *J. Am. Chem. Soc.* **1988**, *110*, 5860.

⁶⁵ E_s , ν , and V^a values are taken from longer tables in respectively, Ref. 62, Charton *J. Am. Chem. Soc.* **1975**, *97*, 1552; *J. Org. Chem.* **1976**, *41*, 2217; and Ref. 69.

⁶⁶In Taft's original work, Me was given the value 0. The E_s values in Table 9.7 can be converted to the original values by adding 1.24.

⁶⁷Charton *J. Am. Chem. Soc.* **1969**, *91*, 615.

⁶⁸Charton, Ref. 65. See also Charton *J. Org. Chem.* **1978**, *43*, 3995; Idoux; Schreck *J. Org. Chem.* **1978**, *43*, 4002.

⁶⁹Meyer *J. Chem. Soc., Perkin Trans. 2* **1986**, 1567.

⁷⁰For a discussion of the various steric parameters, see DeTar, Ref. 57.

perfect, correlation among the E_s , v , and V^a values. Other sets of steric values, e.g., E_s' ,⁷¹ E_s^* ,⁷² Ω_s ,⁷³ and δ_s ,⁷⁴ have also been proposed.⁷⁰

Since the Hammett equation has been so successful in the treatment of the effects of groups in the meta and para positions, it is not surprising that attempts have been made to apply it to ortho positions also.⁷⁵ The effect on a reaction rate or equilibrium constant of a group in the ortho position is called the *ortho effect*.⁷⁶ Despite the many attempts made to quantify ortho effects, so far no set of values commands general agreement. However, the Hammett treatment is successful for ortho compounds when the group Y in *o*-XC₆H₄Y is separated from the ring; e.g., ionization constants of *o*-XC₆H₄OCH₂COOH can be successfully correlated.⁷⁷

Linear free-energy relationships can have mechanistic implications. If $\log(k/k_0)$ is linear with the appropriate σ , it is likely that the same mechanism operates throughout the series. If not, a smooth curve usually indicates a gradual change in mechanism, while a pair of intersecting straight lines indicates an abrupt change,⁷⁸ though nonlinear plots can also be due to other causes, such as complications arising from side reactions. If a reaction series follows σ^+ or σ^- better than σ it generally means that there is extensive resonance interaction in the transition state.⁷⁹

Information can also be obtained from the magnitude and sign of ρ . For example, a strongly negative ρ value indicates a large electron demand at the reaction center, from which it may be concluded that a highly electron-deficient center, perhaps an incipient carbocation, is involved. Conversely, a positive ρ value is associated with a developing negative charge in the transition state.⁸⁰ The $\sigma\rho$ relationship even applies to free-radical reactions, because free radicals can have some polar character (p. 679), though ρ values here are usually small (less than about 1.5) whether positive or negative. Reactions involving cyclic transition states (p. 206) also exhibit very small ρ values.

⁷¹MacPhee; Panaye; Dubois *Tetrahedron* **1978**, *34*, 3553, *J. Org. Chem.* **1980**, *45*, 1164; Dubois; MacPhee; Panaye *Tetrahedron Lett.* **1978**, 4099; *Tetrahedron* **1980**, *36*, 919. See also Datta; Sharma *J. Chem. Res. (S)* **1987**, 422.

⁷²Fellous; Luft *J. Am. Chem. Soc.* **1973**, *95*, 5593.

⁷³Komatsuzaki; Sakakibara; Hirota *Tetrahedron Lett.* **1989**, *30*, 3309, *Chem. Lett.* **1990**, 1913.

⁷⁴Beckhaus *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 593 [*Angew. Chem.* **90**, 633].

⁷⁵For reviews, see Fujita; Nishioka *Prog. Phys. Org. Chem.* **1976**, *12*, 49-89; Charton *Prog. Phys. Org. Chem.* **1971**, *8*, 235-317; Shorter, Ref. 55, pp. 103-110. See also Segura *J. Org. Chem.* **1985**, *50*, 1045; Robinson; Horton; Foshee; Jones; Hanissian; Slater *J. Org. Chem.* **1986**, *51*, 3535.

⁷⁶This is not the same as the ortho effect discussed on p. 514.

⁷⁷Charton *Can. J. Chem.* **1960**, *38*, 2493.

⁷⁸For a discussion, see Schreck *J. Chem. Educ.* **1971**, *48*, 103-107.

⁷⁹See, however, Gawley *J. Org. Chem.* **1981**, *46*, 4595.

⁸⁰For another method of determining transition state charge, see Williams *Acc. Chem. Res.* **1984**, *17*, 425-430.

PART TWO

In Part 2 of this book we shall be directly concerned with organic reactions and their mechanisms. The reactions have been classified into 10 chapters, based primarily on reaction type: substitutions, additions to multiple bonds, eliminations, rearrangements, and oxidation–reduction reactions. Five chapters are devoted to substitutions; these are classified on the basis of mechanism as well as substrate. Chapters 10 and 13 include nucleophilic substitutions at aliphatic and aromatic substrates, respectively. Chapters 12 and 11 deal with electrophilic substitutions at aliphatic and aromatic substrates, respectively. All free-radical substitutions are discussed in Chapter 14. Additions to multiple bonds are classified not according to mechanism, but according to the type of multiple bond. Additions to carbon–carbon multiple bonds are dealt with in Chapter 15; additions to other multiple bonds in Chapter 16. One chapter is devoted to each of the three remaining reaction types: Chapter 17, eliminations; Chapter 18, rearrangements; Chapter 19, oxidation–reduction reactions. This last chapter covers only those oxidation–reduction reactions that could not be conveniently treated in any of the other categories (except for oxidative eliminations).

Each chapter in Part 2 consists of two main sections. The first section of each chapter (except Chapter 19) deals with mechanism and reactivity. For each reaction type the various mechanisms are discussed in turn, with particular attention given to the evidence for each mechanism and to the factors that cause one mechanism rather than another to prevail in a given reaction. Following this, each chapter contains a section on reactivity, including, where pertinent, a consideration of orientation and the factors affecting it.

The second main section of each chapter is a treatment of the reactions belonging to the category indicated by the title of the chapter. It is not possible to discuss in a book of this nature all or nearly all known reactions. However, an attempt has been made to include all the important reactions of standard organic chemistry which can be used to prepare relatively pure compounds in reasonable yields. In order to present a well-rounded picture and to include some reactions that are traditionally discussed in textbooks, a number of reactions that do not fit into the above category have been included. The scope of the coverage is apparent from the fact that more than 90% of the individual preparations given in *Organic Syntheses* are treated. However, certain special areas have been covered only lightly or not at all. Among these are electrochemical and polymerization reactions, and the preparation and reactions of heterocyclic compounds, carbohydrates, steroids, and compounds containing phosphorus, silicon, arsenic, boron, and mercury. The basic principles involved in these areas are of course no different from those in the areas more fully treated. Even with these omissions, however, some 580 reactions are treated in this book.

Each reaction is discussed in its own numbered section.¹ These are numbered consec-

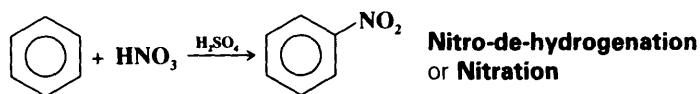
¹The classification of reactions into sections is, of course, to some degree arbitrary. Each individual reaction (for example, $\text{CH}_3\text{Cl} + \text{CN}^- \rightarrow \text{CH}_3\text{CN}$ and $\text{C}_2\text{H}_5\text{Cl} + \text{CN}^- \rightarrow \text{C}_2\text{H}_5\text{CN}$) is different, and custom generally decides how we group them together. Individual preferences also play a part. Some chemists would say that $\text{C}_6\text{H}_5\text{N}_2^+ + \text{CuCN} \rightarrow \text{C}_6\text{H}_5\text{CN}$ and $\text{C}_6\text{H}_5\text{N}_2^+ + \text{CuCl} \rightarrow \text{C}_6\text{H}_5\text{Cl}$ are examples of the "same" reaction. Others would say that they are not, but that $\text{C}_6\text{H}_5\text{N}_2^+ + \text{CuCl} \rightarrow \text{C}_6\text{H}_5\text{Cl}$ and $\text{C}_6\text{H}_5\text{N}_2^+ \rightarrow \text{CuBr} + \text{C}_6\text{H}_5\text{Br}$ are examples of the "same" reaction. No claim is made that the classification system used in this book is more valid than any other. For another way of classifying reactions, see Fujita *J. Chem. Soc., Perkin Trans. 2* **1988**, 597.

atively within a chapter. The *first* digit in each number is the *second* digit of the chapter number. Thus, reaction **6-1** is the first reaction of Chapter 16 and reaction **3-21** is the twenty-first reaction of Chapter 13. The second part of the reaction number has no other significance. The order in which the reactions are presented is not arbitrary but is based on an orderly outline that depends on the type of reaction. The placement of each reaction in a separate numbered section serves as an aid to both memory and understanding by setting clear boundary lines between one reaction and another, even if these boundary lines must be arbitrary, and by clearly showing the relationship of each reaction to all the others. Within each section, the scope and utility of the reaction are discussed and references are given to review articles, if any. If there are features of the mechanism that especially pertain to that reaction, these are also discussed within the section rather than in the first part of the chapter where the discussion of mechanism is more general.

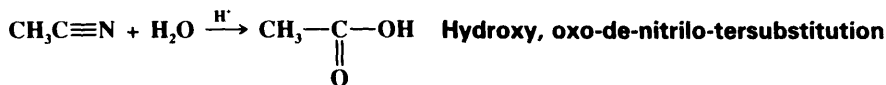
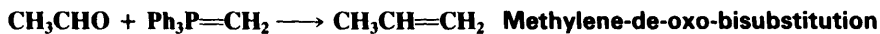
IUPAC Nomenclature for Transformations

There has long been a need for a method of naming reactions. As most students know well, many reactions are given the names of their discoverers or popularizers (e.g., Clemmensen, Diels–Alder, Prins, Wittig, Cope, Corey–Winter). This is useful as far as it goes, but each name must be individually memorized, and there are many reactions that do not have such names. The IUPAC Commission on Physical Organic Chemistry has produced a *system* for naming not reactions, but transformations (a reaction includes all reactants; a transformation shows only the substrate and product, omitting the reagents). The advantages of a systematic method are obvious. Once the system is known, no memorization is required; the name can be generated directly from the equation. The system includes rules for naming eight types of transformation: substitutions, additions, eliminations, attachments and detachments, simple rearrangements, coupling and uncoupling, insertions and extrusions, and ring opening and closing. We give here only the most basic rules for the first three of these types, which however will suffice for naming many transformations.² The complete rules give somewhat different names for speech-writing and indexing. In this book we give only the speech-writing names.

Substitutions. A name consists of the entering group, the syllable "de," and the leaving group. If the leaving group is hydrogen, it may be omitted (in all examples, the substrate is written on the left).



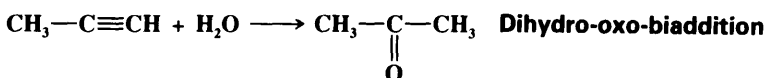
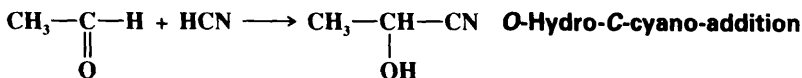
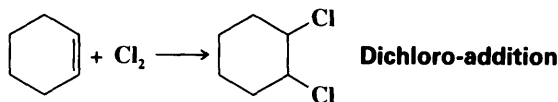
Multivalent substitutions are named by a modification of this system that includes suffixes such as "bisubstitution" and "tersubstitution."



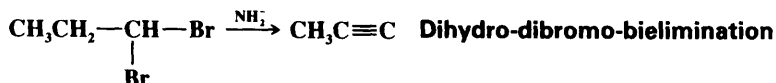
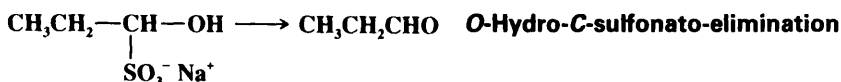
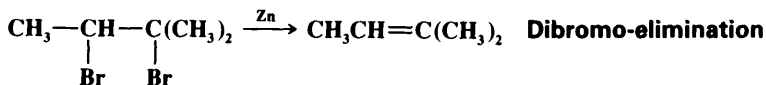
(Note: the nitrilo group is $\equiv\text{N}$.)

²For the complete rules, as so far published, see Jones; Bunnett *Pure Appl. Chem.* **1969**, *61*, 725-768.

Additions. For simple 1,2-additions, the names of both addends are given followed by the suffix "addition." The addends are named in order of priority in the Cahn-Ingold-Prelog system (p. 109), the lower-ranking addend coming first. Multivalent addition is indicated by "biaddition," etc.



Eliminations are named the same way as additions, except that "elimination" is used instead of "addition."



In the reaction sections of this book, we shall give IUPAC names for most transformations (these names will be printed in the same typeface used above), including examples of all eight types.³ As will become apparent, some transformations require more rules than we have given here.² However, it is hoped that the simplicity of the system will also be apparent.

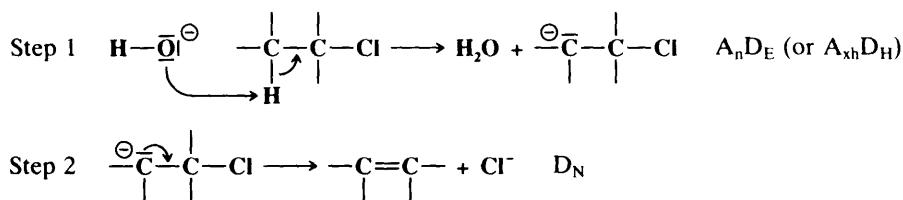
Two further notes: (1) Many transformations can be named using either of two reactants as the substrate. For example, the transformation **methylene-de-oxo-bisubstitution** above, can also be named **ethylidene-de-triphenylphosphorandiyl-bisubstitution**. In this book, unless otherwise noted, we will show only those names in which the substrate is considered to undergo the reactions indicated by the titles of the chapters. Thus the name we give to **1-12** ($\text{ArH} + \text{RCI} \rightarrow \text{ArR}$) is **alkyl-de-hydrogenation**, not **aryl-de-chlorination**, though the latter name is also perfectly acceptable under the IUPAC system. (2) The IUPAC rules recognize that some transformations are too complex to be easily fitted into the system, so they also include a list of names for some complex transformations, which are IUPAC approved, but nonsystematic (for some examples, see reactions **2-44**, **8-36**, **9-63**).

³For some examples, see: attachments (**8-29**, **9-28**), detachments (**9-48**, **9-56**), simple rearrangements (**8-7**, **8-31**), coupling (**0-86**, **9-35**), uncoupling (**9-9**, **9-61**), insertions (**2-20**, **8-9**), extrusions (**7-47**, **7-51**), ring opening (**0-18**, **0-49**), ring closing (**0-13**, **5-47**).

IUPAC System for Symbolic Representation of Mechanisms

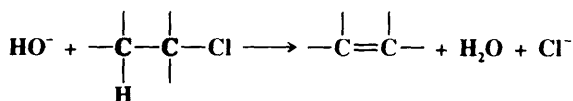
In addition to providing a system for naming transformations, the IUPAC Commission on Physical Organic Chemistry has also produced one for representing mechanisms.⁴ As we shall see in Part Two, many mechanisms (though by no means all) are commonly referred to by designations such as S_N2 , $AAC2$, $E1cB$, $S_{RN}1$, etc., many of them devised by C.K. Ingold and his co-workers. While these designations have been useful (and we shall continue to use them in this book), the sheer number of them can be confusing, especially since the symbols do not give a direct clue to what is happening. For example, there is no way to tell directly from the symbols how S_N2' is related to S_N2 (see p. 328). The IUPAC system is based on a very simple description of bond changes.⁵ The letter A represents formation of a bond (association); D the breaking of a bond (dissociation). These are *primitive changes*. The basic description of a mechanism consists of these letters, with subscripts to indicate where the electrons are going. In any mechanism the *core atoms* are defined as (a) the two atoms in a multiple bond that undergoes addition, or (b) the two atoms that will be in a multiple bond after elimination, or (c) the single atom at which substitution takes place.

As an example of the system, this is how an $E1cB$ mechanism (p. 991) would be represented:



Overall designation: $A_n D_E + D_N$ (or $A_{xh} D_H + D_N$)

In this case the overall reaction is:



and the core atoms are the two shaded carbons.

Step 1, First Symbol

A bond is being formed between O and H. Bond formation is represented by A. For this particular case the system gives two choices for subscript. In any process, the subscript is N if a core atom is forming a bond to a nucleophile (A_n) or breaking a bond to a nucleofuge (D_N). If a noncore atom is doing the same thing, lowercase n is used instead. Since H and O are non-core atoms, the lowercase n is used, and the formation of the O—H bond is designated by A_n . However, because involvement of H^+ is so common in organic mechanisms, the rules allow an alternative. The subscript H or h may replace N or n. The symbol xh denotes that the H^+ comes from or goes to an unspecified carrier atom X. Thus the

⁴Guthrie *Pure Appl. Chem.* **1989**, *61*, 23-56. For a briefer description, see Guthrie and Jencks *Acc. Chem. Res.* **1989**, *22*, 343-349.

⁵There are actually two IUPAC systems. The one we use in this book (Ref. 4) is intended for general use. A more detailed system, which describes every conceivable change happening in a system, and which is designed mostly for computer handling and storage, is given by Littler *Pure Appl. Chem.* **1989**, *61*, 57-81. The two systems are compatible; the Littler system uses the same symbols as the Guthrie system, but has additional symbols.

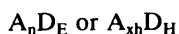
term A_{xh} means that a bond is being formed between H (moving without electrons) and an outside atom, in this case O. The same subscript, xh , would be used if the outside atom were any other nucleophilic atom, say, N or S.

Step 1, Second Symbol

A bond is being broken between C and H. The symbol is D. In any process, the subscript is E if a core atom is forming a bond to an electrophile (A_E) or breaking a bond to an electrofuge (D_E). Since C is a core atom, the symbol here is D_E . Alternatively, the symbol could be D_H . The rules allow A_H or D_H to replace A_E or D_E if the electrophile or electrofuge is H^+ . Because a core atom is involved in this primitive change the H in the subscript is capitalized.

Step 1, Combined Symbols

In step 1 two bond changes take place simultaneously. In such cases they are written together, with no space or punctuation:



Step 2

Only one bond is broken in this step and no bonds are formed. (The movement of a pair of unshared electrons into the C—C bond, forming a double bond, is not designated by any symbol. In this system bond multiplicity changes are understood without being specified.) Thus the symbol is D. The broken bond is between a core atom (C) and a nucleofuge (Cl), so the designation is D_N .

Overall Designation

This can be either $A_n D_N + D_N$ or $A_{xh} D_H + D_N$. The + symbol shows that there are two separate steps. If desired, rate-limiting steps can be shown by the symbol ‡. In this case, if the first step is the slow step [old designation (E1cB)], the designation would be $A_n D_E^\ddagger + D_N$ or $A_{xh} D_H^\ddagger + D_N$.

For most mechanisms (other than rearrangements), there will be only two A or D terms with uppercase subscripts, and the nature of the reaction can be immediately recognized by looking at them. If both are A, the reaction is an addition; if both are D (as in $A_n D_E + D_N$) it is an elimination. If one is A and the other D, the reaction is a substitution.

We have given here only a brief description of the system. Other IUPAC designations will be shown in Part Two, where appropriate. For more details, further examples, and additional symbols, see Ref. 4.

Organic Syntheses References

At the end of each numbered section there is a list of *Organic Syntheses* references (abbreviated OS). With the exception of a few very common reactions (**2-3**, **2-22**, **2-24**, and **2-38**) the list includes *all* OS references for each reaction. The volumes of OS that have been covered are Collective Volumes I to VII and individual volumes **66** to **69**. Where no OS references are listed at the end of a section, the reaction has not been reported in OS through volume **69**. These listings thus constitute a kind of index to OS.⁶ Certain ground

⁶Two indexes to *Organic Syntheses* have been published as part of the series. One of these, Liotta; Volmer *Organic Syntheses Reaction Guide*; Wiley: New York, 1991, which covers the series through volume 68, is described on p. 1257. The other, which covers the series through Collective Volume V, is Shriner; Shriner *Organic Syntheses Collective Volumes I, II, III, IV, V, Cumulative Indices*; Wiley: New York, 1976. For an older index to *Organic Syntheses* (through volume 45), see Sugawara; Nakai *Reaction Index of Organic Syntheses*; Wiley: New York, 1967.