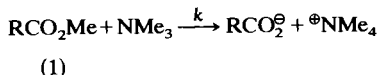


LINEAR FREE ENERGY RELATIONSHIPS

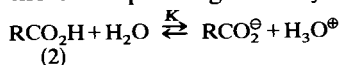
Sykes, P., *A Guide Book to Mechanism in Organic Chemistry*, Longman Scientific and Technical/John Wiley, New York

FIRST HAMMETT PLOTS

The first such relationship, on a thoroughly established basis, was observed by Hammett as long ago as 1933. He showed that for the reaction of a series of methyl esters (1) with NMe_3 ,



the rates of reaction were directly related to the ionisation constants, in water, of the corresponding carboxylic acids (2):



Thus on plotting $\log k$ for reaction of the esters (1) against $\log K$ for ionisation of the acids (2) (he actually plotted the $-\log$ values so as to have more easily handled numbers) a reasonable straight line resulted (Fig. 13.1):

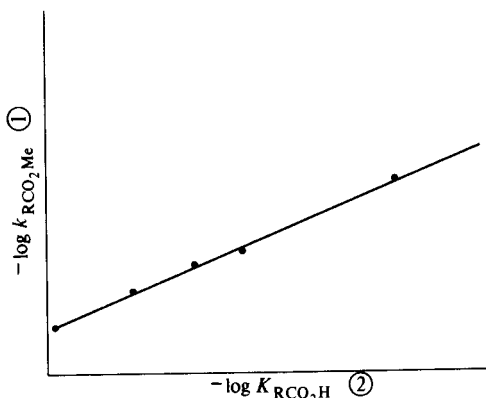


Fig. 13.1

Equilibrium constants, K , and rate constants, k , are each related to free energy changes (pp. 34, 38) in the relevant reactions in the following way:

$$\log K = \frac{-\Delta G^\ominus}{2.303 RT}$$

$$\log k = \frac{-\Delta G^\ddagger}{2.303 RT} + \log \left[\frac{k'T}{h} \right]$$

$$\left[\begin{array}{l} k' = \text{Boltzmann's constant} \\ h = \text{Planck's constant} \end{array} \right]$$

The fact that there is in Fig. 13.1 a straight line relationship between $-\log k$ for reaction of the esters (1), and $-\log K$, for ionisation in

water of the corresponding carboxylic acids (2), implies that there is also a straight line relationship between ΔG^\ddagger , the free energy of activation for the ester reaction, and ΔG^\ominus , the standard free energy change for ionisation in water of the acids. Because of this straight line relationship between the free energy terms for these two different reaction series, straight line plots like the one in Fig. 13.1 are generally referred to as *linear free energy relationships*.

Another early example of Hammett's is shown in Fig. 13.2, which represents a plot of $\log k$ for base-catalysed hydrolysis of a group of ethyl esters (3) against $\log K$ for ionisation in water of the corresponding carboxylic acids (2). Judged

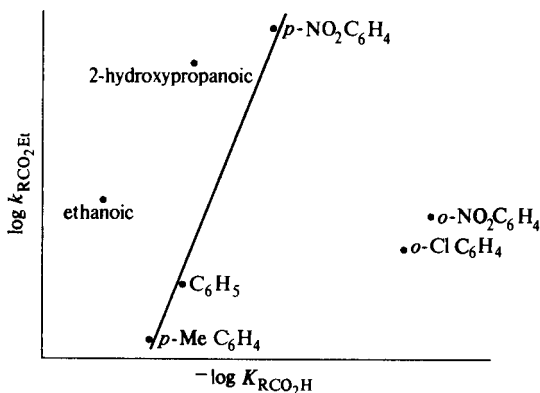
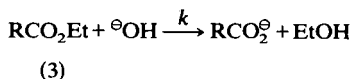


Fig. 13.2

by the standards of Fig. 13.1, the plot in Fig. 13.2 is pretty disappointing: there is a straight line relationship for benzoic acid and its $p\text{-Me}$ and $p\text{-NO}_2$ derivatives, but the $o\text{-NO}_2$ and $o\text{-Cl}$ benzoic acid derivatives then lie far off to one side of this straight line, while the aliphatic derivatives, of ethanoic and 2-hydroxypropanoic acids, lie far off to the other side. Hammett found indeed that straight lines were not generally obtained if reaction data for either o -substituted benzene derivatives, or aliphatic species, were included in the plot. He did, however, find that if consideration was restricted to reactions of m - and p -substituted benzene derivatives, then—as shown for ester hydrolysis in Fig. 13.3 (p. 361)—excellent linearity resulted, and this held for a very wide range of different reactions of such derivatives.

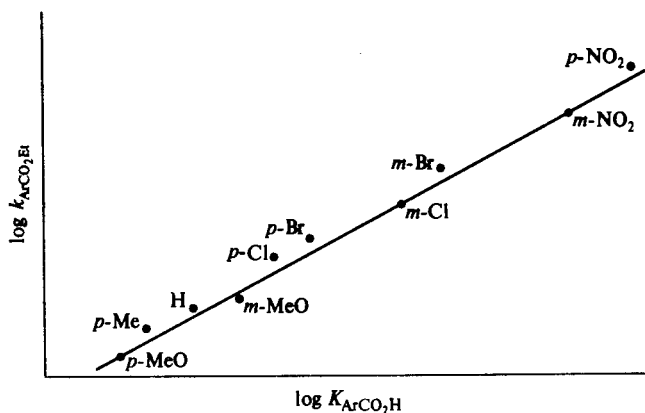
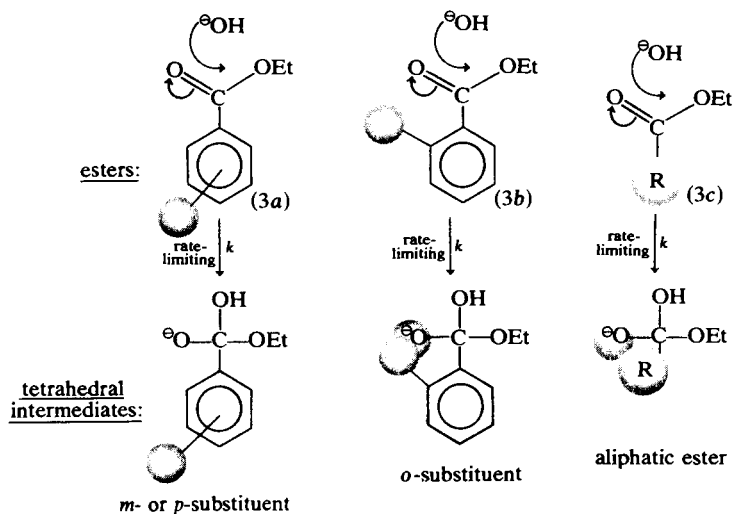


Fig. 13.3

A reason for such non-conformity on the part of *o*-substituted benzene, and of aliphatic, derivatives is not far to seek. Thus for the base-catalysed hydrolysis (p. 238) of the esters (3) in Figs 13.2 and



13.3, the *m*- or *p*-substituent in (3a) is far removed from the reaction centre and, in this rigid molecule, can exert no steric effect upon it. By contrast, the *o*-substituent in (3b) is close at hand (cf. p. 242), and leads to increasing crowding in the transition state leading to the tetrahedral intermediate produced in slow, rate-limiting attack on ester (3b) by $^{\ominus}\text{OH}$; very much the same is true also for the

more flexible molecules of the aliphatic ester (3c). Such steric effects will be much smaller, if indeed apparent at all, in the removal of the peripheral H from the CO₂H group by H₂O (i.e., in acid ionisation).

THE HAMMETT EQUATION

Despite establishing such linear relationships for a wide range of reactions of *m*- and *p*-substituted benzene derivatives, we still lack any simple form of this quantitative relationship that can actually be used to investigate new situations: here again, it was Hammett who supplied the answer.

Derivation of Hammett equation

The general equation for a straight line is $y = mx + c$, and this can be applied to the straight line in Fig. 13.3 to give,

$$\log k_X = \rho \log K_X + c \quad [1]$$

where ρ is the slope of this straight line, c the intercept, and X is the particular *m*- or *p*-substituent in the benzene ring of the species concerned. It is also possible to write an exactly analogous equation that is restricted to the *unsubstituted* ester and acid, i.e. where X = H:

$$\log k_H = \rho \log K_H + c \quad [2]$$

Subtracting [2] from [1], we obtain,

$$\log k_X - \log k_H = \rho(\log K_X - \log K_H) \quad [3]$$

which may also be written in the form:

$$\log \frac{k_X}{k_H} = \rho \log \frac{K_X}{K_H} \quad [4]$$

Substituent constant, σ_X

Hammett then designated the ionisation, in water at 25°, of *m*- and *p*-substituted benzoic acids as his *standard reference reaction*. He chose this reaction because reasonably precise aqueous ionisation constant, K_X , data were already available in the literature for quite a range of differently *m*- and *p*-substituted benzoic acids. Knowing K_H and K_X for a variety of differently X-substituted benzoic acids, it is then possible to define a quantity, σ_X , as

$$\sigma_X = \log \frac{K_X}{K_H} \quad [5]^*$$

* [5] may, of course, also be written in the form, $\sigma_X = pK_{a(H)} - pK_{a(X)}$; so that the numerical value of σ_X for a particular substituent is obtained by simple subtraction of the pK_a value for the substituted acid (where this is known) from the pK_a value for benzoic acid itself.

where σ_x is a *substituent constant*, whose value will remain constant for a specific substituent in a specific position (*m*- or *p*-), irrespective of the nature of the particular reaction in which a benzene derivative, carrying this substituent, is involved.

Substituting [5] into [4] we then get,

$$\log \frac{k_x}{k_H} = \rho \sigma_x \quad [6]$$

which is the usual form of what has come to be called the Hammett equation.

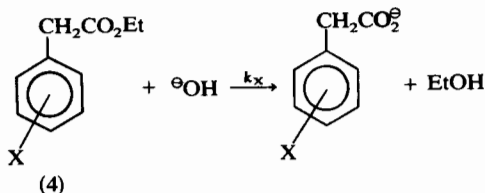
By using known values of K_x (or pK_a) for aqueous ionisation of *m*- and *p*-substituted benzoic acids (or measuring K_x [pK_a] where the value is not already available for a particular *m*- or *p*-substituent) it is possible to calculate σ_x as required, and a selection of values obtained in this way is shown below:

Substituent, X	σ_{m-x}	σ_{p-x}	
Me ₃ C	-0.10	-0.20	
Me	-0.07	-0.17	
H	0	0	(by definition)
MeO	+0.12	-0.27	
HO	+0.12	-0.37	
F	+0.34	+0.06	
Cl	+0.37	+0.23	
MeCO	+0.38	+0.50	
Br	+0.39	+0.23	
CN	+0.56	+0.66	
NO ₂	+0.71	+0.78	

Hardly surprisingly, the value of σ_x for a particular substituent is found to depend on the location of the substituent, having a different value in the *m*-position from that in the *p*-position.

Reaction constant, ρ

Having thus obtained a range of substituent constant, σ_x , values it is now possible to use them to calculate the value of ρ , the *reaction constant*, in [6] for any further reactions in which we may be interested: this is often done graphically. Thus to evaluate ρ for, say, the base-catalysed hydrolysis of *m*- and *p*-substituted ethyl 2-arylethanoates (4) we would, from kinetic measurements (or from



the literature if we're lucky!), obtain k_H for the unsubstituted ester, and k_X for at least three different substituted esters. Knowing the value of σ_X for each of these substituents, we can then plot $\log(k_X/k_H)$ against σ_X and, from [6], the slope of the resulting straight line will be the value of ρ for this reaction: it turns out to be +0.82 for this particular hydrolysis, when carried out in aqueous ethanol at 30°. The ρ values for quite a wide range of different reactions of *m*- and *p*-substituted benzene derivatives are shown below:

Reaction	Type	ρ
(1) ArNH ₂ with 2,4-(NO ₂) ₂ C ₆ H ₃ Cl in EtOH(25°)	<i>k</i>	-3.19
(2) ArNH ₂ with PhCOCl in C ₆ H ₆ (25°)	<i>k</i>	-2.69
(3) ArCH ₂ Cl solvolysis in aq. Me ₂ CO(69.8°)	<i>k</i>	-1.88
(4) ArO [⊖] with EtI in EtOH(25°)	<i>k</i>	-0.99
(5) ArCO ₂ H with MeOH (acid-catalysed, 25°)	<i>k</i>	-0.09
(6) ArCO ₂ Me hydrolysis (acid) in aq. MeOH(25°)	<i>k</i>	+0.03
(7) ArCH ₂ CO ₂ H ionisation in H ₂ O(25°)	<i>K</i>	+0.47
(8) ArCH ₂ Cl with I [⊖] in Me ₂ CO(20°)	<i>k</i>	+0.79
(9) ArCH ₂ CO ₂ Et hydrolysis (base) in aq. EtOH(30°)	<i>k</i>	+0.82
(10) ArCO ₂ H ionisation in H ₂ O(25°)	<i>K</i>	+1.00 (standard reaction)
(11) ArOH ionisation in H ₂ O(25°)	<i>K</i>	+2.01
(12) ArCN with H ₂ S (base) in EtOH(60.6°)	<i>k</i>	+2.14
(13) ArCO ₂ Et hydrolysis (base) in aq. EtOH(25°)	<i>k</i>	+2.51
(14) ArNH ₃ [⊕] ionisation in H ₂ O(25°)	<i>K</i>	+2.73

The standard reaction, the aqueous ionisation of *m*- and *p*-substituted benzoic acids at 25°, will have a ρ value of 1.00 as a necessary concomitant of the definition of σ_X in [5], and its use in [6]. The value of the reaction constant, ρ , for a particular reaction, carried out under specified conditions, remains constant no matter what the *m*- or *p*-substituents present in the compounds involved.

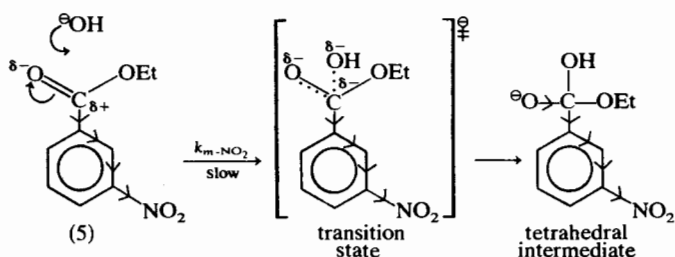
Physical significance of σ_X

Before we can go on to consider the actual use that may be made of Hammett plots, it is necessary to provide some physical justification for σ_X and ρ in terms of the more familiar factors that we have already seen influencing reaction rates and equilibria.

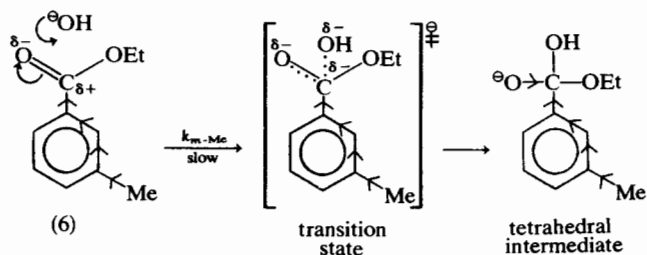
If we consider σ_X , the substituent constant, first and look at the list of σ_{m-X} values (p. 363), we can see that *m*-Me₃C and *m*-Me each have a small -ve value, H has the value—by definition—of zero, while all the other *m*-substituents have (increasing) +ve values. The change in sign (-ve → +ve) does, of course, parallel the change in direction (electron-donating → electron-withdrawing) of the inductive effect exerted by these substituents. The substituents may also exert a field effect (p. 22), operating through the medium, but this will act in the same direction as the inductive effect. It

would thus seem that σ_{m-X} represents, both in direction and magnitude, a measure of the *total polar effect* exerted by the substituent X on the reaction centre.

This is borne out by a comparison of the rates of base-catalysed hydrolysis (*cf.* p. 238) of *m*-NO₂ (5), and of *m*-Me (6), substituted ethyl benzoates with that of the unsubstituted ester: a reaction in which the slow, and hence rate-limiting, step is initial attack on the ester by [⊖]OH (p. 239):



$$\sigma_{m-\text{NO}_2} = +0.71 \quad \frac{k_{m-\text{NO}_2}}{k_{\text{H}}} = 63.5$$

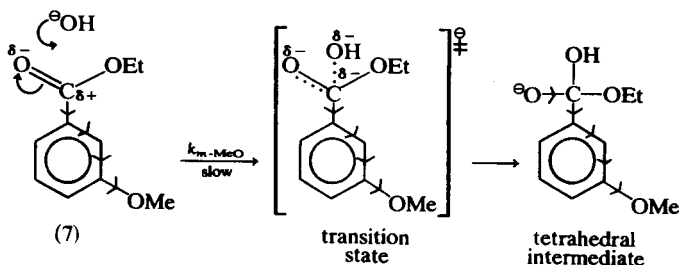


$$\sigma_{p-\text{MeO}} = -0.27 \quad \frac{k_{m-\text{Me}}}{k_{\text{H}}} = 0.66$$

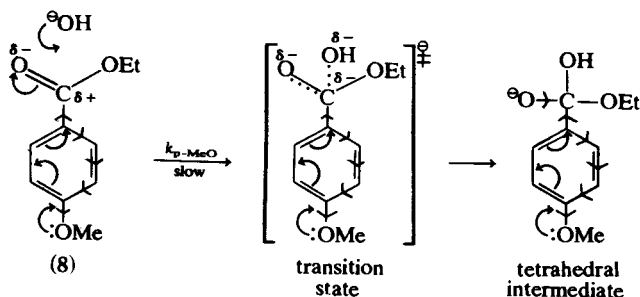
The *m*-nitro ester (5), with $\sigma_{m-\text{NO}_2} = +0.71$, is hydrolysed 63.5 times as fast as the unsubstituted ester (powerful electron-withdrawal markedly assisting [⊖]OH attack on the carbonyl carbon atom, and stabilising the transition state leading to the negatively charged tetrahedral intermediate); while the *m*-Me ester (6), with $\sigma_{m-\text{Me}} = -0.07$, is hydrolysed 0.66 times as fast as the unsubstituted ester (very weak electron-donation slightly inhibiting [⊖]OH attack, etc.).

If we now look at the list of σ_{p-X} values (p. 363), it is apparent that not only does the σ_{p-X} value for a particular substituent, X, vary in *magnitude* from the σ_{m-X} value for the same substituent, it may differ in *sign* too: as is the case with *m*- and *p*-MeO. An examination of the effect of a *m*-MeO (7) and a *p*-MeO (8) substituent on the same reaction as above (base-catalysed ester

hydrolysis) makes plain the reason for this change in sign:



$$\sigma_{m-\text{MeO}} = +0.12 \quad k_{m-\text{MeO}} > k_{\text{H}}$$



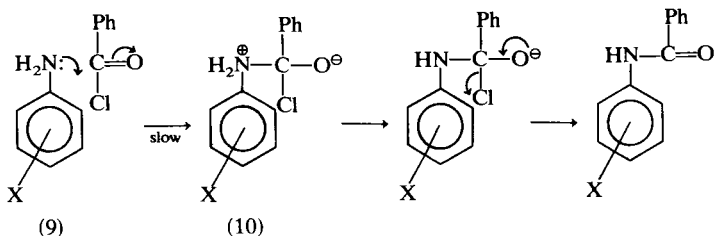
$$\sigma_{p-\text{MeO}} = -0.27 \quad k_{\text{H}} > k_{p-\text{MeO}}$$

In the *m*-position, the electronegative oxygen atom of the MeO group exerts an electron-withdrawing inductive effect ($\sigma_{m-\text{MeO}} = +0.12$) and hydrolysis is faster than with the unsubstituted ester [cf. the *m*-NO₂ ester (5)]. In the *p*-position, MeO will still exert an electron-withdrawing inductive effect, but in addition it can, through its electron pairs, exert an electron-donating mesomeric effect on the ring carbon atom to which the CO₂Et group is attached. The latter effect, because it involves the more readily polarisable π electron system, is the greater of the two, and the overall result is therefore *net* electron-donation ($\sigma_{p-\text{MeO}} = -0.27$); as is required by the observation that the *p*-MeO ester is hydrolysed markedly more slowly than the unsubstituted compound (cf. p. 154).

Thus σ_{X} can be regarded as a measure of the *overall polar effect* exerted by a substituent, X, on the reaction centre. Its *sign* indicates the *direction* ($-ve =$ electron-donating; $+ve =$ electron-withdrawing), and its *magnitude* the *extent*, of the effect that X exerts—compared, of course, with the effect exerted by H. Indeed, the assumed constancy of a substituent's σ_{X} value, over a wide range of different reactions, does not necessarily imply that the *absolute* polar effect of X always remains constant, but only that its effect *relative* to H remains constant.

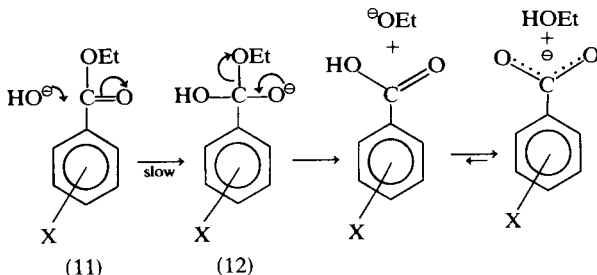
Physical significance of ρ

Now let us consider ρ , the reaction constant. Looking at the list of ρ values (p. 364), we can select first a reaction with a sizeable $-ve$ ρ value, say reaction 2—the benzylation of *m*- and *p*-substituted anilines (9)—with $\rho = -2.69$, and look at this reaction rather more closely:



The slow, rate-limiting step of this reaction is found to be initial attack by the electron pair of the nitrogen atom of the substituted aniline (9) on the carbonyl carbon atom of the acid chloride. This results in the development of $+ve$ charge at the reaction centre—the N atom attached directly to the substituted benzene ring in the forming intermediate (10). The reaction is thus accelerated by electron-donating substituents, which help delocalise this forming $+ve$ charge in the transition state leading to the intermediate (10), and correspondingly retarded by electron-withdrawing substituents; this behaviour is found to hold in general for reactions with $-ve$ ρ values.

We have already had some discussion of a reaction with a $+ve$ ρ value, reaction 13 in the list (p. 364), the base-catalysed hydrolysis of *m*- and *p*-substituted ethyl benzoates (11):



This has ρ value of $+2.51$, the known slow, rate-limiting step in this reaction is attended by the development of $-ve$ charge adjacent to the reaction centre in the transition state leading to the intermediate (12), and the overall reaction is, as we have already seen (p. 365),

accelerated by electron-withdrawing, and retarded by electron-donating, substituents.

Thus ρ can be regarded as a measure of the *susceptibility* of a reaction to the electron-donating or- withdrawing effect exerted by a substituent X; relative, of course, to the susceptibility (towards such a substituent) of the standard reaction—the aqueous dissociation of *m*- and *p*-substituted benzoic acids at 25°—for which $\rho = +1.00$, by definition. The *sign* of ρ is of diagnostic value, as we have seen, in that a -ve value indicates the development of +ve charge (or, of course, the disappearance of -ve charge) at the reaction centre during formation of the T.S. in the rate-limiting step of the overall reaction; while, *vice versa*, a +ve value indicates the development of -ve charge (or the disappearance of +ve charge) at that centre. The *magnitude* of ρ can be regarded, therefore, as a measure of the *change* in charge density at the reaction centre during formation of the T.S., or on proceeding from one side of an equilibrium to the other.

On this basis, it might well be expected that the ρ value, of otherwise similar reactions, would decrease as the reaction centre is moved further away from the substituents that are exerting a polar, electronic effect upon it. This is borne out by the ρ values for the aqueous ionisation of the acids (13)–(16):

Acid ionisation (H ₂ O)	ρ
(13) XC ₆ H ₄ CO ₂ H	1.00 (standard reaction)
(14) XC ₆ H ₄ CH ₂ CO ₂ H	0.49
(15) XC ₆ H ₄ CH ₂ CH ₂ CO ₂ H	0.21
(16) XC ₆ H ₄ CH=CHCO ₂ H	0.47

Introduction of first one, and then two, CH₂ groups between the benzene ring and CO₂H progressively reduces the susceptibility of the acid's ionisation to the polar effect of the substituent X in the benzene ring. The susceptibility, as revealed by the value of ρ , rises again for (16), however, as CH=CH is a markedly better transmitter of electronic effects than is CH₂—CH₂.