

PREDICTION OF THE STRENGTHS OF ORGANIC ACIDS

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THE strength of an acid, HA, in water is expressed quantitatively by its pK ($= -\log K$) value, where

$$K = (H^+)(A^-)/(HA)$$

the parentheses denoting activities. Often, when experimental results are not available, useful estimates of the approximate thermodynamic pK values of organic acids in water can be made, either from consideration of substituent effects or by analogy with substances of known pK . The present Review shows how such treatments, that have already been discussed for organic bases,¹ can be applied to organic acids. Except where stated, all experimental pK values are from reference 2. In almost all cases they refer to temperatures within the range 18–25° (usually 25°).

For convenience, acids are considered under the headings: (1) Aromatic acids; (a) carboxylic acids, (b) phenols, naphthols, and tropolones, (c) thiophenols, (d) other acids; (2) Aliphatic and alicyclic acids; (a) carboxylic acids, (b) alcohols and aldehydes, (c) thio-acids and -alcohols; (3) Heterocyclic acids; (a) carboxylic acids, (b) substituted azoles, (c) hydroxy-compounds.

Other types, such as amides, imides, β -ketones (enolic and ketonic forms), hydroxynaphthaquinones, and aromatic thio-acids, are also dealt with in the Discussion.

Representative pK values are given in Table 1, in which the acids are arranged in order of decreasing strength.

Qualitatively, the same factors¹ govern the strengths of acids and bases. At any given temperature, the pK_a value of an acid or a base is directly proportional to the free energy change in the ionisation reaction, so that the effect of substituents on pK values can be discussed in terms of factors affecting free energies. These factors are mainly polar, resonance, and steric interactions.¹ Of these, polar effects are approximately constant for any substituent and cumulative when more than one group is involved, so long as two or more highly polar groups are not attached to the same atom.

Resonance contributions often roughly parallel polar effects, whereas steric factors usually vary from one class of reaction to another. Carboxylic acid and phenolic groups are able, both in their ions and in their neutral molecules, to exhibit resonance interaction with the remainder of the molecule. In an amine, on the other hand, the lone pair of electrons on the

¹ J. Clark and D. D. Perrin, *Quart. Rev.*, 1964, **18**, 295.

² G. Kortüm, W. Vogel, and K. Andrussov, "Dissociation Constants of Organic Acids in Aqueous Solution", Butterworths, London, 1961.

TABLE 1. *Representative pK values of organic acids at 25°*

Phenylphosphonic acid	1.84, ^a 6.97 ^a	Benzeneseleninic acid	4.78 ^e
Pyridine-3-carboxylic acid	2.05	Cyclohexanecarboxylic acid	4.90
Aminoacetic acid	2.35	Thiophenol	6.52 ^f
2-Furoic acid	3.16 ^b	Acetylacetone (enolic form)	8.13 ^g
Thiophen-2-carboxylic acid	3.53 ^b	Benzenesulphonanilide	8.31 ^h
Phenylarsonic acid	3.54, ^a 8.49 ^a	Purine	8.93
Thioacetic acid	3.62 ^c	Phenol	10.00
Formic acid	3.75	Ethanethiol	10.54 ^e
Benzoic acid	4.21	2-Pyridone	11.65
Succinic acid	4.22, 5.64	Formaldehyde	13.29 ⁱ
Pyrrole-2-carboxylic acid	4.45 ^d	Methanol	15.5 ^j
Acetic acid	4.76	Pyrrole	~16.5

^aH. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191. ^bP. Lumme, *Suomen Kem.*, 1960, **33B**, 87. ^cR. J. Irving, L. Nelander, and I. Wadsö, *Acta Chem. Scand.*, 1964, **18**, 769. ^dA. Albert, "Physical Methods in Heterocyclic Chemistry", vol. 1, ed. A. R. Katritzky, Academic Press, New York, 1963, ch. 1. ^eJ. D. McCullough and E. S. Gould, *J. Amer. Chem. Soc.*, 1949, **71**, 674; E. S. Gould and J. D. McCullough, *ibid.*, 1951, **73**, 1109. ^fM. M. Kreevoy, B. E. Eichinger, F. E. Stary, E. A. Katz, and J. H. Sellstedt, *J. Org. Chem.*, 1964, **29**, 1641. ^gG. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, 1944, **27**, 1701. ^hA. V. Willi, *Helv. Chim. Acta*, 1956, **39**, 46. ⁱR. P. Bell and P. T. McTigue, *J. Chem. Soc.*, 1960, 2983, ^jP. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1960, **82**, 795.

nitrogen atom is available for such interaction only in the neutral molecule.

Because of its greater size, a carboxyl group is more susceptible than a primary amino-group to steric interactions. Conformational effects, which are important in cyclic molecules such as the cyclohexanedicarboxylic acids, are also partly steric in character.

In aqueous systems, the ordering influence of ionic hydration, the co-operative structure of liquid water, and the dependence of both of these factors on temperature, are likely to be very important. The absence of mathematical models by which these factors can be discussed quantitatively largely explains why no simple treatment exists for estimating pK values in water from results obtained in partly- or non-aqueous solutions. Qualitatively, organic acids are much weaker (have higher pK values) in solvents of lower dielectric constant. This is because of the greater electrostatic work required in such solvents to form, and separate, two oppositely charged species from a neutral molecule.

When steric effects are negligible, the additivity of polar effects can be made the basis of linear free energy relations such as the Hammett³ and Taft⁴ equations, which are used for predictive purposes in aromatic and aliphatic systems, respectively. However, the underlying theoretical basis of such relations is often less simple than at first appears. For example, insertion of two ethyl groups into acetic acid produces little change in ΔG° , and hence in pK, at 25° only because the corresponding enthalpy and

³ L. P. Hammett, "Physical Organic Chemistry", McGraw-Hill, New York, 1940, ch. 7; *Chem. Rev.*, 1935, **17**, 125.

⁴ R. W. Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 3120; 1953, **75**, 4231.

entropy changes are very nearly self-cancelling.⁵ Similarly, a linear dependence of ΔH° and $T\Delta S^\circ$ is found for many alkyl substituted acetic acids in water. Such linear enthalpy-entropy relations, which are very common,⁶ are to be expected for types of aqueous systems in which differences are due mainly to the extent of solvation changes.⁷

The pK values of many of the common acids pass through minima at ambient temperatures, possibly because of variations in the structure of water. For this reason, no simple relation is likely for the temperature coefficients of acids. Although the pK values of carboxylic acids are rather insensitive to changes in temperature, the predictions set out in this Review are intended to apply only to temperatures around 18—25°.

Aromatic Acids

Carboxylic Acids.—The Hammett equation

$$\log (k/k_0) = \rho\sigma$$

is applicable to many rate processes and equilibria involving *meta*- and *para*-substituted aromatic compounds, provided that the resonance interaction between the substituent and the reaction centre is either small or proportional to the polar effect. (The substituents are too far from the reaction centre to exert any steric effects on it.) In this equation, values of the rate (or equilibrium) constant, k , vary with the substituent, and k_0 denotes the value for the parent substance. For any given substituent, a particular value of the parameter, σ , is assigned; it is independent of the nature of the reaction. Conversely, each reaction is characterised by a particular value of ρ , which depends only on the experimental conditions. The original σ constants of the Hammett equation were defined in terms of the ionisation constants of benzoic acid and its derivatives in water at 25° ($\rho = 1$ being taken for this series) so that, in principle, the pK values of di- and tri-substituted benzoic acids can be predicted by summing the σ constants of the substituents and subtracting the total from the pK of benzoic acid. Hence, for these acids,

$$pK = 4.20 - \Sigma\sigma$$

In general, the σ constants summarised in Table 2 have been obtained from the corresponding monosubstituted benzoic acids so that they allow for any resonance effects in this particular series.

Charton⁸ has described a convenient graphical method for estimating the value of an unknown σ constant for a group XY^- , (*e.g.*, $CF_3\cdot NH^-$), where Y may be O, S, NH, CO, or *o*-, *m*-, or *p*-phenylene. In this method,

⁵ D. H. Everett, D. A. Landsman, and B. R. Pinsent, *Proc. Roy. Soc.*, 1952, A, 215, 403.

⁶ J. E. Leffler, *J. Org. Chem.*, 1955, 20, 1202; R. F. Brown, *ibid.*, 1962, 27, 3015.

⁷ D. J. G. Ives and P. D. Marsden, *J. Chem. Soc.*, 1965, 649.

⁸ M. Charton, *J. Org. Chem.*, 1963, 28, 3121.

TABLE 2. *Substituent constants^a for the Hammett equation*

Substituent	<i>meta</i>	<i>para</i>	Substituent	<i>meta</i>	<i>para</i>
H	0	0	OH	0.10 ^b	-0.37 ^c
Me	-0.07	-0.17	O ⁻	-0.71	-0.52
Et	-0.07 ^c	-0.15	OMe	0.08 ^b	-0.27
					(-0.11) ^{df}
Pr ⁿ	-0.05 ^e	-0.13	OEt	0.07 ^b	-0.24 ^c
Pr ⁱ	-0.07 ^e	-0.15	OPr ⁿ	0.1 ^c	-0.25 ^c
Bu ⁿ	-0.07 ^e	-0.16	OPr ⁱ	0.1 ^c	-0.45 ^c
Bu ^t		-0.12	OBu ⁿ	0.1 ^c	-0.32
CHMeEt		-0.12	OC ₅ H ₁₁	0.1 ^c	-0.34
Bu ^t	-0.10 ^c	-0.20	O·[CH ₂] ₅ ·CHMe ₂		-0.27
CH ₂ Bu ^t		-0.23	O·CH ₂ Ph		-0.42
CMe ₂ Et		-0.19	OPh	0.25 ^c	-0.32 ^c
CH ₂ OH	0.08 ^f	0.08 ^f	3,4-O·CH ₂ -O ⁻		-0.16
CH ₂ Cl		0.18	O·CF ₃	0.36 ^g	0.32 ^g
CH ₂ ·CN		0.01	OAc	0.39 ^c	0.31 ^c
CH ₂ ·CH ₂ ·CO ₂ H	-0.03	-0.07	SH	0.25 ^c	0.15 ^c
CH=CHPh	0.14		SMe	0.15 ^c	0.00 ^c
					(0.21) ^{df}
3,4-[CH ₂] ₃ (fused ring)		-0.26	SEt		0.03 ^c
3,4-[CH ₂] ₄ (fused ring)		-0.48	SPr ⁱ		0.07 ^c
Ph	0.06 ^c	0.01 ^c	SMe ₂ ⁺	1.00 ^c	0.90 ^c
3,4-[CH] ₄ (β -naphthyl)		0.04 ^c	SO·Me	0.52 ^c	0.49 ^c
		(0.11) ^f			
CH ₂ SiMe ₂	-0.16 ^c	-0.21 ^c	SO ₂ ·Me	0.68 ^b	0.72 ^c
					(0.92) ^f
CHO	0.36	0.22	SO ₂ ·NH ₂	0.46 ^c	0.57 ^c
		(1.03) ^f			
CF ₃	0.47 ^b	0.54 ^c	SO ₃ ⁻	0.05 ^c	0.09 ^c
					(0.39) ^f
CO ₂ H	0.37 ^c	0.41 ^b	-SCN		0.52 ^c
CO ₂ ⁻	-0.1 ^c	0.0 ^c	SAc	0.39 ^c	0.44 ^c
		(0.31) ^f			
CO ₂ Me	0.32	0.39 ^b	S·CF ₃	0.35 ^g	0.38 ^g
CO ₂ Et	0.37 ^c	0.45 ^c	B(OH) ₂	0.01	0.45
CO·NH ₂	0.28	0.36 ^e	SiMe ₃	-0.04 ^c	-0.07 ^c
Ac	0.38 ^c	0.50 ^c	SiEt ₃		0.0 ^c
		(0.84) ^f			
Bz	0.34 ^h	0.46	GeMe ₃		0.0 ^c
-CN	0.61 ^b	0.66 ^c	GeEt ₃		0.0 ^c
		(0.88) ^f			
CO·CF ₃	0.65 ^k		SnMe ₃		0.0 ^c
NH ₂	-0.04 ^b	-0.66	SnEt ₃		0.0 ^c
		(-0.15) ^{df}			
NHMe	-0.30	-0.84 ^c	PO ₃ H ⁻	0.2 ^c	0.26 ^c
NHEt	-0.24	-0.61 ^e	F	0.34	0.06
NHBu ⁿ	-0.34	-0.51 ^e	Cl	0.37	0.23

TABLE 2.—*continued*

Substituent	<i>meta</i>	<i>para</i>	Substituent	<i>meta</i>	<i>para</i>
NMe ₂	-0.05 ^b	-0.83 ^c	Br	0.39	0.27 ^b
		(-0.12) ^{d,f}			
NH ₃ ⁺	1.13 ⁱ	1.70 ⁱ	I	0.35	0.30 ^b
NH ₂ Me ⁺	0.96		IO ₂	0.70 ^c	0.76 ^c
NMe ₃ ⁺	0.86 ^f	0.82 ^c	AsO ₃ H ⁻		-0.02
NH ₂ Et ⁺	0.96		SeMe	0.1 ^c	0.0 ^c
NHAc	0.21 ^c	0.00 ^c	-SeCN		0.66
NHBz	0.22	0.08			
NH·NH ₂	-0.02	-0.55			
NH·OH	-0.04	-0.34			
N=NPh		0.64			
NO ₂	0.71	0.78			
		(1.24) ^f			
NO		0.12			

^aExcept where indicated, all values are from H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191. ^bH. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. chim.*, 1959, **78**, 815. ^cD. H. McDaniel and H. C. Brown, *J. Org. Chem.*, 1958, **23**, 420. ^dF. G. Bordwell and P. J. Boutan, *J. Amer. Chem. Soc.*, 1956, **78**, 854. ^eM. Charton, *J. Org. Chem.*, 1963, **28**, 3121. ^fFor phenols. ^gL. M. Yagupolskii and L. N. Yagupolskaya, *Doklady Akad. Nauk S.S.S.R.*, 1960, **134**, 1381. ^hW. N. White, R. Schlitt, and D. Gwynn, *J. Org. Chem.*, 1961, **26**, 3613. ⁱFrom data in D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution", Butterworths, London, 1965. ^jFrom data in G. Kortüm, W. Vogel, and K. Andrussov, "Dissociation Constants of Organic Acids in Aqueous Solution", Butterworths, London, 1961. ^kEstimated by use of Charton's graphical method (see ref. 8).

the σ constant for a substituent X (e.g., X = H, Me, Ac, Bz) is plotted against the σ constant for XY (e.g., NH₂, NH·Me, NH·Ac, NH·Bz) to give a straight line. Because σ_p for CF₃ is known, the value of σ_p for CF₃·NH- can be read from such a line.

To illustrate the use of Table 2, the pK of 4-methyl-3,5-dinitrobenzoic acid is predicted (from $\sigma_m = 0.71$ for each -NO₂ group, and $\sigma_p = -0.17$ for -CH₃) to be 2.95; the experimental value is 2.97. Similarly, for 3,4-dinitrobenzoic acid the values are 2.71 and 2.82, respectively.

Mainly because of steric effects, no generally applicable σ constants can be assigned to *ortho* substituents. Nevertheless, the apparent σ constants obtained for a particular series can often be used in predicting the effects of further substituents. For this reason, Table 3 lists some of the constants for *ortho*-substituted benzoic acids, while Table 4 gives examples in which these values are used. In all of these cases, agreement with experiment is within ± 0.2 pH unit.

However, as Dippy and Hughes⁹ have pointed out from an examination of the strengths of disubstituted benzoic acids, the additivity principle breaks down when the parent acid is sterically disturbed by a substituent group or when strong supplementary resonance interaction is to be expected in view of the relative orientation (e.g., in 2-hydroxy-3-nitrobenzoic

⁹ J. F. J. Dippy and S. R. C. Hughes, *Tetrahedron*, 1963, **19**, 1527.

acid). Examples where these effects lead to differences exceeding ± 0.2 pH unit are given in Table 5. Most of these exceptions have two *ortho* substituents.

TABLE 3. *Apparent σ constants for ortho substituents in benzoic acids*

Substituent	σ_{ortho}	Substituent	σ_{ortho}
Me	0.29	OH	1.22
Et	0.41	OMe	0.12
Pr ^l	0.56	OEt	-0.01
Ph	0.74	OPr ⁿ	-0.04
2,3-[CH] ₄ (α -naphthyl)	0.50	OPr ^l	-0.04
-CN	~ 1.06	OPh	0.67
CO ₂ H	0.95 ^a	OAc	-0.37
CO ₂ ⁻	-0.91 ^a	F	0.93
CO-NH ₂	~ 0.45	Cl	1.28
NO ₂	1.99	Br	1.35
NH ₃ ⁺	2.15	I	1.34

^aStatistical correction applied.

TABLE 4. *Some pK values of substituted benzoic acids, predicted from the constants in Tables 2 and 3*

Substituent	pK		Substituent	pK	
	Calc.	Found		Calc.	Found
2,4-Me ₂	4.08	4.18	2,4-(NO ₂) ₂	1.43	1.42
2,5-Me ₂	3.98	3.98	2,5-(NO ₂) ₂	1.50	1.62
3,4-Me ₂	4.44	4.41 ^a	3,4-(NO ₂) ₂	2.71	2.82 ^a
3,5-Me ₂	4.34	4.30 ^a	3,5-(NO ₂) ₂	2.78	2.82 ^b
3,4,5-(OMe) ₃	4.31	4.13 ^c	4-Me-3,5-(NO ₂) ₂	2.95	2.97 ^a
2,3-(OH) ₂	2.88	2.91 ^a	2-Cl-3-NO ₂	2.21	2.02
2,4-(OH) ₂	3.35	3.22	2-Cl-4-NO ₂	2.14	1.96
2,5-(OH) ₂	2.88	2.95 ^a	2-Cl-5-NO ₂	2.21	2.17
3,4-(OH) ₂	4.47	4.49 ^a	2,4-Cl ₂	2.69	2.68 ^a
3,5-(OH) ₂	4.00	4.04 ^a	2,5-Cl ₂	2.55	2.47 ^a
2-OH-4-NO ₂	2.20	2.23 ^a	2,6-Cl ₂	1.64	1.59 ^a
2-OH-5-NO ₂	2.27	2.12 ^a	2-OH-5-Cl	2.61	2.63 ^a
			2-OH-5-Br	2.59	2.61 ^a

^aJ. F. J. Dippy and S. R. C. Hughes, *Tetrahedron*, 1963, **19**, 1527. ^bS. L. Gupta and M. C. Gupta, *J. Indian Chem. Soc.*, 1963, **40**, 321. ^cC. G. Nordstrom, J. J. Lindberg, and L. J. Karumaa, *Suomen Kem.*, 1963, **36**, B, 105.

The naphthalenecarboxylic acids are derived from benzoic acid by annelation of a benzene ring which has a σ constant of either 0.50 or 0.04, depending on whether the carboxylic acid is in an α or a β position. Hence, the pK values of naphthoic acids substituted in one or more of positions 2, 3, and 4 can be predicted from the constants in Tables 2 and 3. Thus, for 2-methyl-1-naphthoic acid, predicted pK 3.41, experimental pK 3.11; for 2,3-dimethyl-1-naphthoic acid, predicted 3.48, experimental 3.33. From

the small value of σ for the benzene ring in β -naphthoic acid, replacement of the benzene ring by naphthalene or higher ring systems should have a negligible effect on the pK value. This also suggests that the σ constant for 1-naphthoic acid is due mainly to steric effects. Consistent with this, the experimental pK values for anthracene-1- and -2-carboxylic acids (3.68 and 4.18) agree well with those for the corresponding naphthoic acids (3.70 and 4.16, respectively).

TABLE 5. *Some ortho-substituted benzoic acids for which pK predictions show greater deviations*

Substituent	pK		Substituent	pK	
	Calc.	Found ^a		Calc.	Found ^a
2,3-Me ₂	3.98	3.74	2-Br-6-NO ₂	0.86	1.37
2,6-Me ₂	3.62	3.25	2,6-(OH) ₂	1.76	1.08
4-Bu ^t -2,6-Me ₂	3.84	3.44	2-OH-3-NO ₂	2.27	1.87
2,4,6-Me ₃	3.79	3.44	2-OH-6-NO ₂	0.99	2.24
2,3-(NO ₂) ₂	1.50	1.85	2-OH-3,5-(NO ₂) ₂	1.56	0.70
2,6-(NO ₂) ₂	0.22	1.14	2-OH-6-Cl	1.70	2.63
2,4,6-(NO ₂) ₃	-0.44	0.65	2-OH-6-Me	2.69	3.32
2-Cl-6-NO ₂	0.93	1.34			

^aJ. F. J. Dippy and S. R. C. Hughes, *Tetrahedron*, 1963, **19**, 1527.

Although experimental pK values of 5-, 6-, 7-, and 8-substituted naphthoic acids in water are not at present available, the effects of the substituents can be predicted from a recently suggested quantitative theory for aromatic systems.¹⁰ The σ constant for a substituent at position j , when the reaction centre is at position i , is assumed to be given by

$$\sigma_{ij} = F/r_{ij} + Mq_{ij}$$

where r_{ij} is the distance (in benzene C-C bond lengths) between the atoms to which the substituent and the reaction centre are attached, and q_{ij} is the formal charge at position j produced by attaching $-\text{CH}_2^-$ at position i . The parameter F is a measure of the field set up by the substituent, and M is a measure of the combined π -inductive-mesomeric effect of the substituent. Using this approach, known σ constants for naphthalene are found to be self-consistent within a standard deviation of 0.083 σ unit.¹⁰

In substituted benzene, the relations reduce to

$$\begin{aligned}\sigma_m &= 0.577F \\ \sigma_p &= 0.500F + 0.143M\end{aligned}$$

enabling F and M to be determined. For present purposes, it is convenient to express F and M in terms of σ_m and σ_p , so that, for substituted naphthalenes, any σ_{ij} constant can readily be calculated if σ_m and σ_p are known. The appropriate relationships are given in Table 6. The treatment can be expected to fail if mutual conjugation, hydrogen bonding, or steric interaction is important.

¹⁰ M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, 1962, **84**, 3548.

TABLE 6. *Theoretical σ constants for naphthalene derivatives*

Reaction centre	Substituent	Value ^a of σ_{ij}
1	3	σ_m
1	4	$1.40 \sigma_p - 0.35 \sigma_m$
1	5	$0.35 \sigma_m + 0.35 \sigma_p$
1	6	$0.58 \sigma_m$
1	7	$0.35 \sigma_m + 0.35 \sigma_p$
1	8	σ_m
2	4	σ_m
2	5	$0.58 \sigma_m$
2	6	$0.58 \sigma_m$
2	7	$0.50 \sigma_m$
2	8	$0.35 \sigma_m + 0.35 \sigma_p$

^aDeduced from relations given by M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, 1962, **84**, 3548.

Phenols.—The pK values of phenols at 25° can be predicted from the σ constants for *meta* and *para* substituents, listed in Table 2, by using the relation¹¹

$$pK = 9.92 - 2.23 \sigma$$

Biggs and Robinson¹¹ found that this relation fitted the experimental pK values for fourteen phenols, with a mean deviation of ± 0.04 in pK . Rapoport, Hancock, and Meyers¹² could similarly reproduce the pK values (uncorrected for differences in ionic strength) of thirteen 4-substituted 2-nitrophenols at 25°, with a standard deviation of 0.14, using the equation

$$pK = 6.89 - 2.16 \sigma$$

By including apparent σ constants obtained for *ortho*-substituted phenols, the predictions can be extended to cover phenols substituted in any positions. These apparent σ constants are given in Table 7. Some examples of pK values obtained from them by using the relation

$$pK = 9.92 - 2.23 \Sigma\sigma$$

are included in Table 8.

As an example, the two pK values of vanillic acid (4-hydroxy-3-methoxybenzoic acid) can be predicted as follows: For the carboxylic acid, $\sigma_p\text{OH} = -0.37$, and $\sigma_m\text{OMe} = 0.08$, hence $pK = 4.20 - (0.08 - 0.37) = 4.49$. For the phenol, $\sigma_p\text{CO}_2^- = 0.31$, and $\sigma_o\text{OMe} = 0.00$, hence $pK = 9.92 - 2.23 \times 0.31 = 9.23$. The experimental values are 4.51 and 9.39, respectively.¹³

The smaller size of the hydroxyl group than of the carboxyl group causes less steric interaction with substituents in positions 2 and 6, so that 2,6-

¹¹ A. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 1961, 388.

¹² M. Rapoport, C. K. Hancock, and E. A. Meyers, *J. Amer. Chem. Soc.*, 1961, **83**, 3489.

¹³ C. G. Nordstrom, J. J. Lindberg, and L. J. Karumaa, *Suomen Kem.*, 1963, **36B**, 105.

disubstituted phenols show less deviation from prediction than do the corresponding acids. Results in Table 8 show, however, that resonance stabilisation, either in the anion or in the neutral molecule of a phenol,

TABLE 7. Apparent σ constants for ortho substituents in phenols

Substituent	σ_{ortho}	Substituent	σ_{ortho}
Me	-0.13	CH ₂ OH	0.04
Ph	0.00	CO·NH ₂	0.72
OMe	0.00	F	0.54 ^a
2,3-[CH] ₄ †	0.28	Cl	0.68
CHO	0.75 ^b	Br	0.70
Pr ^l	-0.23	I	0.63 ^a
Bu ^t	-0.52	NO ₂	1.24

^aA. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 1961, 388. ^bC. Postmus, I. A. Kaye, C. A. Craig, and R. S. Matthews, *J. Org. Chem.*, 1964, 29, 2693.

† α -Naphthyl.

TABLE 8. Some pK values of phenols, predicted from the constants in Tables 2 and 7.

Substituent	pK		Substituent	pK	
	Calc. ^a	Found		Calc. ^a	Found
3-Me	10.08	10.09	4-Me	10.30	10.26
3,4-Me ₂	10.46	10.32	3,5-Me ₂	10.23	10.15
2,6-Me ₂	10.50	10.59	2,4,5-Me ₃	10.75	10.57 ^b
3-Ph	9.79	9.64	2,4,6-Me ₃	10.88	10.88
2-CH ₂ OH-4-Me	10.21	10.15	2,4-(CH ₂ OH) ₂	9.65	9.77
2,6-(CH ₂ OH) ₂	9.74	9.66	2,6-(CH ₂ OH) ₂ -4-Me	10.12	9.92
3-OMe	9.74	9.65	4-OMe	10.52	10.21
3-Ac	9.07	9.19	4-Ac	8.81	8.05
3-SMe	9.59	9.53	4-SMe	9.92	9.53
3-SO ₂ ·Me	8.40	9.33	4-SO ₂ ·Me	8.31	7.83
3-F	9.16	9.28	4-F	9.79	9.81
3-Cl	9.09	9.02	4-Cl	9.41	9.38
2,3-Cl ₂	7.58	7.70 ^c	2,4-Cl ₂	7.89	7.85
2,5-Cl ₂	7.58	7.51 ^c	2,6-Cl ₂	6.89	6.79 ^c
3,4-Cl ₂	8.58	8.59 ^c	3,5-Cl ₂	8.27	8.19 ^c
3-Br	9.05	9.03 ^d	4-Br	9.32	9.34
3-I	9.14	0.06 ^d	4-I	9.25	9.31 ^d
3-NO ₂	8.34	8.39 ^d	4-NO ₂	8.18	7.15
2,5-(NO ₂) ₂	5.57	5.22	2,6-(NO ₂) ₂	4.40	3.71
2,4,6-(NO ₂) ₃	2.65	0.42	3,5-Me ₂ -4-NO ₂	8.49	8.24
	(1.62) ^e			(7.47) ^e	
2,4,6-Me ₃ -3-NO ₂	9.30	8.98	2-OMe-5-CHO	9.12	8.89
3-CN	8.56	8.57 ^b	4-CN	8.45	7.95

^aFrom pK = 9.92 - 2.23 $\Sigma\sigma$, with σ constants for *meta*- and *para*-substituted benzoic acids, and from Table 7, unless otherwise indicated. ^bH. C. Ko, W. F. O'Hara, T. Hu, and L. G. Hepler, *J. Amer. Chem. Soc.*, 1964, 86, 1003. ^cR. A. Robinson, *J. Res. Nat. Bur. Stand.*, 1964, A68, 159. ^dA. I. Biggs and R. A. Robinson, *J. Chem. Soc.*, 1961, 388.

^eUsing σ constants for phenols.

can cause predictions to err if σ_p constants from benzoic acids are taken. This effect is marked with *para* substituents such as $-\text{CHO}$, $-\text{NMe}_2$, $-\text{NH}_2$, $-\text{NO}_2$, $-\text{SO}_3^-$, $-\text{CO}_2^-$, and $-\text{COCH}_3$. For this reason, Table 2 includes other values of these constants which should be used for phenols.

Annulation of a benzene ring gives α - or β -naphthol, which, from the σ constants for naphthoic acids, would be expected to have pK values of 8.80 and 9.83 respectively. The experimental values are 9.39 and 9.59. The rather poor agreement probably reflects differences in resonance contributions for acids and phenols, so that it is better to assign specific σ constants of 0.28 and 0.11 (which are obtained from experimental values) for the annelated benzene ring in α - and β -naphthol. Experimental and predicted values for substituted naphthols are compared in Table 9.

TABLE 9. *Predicted and experimental pK values for some substituted naphthols*

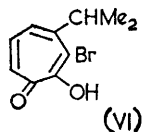
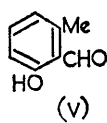
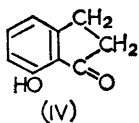
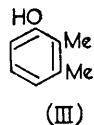
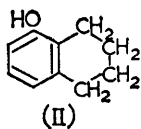
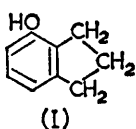
1-Naphthol deriv.	pK		2-Naphthol deriv.	pK	
	Calc. ^a	Found ^b		Calc. ^a	Found ^b
Unsubst.	—	(9.39)	Unsubst.	—	(9.59)
3-NO ₂	7.71	7.86	4-NO ₂	8.09	8.09
3-Cl	8.47	8.40	4-Cl	8.85	8.82
3-Br	8.43	8.34	4-Br	8.80	8.74
3-I	8.52	8.36	4-I	8.89	8.81
3-CO ₂ Me	8.58	8.75	4-CO ₂ Me	8.96	8.88
3-CO ₂ ⁻	9.52	9.52	4-CO ₂ ⁻	9.90	9.78
3-NH ₂	9.39	9.36	4-NH ₂	9.76	9.84
3-NHAc	8.83	8.87	4-NHAc	9.21	9.31
3-CN	7.94	—	4-CN	8.31	8.41

^aFrom $\text{pK} = 9.92 - 2.23 \sum \sigma$, with $\sigma = 0.28$ and 0.11 , respectively, for the annelated benzene ring in 1- and 2-naphthol. ^bA. Bryson and R. W. Matthews, *Austral. J. Chem.*, 1963, **16**, 401.

As discussed for bases,¹ saturated rings fused to aromatic rings have similar effects to two methyl groups attached at the points of fusion. Thus, 5,6,7,8-tetrahydro-2-naphthol (pK 10.42) is comparable with 3,4-dimethylphenol (pK 10.32), while 4-hydroxyindane (I) (pK 10.28) and 5,6,7,8-tetrahydro-1-naphthol (II) (pK 10.29) are comparable with each other and with 2,3-dimethylphenol (III) (pK 10.4—10.6). Similarly, 7-hydroxy-1-indanone (IV) would be expected to have a pK value near to that of 2-formyl-3-methylphenol (V) (predicted 8.40): the reported value¹⁴ (corrected to $I = 0$) is 8.60 at 25°. Experimental pK values for 5-hydroxy-1-indanone (7.70) and 4-hydroxybenzaldehyde (7.63)¹⁵ confirm this similarity. The aromatic character of tropolone suggests that the σ constants for

¹⁴ L. B. Magnusson, C. A. Craig, and C. Postmus, *J. Amer. Chem. Soc.*, 1964, **86**, 3958.

¹⁵ L. B. Magnusson, C. Postmus, and C. A. Craig, *J. Amer. Chem. Soc.*, 1963, **85**, 1711.



phenols might be used for prediction of pK in this series. Results for 5-substituted tropolones support this. Except for 5-SO₃⁻, where the difference is 0.5 pH unit, the experimental pK values¹⁶ of six 5-substituted tropolones fit, within ± 0.1 pH unit, the relation

$$pK = 6.42 - 3.10 \sigma$$

if σ_p constants for phenols are used. (The pK values range from 2.64 to 6.85.) If positions 3 and 4 in tropolones are equated with positions 2 and 3 in phenol, the relation serves to predict pK values for derivatives such as hinokiol (predicted 6.6; experimental 7.21) and 3-bromohinokiol (VI) (4.4, 4.68, respectively).

The similarity of σ constants (including apparent σ_o constants) for anilines and phenols is the basis of the empirical relation¹⁷

$$pK_{\text{phenol}}^{\text{subst.}} = 6.458 + 0.721 pK_{\text{aniline}}^{\text{subst.}}$$

which applies even when one or two substituents are in *ortho* positions. This enables the pK values of phenols to be predicted from the corresponding pK values of anilines.

Thiophenols.—Except for thiophenol itself (pK 6.52)¹⁸, experimental pK values for these compounds in water are not, apparently, available. By refining an earlier treatment,¹⁹ van Bekkum, Verkade, and Wepster²⁰ have found that for the pK values of thiophenols in 48% ethanol (at 25°), 49% ethanol (at 21°), and 95% ethanol (at 21°), ρ is 2.62, 2.42, and 3.02 respectively. The corresponding figures for phenols²⁰ are —, 2.69, and 3.14. This general similarity of substituent effects in thiophenols and phenols can be expected to apply also to purely aqueous solutions, so that ρ for thiophenols in water is unlikely to be very different from 2.2, the

¹⁶ Y. Oka, M. Umehara, and T. Nozoe, *Nippon Kagaku Zasshi*, 1962, **83**, 1197.

¹⁷ R. A. Robinson, *J. Res. Nat. Bur. Stand.*, 1964, **A68**, 159.

¹⁸ M. M. Kreevoy, B. E. Eichinger, F. E. Stary, E. A. Katz, and J. H. Sellstedt, *J. Org. Chem.*, 1964, **29**, 1641.

¹⁹ H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191.

²⁰ H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. chim.*, 1959, **78**, 815.

value for phenols. Hence, the pK values of thiophenols should be given, at least as to order of magnitude, by

$$pK = 6.52 - 2.2 \Sigma\sigma$$

From $\sigma_p\text{CO}_2^- = 0.31$ in Table 2, the predicted pK of *p*-carboxythiophenol is 5.84; the experimental value²¹ is 5.80.

Other Acids.—Published pK values²² at 25° for eighteen monosubstituted benzeneseleninic acids (RSeO_2H) are fitted within ± 0.2 pH unit by the equation

$$pK = 4.78 - 1.03 \sigma$$

Comparable equations, also based on the Hammett equation, have been proposed for arenearsonic acids¹⁹

$$pK_1 = 3.54 - 1.05 \sigma$$

$$pK_2 = 8.49 - 0.87 \sigma$$

arenephosphonic acids¹⁹

$$pK_1 = 1.84 - 0.76 \sigma$$

$$pK_2 = 6.97 - 0.95 \sigma$$

benzenesulphonamides, $\text{X-C}_6\text{H}_4\text{-SO}_2\text{NH}_2$, at 20° and $I = 0.1$ ²³

$$pK = 10.00 - 1.06 \sigma$$

benzenesulphonanilides of the type $\text{X-C}_6\text{H}_4\text{-SO}_2\text{NH-C}_6\text{H}_5$, at 20° and $I = 0.1$ ²³

$$pK = 8.31 - 1.16 \sigma$$

and for benzenesulphonanilides, $\text{C}_6\text{H}_5\text{-SO}_2\text{NH-C}_6\text{H}_4\text{-X}$, at 20° and $I = 0.1$ ²³

$$pK = 8.31 - 1.74 \sigma$$

Aliphatic and Alicyclic Acids

Carboxylic Acids.—Substituent effects in aliphatic and alicyclic systems are approximately additive, so that a relation (the Taft equation) similar to the Hammett equation can be written, using Taft σ^* constants. Table 10 lists such values for some of the more common substituents. On this scale, σ^* is zero for a methyl group, whereas each replaceable hydrogen atom has a value of 0.49.

Experimental pK values of substituted formic acids, RCO_2H , are fitted, usually within ± 0.1 pH unit, by the relation

$$pK = 4.66 - 1.62 \sigma^*$$

²¹ R. J. Irving, L. Nelander, and I. Wadsö, *Acta Chem. Scand.*, 1964, **18**, 769.

²² J. D. McCullough and E. S. Gould, *J. Amer. Chem. Soc.*, 1949, **71**, 674; E. S. Gould and J. D. McCullough, *ibid.*, 1951, **73**, 1109.

²³ A. V. Willi, *Helv. Chim. Acta*, 1956, **39**, 46.

TABLE 10. Taft σ^* constants for aliphatic systems.

R ^a	σ^*	R ^a	σ^*	R ^a	σ^*
H	0.49	CH ₂ Br	1.00	NH·CHO	1.62 ^b
Me	0.00	CH ₂ I	0.85	NHBz	1.68 ^b
Et	-0.10	CH ₂ ·NMe ₃ ⁺	1.90	NH·CO·Et	1.56 ^b
Pr ⁿ	-0.115	CH ₂ ·SO ₂ ·Me	1.32	NAcPh	1.37 ^b
Pr ^l	-0.19	CH ₂ CN	1.30	NHCONH ₂	1.31 ^b
Bu ⁿ	-0.13	CH ₂ ·CH ₂ NO ₂	0.50	NHCO ₂ Et	1.99
Bu ^t	-0.30	CH ₂ ·NHAc	0.43 ^b	N ₃	2.62 ^b
cyclo-C ₆ H ₁₁	-0.15	CH ₂ ·CONH ₂	0.31	NO ₂	4.0 ^c
CH=CH ₂	0.56 ^b	CH ₂ ·CO ₂ ⁻	-0.06 ^b	OH	1.34
CH=CHMe	0.36	2-Thienyl	1.31 ^b	OMe	1.81
Ph	0.60	2-Furoyl	0.25 ^b	OBu ⁿ	1.68 ^b
CH=CHPh	0.41	3-Indolyl	-0.06 ^b	OPh	2.43 ^b
CHPh ₂	0.41	Ac	1.65	ONO ₂	3.86 ^b
α (and β)-naphthyl	0.75 ^b	Bz	2.2 ^c	SH	1.68 ^b
C \equiv CH	2.18 ^b	CO ₂ H	2.08 ^b	SMe	1.56 ^b
C \equiv CPh	1.35	CO ₂ ⁻	-1.06 ^b	SPh	1.87 ^b
CH ₂ F	1.10	CO ₂ Me	2.00	SO ₂ ·Me	3.68 ^b
CHF ₂	2.05	CO·CF ₃	3.7 ^c	SO·Ph	3.24 ^b
CF ₃	2.61 ^b	CO·NH ₂	1.68 ^b	SO ₂ ·Ph	3.55 ^b
CH ₂ Cl	1.05	CO·NHPh	1.56 ^b	-SCN	3.43 ^b
CHCl ₂	1.94	NH ₂	0.62	-SeCN	3.61 ^b
CCl ₃	2.65	NH ₃ ⁺	3.76 ^b	SiMe ₃	-0.81 ^b

^aMost of the listed values are from R. W. Taft, "Steric Effects in Organic Chemistry", ed. M. S. Newman, John Wiley and Sons, Inc., New York, 1956, ch. 13, pp. 607-610. The σ^* constant for the group CH₂R is approximately 0.36 times σ^* for the group R. ^bFrom a more extensive compilation given by M. Charton, *J. Org. Chem.*, 1964, 29, 1222. ^cEstimated from the plot of σ_m versus σ^* .

For substituted acetic acids, RCH₂·CO₂H, the corresponding equation is,

$$pK = 5.16 - 0.73 \sigma^*$$

These relations are useful in obtaining pK values when experimental measurement is difficult, or for estimating the pK of an acid from the pK of its homologue. For example, from σ^* for CF₃ (2.61) the pK of 3,3,3-trifluoropropionic acid is predicted to be 3.25 (found, 3.06).

For the present purpose, however, it is often more convenient to tabulate substituent effects directly in terms of the changes they produce in the experimental pK value of the appropriate acid. The pK of a multisubstituted acid can then be predicted by adding to the pK of the parent compound the sum of the ΔpK values. A collection of these values is given in Table 11. Substituent effects fall off with increasing distance from the acidic centre: as in the previous Review,¹ it is assumed that the effect of a substituent is halved for each additional carbon atom.

Provided that there is at least one α -hydrogen atom in the resulting acid, further alkyl substitution (including branching) in the acetic acid molecule

has only a small effect on the acid strength. For sixteen of seventeen typical members selected from reference 2, the pK range is 4.80 ± 0.09 . Acids such as $\alpha\alpha$ -dimethylpropionic and $\alpha\alpha$ -dimethylbutyric acids, that lack an α -hydrogen atom, have pK values 0.20 unit higher. These two values are taken as standards for predictive purposes, in conjunction with the ΔpK values in Table 11.

TABLE 11. *Acid-strengthening ($-\Delta pK$) effects of substituents attached to α -carbon atoms of aliphatic acids^a*

Substituent	$-\Delta pK$	Substituent	$-\Delta pK$	Substituent	$-\Delta pK$
CH=CH ₂	0.44	NH ₃ ⁺ , NR ₃ ⁺	2.41	F	2.19
CH=CHR	0.25	NHMe ₂ ⁺	2.81 ^b	Cl	1.92
C≡CH	1.44 ^b	NMe ₃ ⁺	2.93 ^b	Br	1.87
Ph	0.46	N ₃	1.73 ^b	I	1.60
α -naphthyl	0.52	NH·CHO	1.33 ^b	SiMe ₃	-0.46 ^b
β -naphthyl	0.50	NHAc	1.09	SH	1.08 ^b
-CN	2.29	NH·CO·Et	1.04 ^b	SR	~1.04
Ac	~1.14	NPhAc	0.85 ^b	SPh	1.24 ^b
CO·NHPh	1.04 ^b	NH·CO·NH ₂	0.88	SCH ₂ Ph	1.03 ^b
CO·NH ₂	1.12	NO ₂	3.08 ^b	S-cyclo-C ₆ H ₁₁	1.57 ^b
CO ₂ H	1.01	OH	0.93	-SCN	2.28 ^b
CO ₂ ⁻	-0.62	OR	1.11	S·CO·NH ₂	1.27 ^b
CO ₂ R	1.41 ^b	OPh	1.61	SO ₃ ⁻	0.56 ^b
CF ₃	1.70	O-cyclo-C ₆ H ₁₁	1.22 ^b	SO ₂ ·R	~2.36
		O·NO ₂	2.50 ^b		

^aReference pK value of acetic and higher acids in 4.80. Except where indicated, ΔpK values are calculated from reference 2. ^bFrom data tabulated by M. Charton, *J. Org. Chem.*, 1964, 29, 1222.

TABLE 12. *Predicted pK values of substituted aliphatic acids*

Acid		pK	Found
Allylacetic acid	Calc. ^a	4.58	4.70
β -Chloropropionic acid		3.84	4.10
β -Iodopropionic acid		4.00	4.09
β -Aminopropionic acid		3.59	3.66
Glucuronic acid (cyclic form)		2.82	3.18
β -Chloro- α -hydroxypropionic acid		2.91	3.12
α -Chloro- β -hydroxypropionic acid		2.41	2.58
$\gamma\gamma\gamma$ -Trifluoro- β -amino-n-butyric acid		2.74	2.76
Mandelic acid		3.41	3.41
Phenylalanine		2.16	2.16
Thiodiacetic acid	pK_1	3.21	3.30
	pK_2	4.22	4.50

^aFrom data in Table 11, halving ΔpK values progressively beyond the α -carbon.

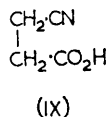
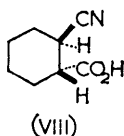
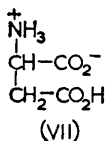
To obtain an estimate of the pK of an aliphatic acid, the effects of alkyl substituents are ignored, so that members of groups such as chloroacetic acid (experimental pK 2.83), α -chloropropionic acid (2.88), and α -chloroisobutyric acid (2.97), or glycine (2.35), alanine (2.34), and α -amino-n-valeric acid (2.32) are assumed to have the same pK . In cases where more than one carboxylic group is present in the molecule, statistical corrections¹ may be necessary.

Some predictions based on Table 11 are compared in Table 12 with experimental values. The examples in Table 13 illustrate the method:

TABLE 13

<i>Succinic acid, pK_1</i>				
pK of simple aliphatic acid	4.80	}	Calc.	3.99
Effect of $-\text{CO}_2\text{H}$ on β -carbon	-0.51		Found	4.22
Statistical factor (log 2)	-0.30			
<i>Succinic acid, pK_2</i>				
pK of simple aliphatic acid	4.80	}	Calc.	5.41
Effect of $-\text{CO}_2^-$ on β -carbon	+0.31		Found	5.64
Statistical factor (log 2)	+0.30			
<i>Cyclohexylcyanoacetic acid</i>				
pK of simple aliphatic acid	4.80	}	Calc.	2.51
Effect of $-\text{CN}$ on α -carbon	-2.29		Found	2.37
<i>Aspartic acid (VII), pK_1 (for $-\text{CO}_2\text{H}$ α- to the $-\text{NH}_3^+$)</i>				
pK of simple aliphatic acid	4.80	}	Calc.	1.88
Effect of $-\text{NH}_3^+$ on α -carbon	-2.41		Found	2.05
Effect of $-\text{CO}_2^-$ on β -carbon	-0.51			
<i>Aspartic acid, pK_2</i>				
pK of simple aliphatic acid	4.80	}	Calc.	3.90
Effect of $-\text{NH}_3^+$ on β -carbon	-1.21		Found	3.87
Effect of $-\text{CO}_2^-$ on β -carbon	+0.31			

(Note that the two $-\text{CO}_2\text{H}$ groups are not equivalent, so that there is no statistical factor.)



Alicyclic acids would be expected to be comparable in strength with the analogous dialkyl aliphatic acids. This is found. Cyclo-propane-, -butane-, -pentane-, and -hexane-carboxylic acids are only slightly weaker (pK range 4.89 ± 0.1) than aliphatic acids. However, unlike open-chain molecules, in cyclic structures the polar groups are restricted in their ability to adopt positions in which their mutual repulsions have a minimum value. Steric interaction, *cis-trans* isomerism, and the possibility of undergoing conformational changes combine to render difficult the prediction

of substituent effects in alicyclic systems. Theoretical treatments that have been tried include those of Bjerrum²⁴ and Kirkwood and Westheimer.²⁵ Bjerrum deduced a quantitative relation between the difference in the pK values of two acidic groups in a diacid and the distance separating them. Kirkwood and Westheimer suggested a more sophisticated mathematical approach to the effect of polar groups on the dissociation of carboxylic acids. In both cases, empirical values must be assigned to the microscopic dielectric constants of the systems and, for alicyclic molecules, any calculations must be based on arbitrarily chosen structures.

Nevertheless, analogy with the corresponding aliphatic acids provides a rough guide to the pK values of alicyclic monocarboxylic acids and to the first (but not to the second) pK values of dicarboxylic acids. For example, *trans*-1-cyanocyclohexane-2-carboxylic acid (VIII) (pK 3.86) is similar to β -cyanopropionic acid (IX) (pK 3.99). The first pK of *trans*-cyclopropane-1,2-dicarboxylic acid (3.80)²⁶ and *trans*-cyclohexane-1,2-dicarboxylic acid (4.18) are comparable with the values (*meso*, 3.77; *racemic*, 3.94) for $\alpha\alpha'$ -dimethylsuccinic acid. Tetramethylsuccinic acid (pK 3.50) serves as a model for *trans*-1,2-dimethylcyclopropane-1,2-dicarboxylic acid (pK 3.70)²⁶. Similarly, the pK values of dimethyl- and diethyl-malonic acids (3.15) and cyclohexane-1,1-dicarboxylic acid (3.45) are comparable. There does not appear to be a simple correlation between the pK values of *cis* and *trans* isomers.²⁶

Stereochemical factors are also important in unsaturated acids such as maleic and fumaric, and the Taft equation is not directly applicable. Charton and Meislich²⁷ have suggested the following empirical correlations between Hammett σ_p constants and the pK values of some non-aromatic unsaturated acids: *trans*-3-substituted acrylic acids, pK = 4.39 — 2.23 σ_p ; *trans*-3-substituted-3-methylacrylic acids, pK = 4.61 — 2.98 σ_p ; *trans*-3-substituted-3-carboxyacrylic acids (substituted maleic acids), pK = 2.02 — 1.92 σ_p . Correlations have also recently been reported²⁸ for *cis*-3-substituted acrylic acids and *cis*-substituted enols (including tetrone acids and 2,5-dihydroxy-1,4-benzoquinones).

Alcohols and Aldehydes.—Alcohols can be regarded as a special class of substituted carboxylic acids in which an oxygen atom has been replaced by two hydrogen atoms. On this basis, the acidities of alcohols and carboxylic acids would be expected to show a similar variation with substituents. This has been found experimentally: the pK values at 25° of seven alcohols of the type R·CH₂OH are reported²⁹ to fit the relation

$$\text{pK} = 15.9 - 1.42 \sigma^*$$

²⁴ N. Bjerrum, *Z. phys. Chem.*, 1923, **106**, 219.

²⁵ J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, 1938, **6**, 506, 513.

²⁶ L. L. McCoy and G. W. Nachtigall, *J. Amer. Chem. Soc.*, 1963, **85**, 1321.

²⁷ M. Charton and H. Meislich, *J. Amer. Chem. Soc.*, 1958, **80**, 5940.

²⁸ M. Charton, *J. Org. Chem.*, 1965, **30**, 974.

²⁹ P. Ballinger and F. A. Long, *J. Amer. Chem. Soc.*, 1960, **82**, 795.

to within about ± 0.2 pH unit for values ranging from 12.24 ($\text{CCl}_3\cdot\text{CH}_2\text{OH}$) to 15.5 (CH_3OH). The slope of the line is similar to that for $\text{R}\cdot\text{CO}_2\text{H}$ (1.62). From the line, the $\text{p}K$ of ethanol in water should be 15.9.

Extension to hydrated aldehydes, $\text{RCH}(\text{OH})_2$, follows if allowance is made for the difference in σ^* constants for H and OH, and for a statistical factor of 0.30 (there are now two equivalent acidic centres), so that the equation becomes

$$\text{p}K = 14.4 - 1.42 \sigma^*$$

Predicted and experimental³⁰ values for formaldehyde are 13.7 and 13.29 respectively.

Thio-alcohols and -acids.—The $\text{p}K$ values at 25° of 24 thiols of the type RCH_2SH are approximately linear with the σ^* constants of the substituents.^{18, 31} The regression line is

$$\text{p}K = 10.22 - 3.50 \sigma^*$$

when σ^* relates to the substituent RCH_2^- , or

$$\text{p}K = 10.54 - 1.47 \sigma^*$$

when σ^* relates to the substituent R^- . The maximum deviation is 0.26 pH unit.

From these relations, and the σ^* constants in Table 10, the following $\text{p}K$ values are predicted—ethanethiol, 10.54; 1,1-dimethylethanethiol (t-butyl mercaptan), 11.27; and 2-hydroxyethanethiol, 9.83. Experimental values (at 25° and $I = 0$) are 10.61, 11.22, and 9.72, respectively.

Because the slope of the line for $\text{R}\cdot\text{CH}_2\text{SH}$ (1.47) is similar to the value (1.42) for the alcohols $\text{R}\cdot\text{CH}_2\text{OH}$, it seems likely that a comparable agreement exists between aliphatic carboxylic acids and the corresponding thio-acids. If so, $\text{p}K$ values of the latter should be predictable from the relation

$$(\text{p}K)_{\text{R}\cdot\text{COSH}} = (\text{p}K)_{\text{R}\cdot\text{CO}_2\text{H}} - 1.14$$

where 1.14 is the difference between the $\text{p}K$ values for $\text{CH}_3\cdot\text{CO}_2\text{H}$ and $\text{CH}_3\cdot\text{COSH}$.²¹

Heterocyclic Acids

Carboxylic Acids.—It has been suggested^{19, 32} that the second, and subsequent, ring nitrogens in heteroaromatic bases such as pyrimidine, quinoxaline, and pteridine can be thought of as substituents to which σ constants can be assigned for use with the appropriate Hammett equation. Rather more tenuously, in 5-membered rings, $-\text{O}-$, $-\text{S}-$, or $-\text{NH}-$ groups

³⁰ R. P. Bell and P. T. McTigue, *J. Chem. Soc.*, 1960, 2983.

³¹ M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgus, and L. T. Ditsch, *J. Amer. Chem. Soc.*, 1960, **82**, 4899.

³² H. H. Jaffé, *J. Chem. Phys.*, 1952, **20**, 1554.

are considered as replacing a $-\text{CH}=\text{CH}-$ portion of a benzene ring. These assumptions, together with the relations given in Table 6, have been shown³³ to lead to satisfactory $\text{p}K_a$ predictions for a wide range of heterocyclic bases. The appropriate σ constants for ring hetero-atoms are listed in Table 14.

TABLE 14. *Sigma constants^a for heteroatoms in heterocyclic rings*

Substnt.	6-membered rings			Substnt.	5-membered rings	
	σ_{ortho}	σ_{meta}	σ_{para}		σ_{ortho}	σ_{meta}
$=\text{NH}-^+$	3.21 ^{bc}	2.18 ^{bc}	2.42 ^{bc}	$-\text{O}-$	1.08 ^{bh}	0.25 ^{bh}
$=\text{N}-$	0.56 ^{cde}	0.73 ^{cde}	0.83 ^{cde}	$-\text{S}-$	0.72 ^{bi}	0.12 ^{bi}
$=\text{NO}^+$ 	—	1.48 ^{fg}	1.35 ^{fg}	$-\text{NH}-$	-0.24 ^{bj}	-0.34 ^{ck}

^aFor aqueous systems at 20–25°. ^bFrom $\text{p}K$ values of parent carboxylic acids. ^cData from D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution", Butterworths, London, 1965. ^dFrom $\text{p}K_a$ values of azapyridines, with $\text{p}K_a = 5.25-5.90$. ^eStatistical factor allowed for. ^fFrom pyridine-1-oxide-carboxylic acids. ^gH. H. Jaffé, *J. Amer. Chem. Soc.*, 1954, **76**, 3527. ^hW. E. Catlin, *Iowa State Coll. J. Sci.*, 1935, **10**, 65. ⁱY. Otsuji, T. Kimura, Y. Sugimoto, and E. Imoto, *Nippon Kagaku Zasshi*, 1959, **80**, 1021. ^jP. Lumme, *Suomen Kem.*, 1960, **33B**, 87. ^kFrom $\text{p}K$ of imidazole.

In applying these values to 5-membered rings, groups attached to the rings are taken to have the same constants as for *ortho*, *meta*, or *para* substitution in benzene rings, depending on the number of carbon atoms by which they are separated from the reaction centre. For example, a 5-substituted 2-furoic acid requires a σ_p constant for the 5-substituent and a σ_o constant for the ring oxygen. Because we are considering this compound to be a substituted benzoic acid, ρ is (by definition) unity. The values of σ_m for $-\text{O}-$, $-\text{S}-$, and $-\text{NH}-$ given in Table 14 (0.25, 0.12, and -0.34) are very similar to the σ_m constants (0.08, 0.15, and -0.30) listed in Table 2 for $-\text{OMe}$, $-\text{SMe}$, and $-\text{NHMe}$. In general, however, some changes in the values of ρ and σ might be expected because the effects of the hetero-atoms are probably modified by the other substituents, especially when the latter occupy *ortho* positions.

Although only a limited number of experimental results are available, predicted and measured $\text{p}K$ values for substituted thiophen-2- and -3-carboxylic acids and 2-furoic acids, given in Table 15, are in reasonable agreement. The same principles might be expected to apply where a ring contains two hetero-atoms, although predictions would be much more uncertain. Thus, for thiazole-2-, -4-, and -5-carboxylic acids (σ constants for $-\text{S}-$ and $-\text{N}-$ being taken from Table 14, and zwitterion formation being assumed negligible) the $\text{p}K$ values are predicted to be 2.92, 3.52, and 2.75 respectively. The experimental values are³⁴ 2.63, 3.81, and 3.18.

³³ D. D. Perrin, *J. Chem. Soc.*, 1965, 5590.

³⁴ Y. Otsuji, T. Kimura, Y. Sugimoto, and E. Imoto, *Nippon Kagaku Zasshi*, 1959, **80**, 1024.

For fused ring systems, annelated benzene rings are taken to have the same σ constants (0.50 and 0.04) as for 1- and 2-naphthoic acids. On this basis, the predicted pK of indole-2-carboxylic acid is 4.40; the experimental value³⁵ is 3.75.

TABLE 15. *Predicted and experimental pK values of substituted thiophen-2- and -3-carboxylic and 2-furoic acids at 25°*

Acid	$\Sigma\sigma^\dagger$	pK	
		Calc. ^a	Found
Thiophen-2-CO ₂ H	(0.72)	(3.49)	3.49 ^b
4-Br	1.11	3.10	3.11 ^c
5-Br	0.99	3.22	3.30 ^b
5-Cl	0.95	3.26	3.41 ^b
4-Pr ^d	0.65	3.56	3.66 ^c
4-Me	0.65	3.56	3.56 ^c
5-Me	0.55	3.66	3.76 ^b
4-NO ₂	1.43	2.78	2.86 ^c
5-NO ₂	1.50	2.71	2.68 ^b
Thiophen-3-CO ₂ H	(0.12)	(4.09)	4.08 ^c
5-Br	0.51	3.70	3.66 ^c
5-Et	0.05	4.16	4.19 ^c
5-NO ₂	0.83	3.38	3.14 ^c
2-Furoic acid	(1.08)	(3.13)	3.12 ^d
5-Br	1.35	2.86	2.84 ^d
5-Cl	1.31	2.90	2.82 ^d
4,5-Cl ₂	1.68	2.53	2.60 ^d
5-I	1.38	2.83	2.94 ^d
5-Me	0.91	3.30	3.42 ^d
5-NO ₂	1.86	2.35	2.06 ^d

[†]Including ring S or O atom.

^aFrom pK of benzoic acid (=4.20) - $\Sigma\sigma$. ^bE. Imoto and R. Motoyama, *Bull. Naniwa Univ.*, 1954, 2A, 127; *CA*, 1955, 49, 9614. ^cY. Otsuji, T. Kimura, Y. Sugimoto, and E. Imoto, *Nippon Kagaku Zasshi*, 1959, 80, 1021. ^dW. E. Catlin, *Iowa State Coll. J. Sci.*, 1935, 10, 65.

Substituted Azoles.—The hydrogen atom attached to the pyrrole nitrogen is feebly acidic, but its acidity is markedly increased if further nitrogens are inserted into the ring. Available experimental results for many substituted azoles, including imidazoles (glyoxalines), pyrazoles, and fused-ring systems such as purines, can be fitted, with an average deviation of ± 0.4 pH unit, by the relation

$$pK = 17.0 - 4.28 \Sigma\sigma$$

if the σ constants from Tables 2 and 14 (for ring nitrogen atoms) are used. Results are given in Table 16.

³⁵ A. Angeli, *Gazzetta*, 1892, 522, ii, 1.

TABLE 16. *Predicted and experimental pK values for the acid dissociation of substituted azoles*

Compound	pK		Compound	pK	
	Calc. ^a	Found ^b		Calc. ^a	Found ^b
Pyrrole	17.0	~16.5	Purine, 2,6-(NH ₂) ₂	10.8	10.81
Pyrazole	14.9	14 ^c	2,6,8-(NH ₂) ₃	12.0	10.85
Imidazole	14.2	14.2	6-Cl	7.8	7.85
4-CONH ₂	12.7	11.8	6-CN	6.8	6.88
4-NO ₂	10.8	9.30	2-NMe ₂	10.0	10.24
4-Ph	13.6	13.42	6-NMe ₂	10.0	10.5
Benzimidazole	13.9	13.2 ^c	6-OMe	9.1	9.18
2-CH ₂ Ph	13.5	12.7	8-OMe	7.6	7.76
2-CH ₂ Ph-6-Me	13.9	13.0	6-Me	9.3	9.05
2-Cl	10.2	9.6	8-Me	9.5	9.40
Naphth[2,3- <i>d</i>]-imidazole	13.9	12.52	6-NHMe	10.4	10.02
3,4-Diazaindole	11.3	11.08 ^c	2-SMe	8.5	8.93
3,5-Diazaindole	11.8	10.88 ^c	6-SMe	8.5	8.76
3-Deazapurine, 2-Cl	10.9	10.19 ^d	8-SMe	7.8	7.70
2,8-Cl ₂	7.5	6.85 ^d	6-CF ₃	7.2	7.35
Purine	9.0	8.93	Pyrazolo[5',4':4,5]-pyrimidine	9.4	9.58
2-NH ₂	9.8	10.00	6-NH ₂	10.5	10.88
6-NH ₂	9.8	9.83	6-SMe	9.2	9.69
8-NH ₂	10.1	9.38			

^aFrom $pK = 17.0 - 4.28 \Sigma\sigma$, and adding a statistical factor where applicable. ^bValues taken from D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution", Butterworths, London, 1965. ^cFrom A. Albert, "Physical Methods in Heterocyclic Chemistry", vol. 1, ed. A. R. Katritzky, Academic Press, New York, 1963, ch. 1. ^dG. B. Barlin, unpublished results.

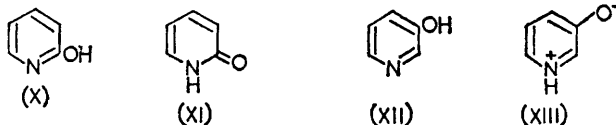
In these calculations, the σ constants for *ortho* substituents are taken from Table 8 (for the pyridine series) of ref. 1. In such cases as pyrazole, where the anion (but not the neutral molecule) has two equivalent reaction centres, a statistical factor of 0.3 (= log 2) is included in the calculated pK value. Extension to substituents in fused-ring systems such as purine has been based on the Dewar and Grisdale relations (given in Table 6), and the σ constants for annelation of benzene rings (to give quinoline and isoquinoline) have been taken to be 0.06 and -0.03, as for pyridine.¹

Predictions fail when there are three or more nitrogen atoms in the 5-membered ring. Thus for 1,2,3-triazole, predicted pK , 12.2; experimental pK , 9.51; and tetrazole, predicted pK , 9.40; experimental pK , 4.59. Even in these cases, however, the equation gives some indication of the effect of adding further substituents. For example the experimental pK of tetrazole is 4.59, and the predicted pK lowering by a 5-iodo-group is 1.50; therefore the predicted pK of 5-iodotetrazole would be 3.09, the experimental value³⁶ being 2.55.

³⁶ A. Albert, "Physical Methods in Heterocyclic Chemistry", vol. 1, ed. A. R. Katritzky, Academic Press, New York, 1963, ch. 1.

Heterocyclic Hydroxy-compounds.—No new principle is involved in the prediction of the pK values of these compounds when they exist as, and are considered as, substituted phenols.

However, when the hydroxyl group is α or γ to a doubly bound ring nitrogen atom, enol–amide tautomerism occurs, as in 2-hydroxypyridine ($X \rightleftharpoons XI$), and the much more weakly acidic amide is the major species.



(In aqueous solutions of 2-hydroxypyridine, the ratio $[XI]/[X]$, is 340.³⁷) Thio–amide–thio–enol ratios are much higher than for the corresponding amide and enol.³⁸

There is appreciable aromaticity in 2-pyridone (XI) and related systems,³⁹ and this is further enhanced by anion formation. Also, ionisation involves the loss of a proton from a ring nitrogen, as in pyrrole, so that, if the Hammett equation is applicable to such systems, a similar ρ value (4.28, see above) might be expected. Table 17 shows that predictions based on the Hammett equation are satisfactory for many substituted hydroxy-pyridines, -quinolines, and -pyrimidines, considered as derived from 2- or 4-pyridone. In 4-hydroxypyrimidines, the amide form having the hydrogen atom on N(3) is preferred. This is an example of the general rule that *in acidic compounds where tautomerism is possible, the weaker acid is favoured* (because it is in this species that the mobile hydrogen is the more strongly bonded). For 2- and 4-pyridones, respectively, the equations are

$$pK = 11.65 - 4.28 \Sigma\sigma$$

$$pK = 11.12 - 4.28 \Sigma\sigma$$

where 11.65 and 11.12 are the experimental values for 2- and 4-pyridone.

However, predictions fail if there is an amino-group in a position *para* to the ring nitrogen atom, as in the following pyrimidines:³⁶ 4-amino-2-hydroxy, (predicted pK 11.35, experimental pK 12.16), 4-amino-6-hydroxy (11.35, 10.05), 4,5-diamino-6-hydroxy (11.5, 9.86), and 4-dimethylamino-6-hydroxy (12.1, 10.49). Agreement is also poor when other ring systems are present, as in 3-hydroxypyridazine (predicted 9.3, experimental³⁶ 10.46), 3-hydroxyisoquinoline (11.8, 9.62), 3-hydroxycinnoline (9.4, 8.61), 4-hydroxyquinazoline (8.7, 9.81), 2-hydroxyquinoxaline (7.9, 9.08), 1-hydroxyphthalazine (9.4, 11.99), 4-hydroxy-1,5-naphthyridine (8.5, 10.01), and 4-hydroxypteridine (4.5, 7.89).

³⁷ A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1956, 1294.

³⁸ A. Albert and G. B. Barlin, *J. Chem. Soc.*, 1959, 2384.

³⁹ J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 1961, 859.

The pK values of thioamides are usually less by 1.9 ± 0.3 pH units than the corresponding amides.

When the hydroxyl group is β to the ring nitrogen, tautomerism leads to zwitterion formation ($XII \rightleftharpoons XIII$) and the tautomeric ratio is much smaller (~ 1 for 3-hydroxypyridine^{37,40}). The ratio is also relatively small where transannular tautomerism is involved.^{41,42} In these cases, the pK value of the phenol (such as XII) can readily be predicted from Tables 2, 6, and 14, and the relation

$$pK_p = 9.92 - 2.23 \Sigma\sigma$$

Similarly, for the zwitterion (such as XIII), considered as a substituted pyridine, the equation is

$$pK_z = 5.25 - 5.90 \Sigma\sigma$$

The equilibrium pK is obtained from the identity

$$pK_{eqm} = \log (1/K_p + 1/K_z)$$

Predicted and experimental values are compared in Table 17.

TABLE 17. Comparison of experimental and predicted pK values of hydroxyheterocycles

(a) α - and γ -hydroxy compounds

Compound	pK		Compound	pK	
	Calc. ^a	Found		Calc. ^a	Found
Pyridine,			Pyridine,		
2-OH-5-CO ₂ Me	10.28	9.92 ^b	2,4-(OH) ₂ (pK_2)	13.9	13 ^b
3-Cl-2-OH	10.07	10.03 ^c	3,5-Cl ₂ -2-OH	8.48	8.48 ^d
4-OH-3-NO ₂	8.08	7.70 ^e	Pyrazine, 2-OH	8.10	8.23 ^b
Quinoline, 2-OH	11.39 ^f	11.76 ^c	Benzimidazole,		
4-OH	10.86 ^f	11.25 ^b	2-OH	12.55 ^{f,g}	11.99 ^h
Pyrimidine, 2-OH	8.83 ^g	9.17 ^b	Pyrimidine, 4-OH	8.53	8.59 ^b
2-OH-5-Br	7.16	7.36 ⁱ	4-OH-6-Cl	7.54	7.43 ^b
2-OH-4-OEt	9.55	10.7 ^j	4-OH-6-OMe	9.68	8.47 ^k
2-OH-4-NMe ₂	12.08	12.30 ^l	4-OH-6-SMe	8.53	8.52 ^m
2-OH-4-NHEt-			4-OH-5-OMe	8.17	8.60 ^b
5-NO ₂	8.10	7.74 ^b	4,5-(OH) ₂ (pK_2)	11.57	11.69 ^h
4-OH-6-CO ₂ ⁻	8.53	8.52 ⁿ	4-OH-2-NH ₂	9.67	9.63 ^h
4-OH-2-OEt-			4-OH-2-NH ₂ -		
5-NO ₂	4.03	4.88 ^o	5-NO ₂	6.77	6.70 ^b
4-OH-5-Me-			4-OH-2-NH ₂ -		
6-SMe	8.83	9.10 ^p	5-Br	8.00	8.05 ^a
4-OH-6-Cl-					
5-Me	7.84	7.77 ^p			

⁴⁰ D. E. Metzler and E. E. Snell, *J. Amer. Chem. Soc.*, 1955, 77, 2431.

⁴¹ S. F. Mason, *J. Chem. Soc.*, 1957, 5010.

⁴² S. F. Mason, *J. Chem. Soc.*, 1958, 674.

TABLE 17.—*continued*
(b) Other hydroxy-compounds

Compound	pK_p	pK_z	pK_{eqm}	Found ^a
	Calc.	Calc.		
Pyridine, 3-OH	8.3	9.4	9.5	8.74
Pyrimidine, 5-OH	6.7	5.4	6.7	6.80
Quinoline, 3-OH	8.0 ₅	9.1	9.1	8.08
5-OH	8.1	7.4	8.2	8.54
6-OH	8.7	7.4	8.7 ₅	8.88
7-OH	8.5	7.5	8.5	8.85
8-OH	7.7	9.1	9.1	9.89
Isoquinoline, 4-OH	7.7	9.6	9.6	8.70
5-OH	8.3 ₅	7.8	8.5	8.45
6-OH	8.7	7.8	8.8	9.15
7-OH	8.9	7.5	8.9	8.88
8-OH	8.1	8.0	8.3	8.40
Cinnoline, 5-OH	7.1	4.5	7.1	7.42
6-OH	7.8	4.5	7.8	7.52
7-OH	7.6 ₅	4.2	7.6 ₅	7.59
8-OH	6.4	4.6	6.4	8.22

^aFrom $pK = 11.65 - 4.28 \Sigma\sigma$ for 2-pyridones, $pK = 11.12 - 4.28 \Sigma\sigma$ for 4-pyridones, and $pK = 9.92 - 2.23 \Sigma\sigma$ for phenols. ^bA. Albert, "Physical Methods in Heterocyclic Chemistry", vol. 1, ed. A. R. Katritzky, Academic Press, New York, 1963, ch. 1. ^cD. J. Brown, personal communication. ^dE. Spinner, personal communication. ^eG. B. Barlin, unpublished results. ^fWith $\sigma = 0.06$ and -0.03 respectively for the annelated benzene ring in quinoline and isoquinoline, as calculated from Table 6 of ref. 1. ^gIncludes a statistical factor of 0.30. ^hD. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution", Butterworths, London, 1965. ⁱD. J. Brown and J. Harper, *J. Chem. Soc.*, 1963, 1276. ^jD. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, 1952, 9, 199. ^kD. J. Brown and T. Teitei, *Austral. J. Chem.*, 1964, 17, 567. ^lI. Wempen, R. Duschinsky, L. Kaplan, and J. J. Fox, *J. Amer. Chem. Soc.*, 1961, 83, 4755. ^mD. J. Brown and J. S. Harper, *J. Chem. Soc.*, 1961, 1298. ⁿM. Claesen and H. Vanderhaeghe, *Bull. Soc. chim. belges*, 1957, 66, 292. ^oD. J. Brown, *J. Chem. Soc.*, 1959, 3647. ^pD. J. Brown and T. Teitei, *J. Chem. Soc.*, 1964, 3204. ^qI. Wempen and J. J. Fox, *J. Med. Chem.*, 1963, 6, 688.

The approximate tautomer ratio, R , can be calculated from the predicted pK values of both forms for a system such as $(XII \rightleftharpoons XIII)^{43}$ or $(X \rightleftharpoons XI)$, by using the relation

$$\log R = pK_{\text{amide}} - pK_{\text{enol}} \\ \text{or } \log R = pK_{\text{amide}} - pK_{\text{ion}}$$

Thus, the predicted pK of 2-quinolone is 11.40, and for (true) 2-hydroxyquinoline it is 8.43, so that the expected tautomer ratio would be $10^{3.0}$; the experimental value³⁷ is $10^{3.5}$.

Discussion

The methods that have been described in this Review emphasise the practical convenience of the Hammett and Taft equations for pK predictions, but by no means exhaust their possible applications. Taft and

⁴³ H. H. Jaffé, *J. Amer. Chem. Soc.*, 1955, 77, 4445.

Lewis⁴⁴ have pointed out that for ionisation reactions in aromatic systems the value of ρ in the Hammett equation depends, in large measure, on the number of atoms, i , between the benzene ring and the acidic or basic centre. They have suggested the general relation $\rho \simeq (2.8 \pm 0.5)^{2-i}$. For purely aqueous systems, the relation $\rho = (2.45 \pm 0.4)^{2-i}$ gives a better fit. Table 18 compares predictions with some experimental results.

TABLE 18. *Hammett ρ values and distance from aromatic rings*

No of atoms from ring	Reaction	ρ	$(2.45)^{2-i}$
$i = 0$	Proton addition to pyridine	5.90 ^a	6.0
	Proton removal from pyrrole	4.28 ^b	
$i = 1$	Proton addition to aniline	2.81 ^a	2.45
	Proton removal from phenol	2.23 ^b	
	Proton removal from benzenesulphonanilides, $C_6H_5-SO_2NH-C_6H_4-X$	1.74 ^c	
$i = 2$	Proton removal from benzoic acid	1.00	1.00
	Proton removal from benzeneseleninic acid	1.03 ^d	
	Proton removal from arenearsonic acids	pK_1 1.05 ^e , pK_2 0.87 ^e	
	Proton removal from arenephosphonic acids	pK_1 0.76 ^e , pK_2 0.95 ^e	
	Proton removal from benzenesulphonamides	1.06 ^c	
	Proton removal from benzenesulphonanilides, $X-C_6H_4-SO_2NH-C_6H_5$	1.16 ^c	
	Proton removal from (hydrated) $\alpha\alpha\alpha$ -trifluoroacetophenones	1.01 ^f	
$i = 3$	Proton removal from phenylacetic acids	1.11 ^f	
$i = 4$	Proton removal from phenylpropionic acids	0.49 ^g	0.41
		0.21 ^{eh}	0.17

^aJ. Clark and D. D. Perrin, *Quart. Rev.*, 1964, **18**, 295. ^bThis work. ^cA. V. Willi, *Helv. Chim. Acta*, 1956, **39**, 46. ^dJ. D. McCullough and E. S. Gould, *J. Amer. Chem. Soc.*, 1949, **71**, 674; E. S. Gould and J. D. McCullough, *ibid.*, 1951, **73**, 1109. ^eH. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191. ^fR. Stewart and R. van der Linden, *Canad. J. Chem.*, 1960, **38**, 399. ^g $pK = 4.30 - 0.49 \sigma$. ^h $pK = 4.55 - 0.21 \sigma$.

From Table 18, the relation appears likely to be useful in predicting the pK values of other types of aromatic acids where, perhaps, experimental values are available for only one or two members in the series. For example, the pK values of aromatic thio-acids should be given, at least approximately, by the equation

$$pK = 2.61 - 1.0 \Sigma \sigma$$

where 2.61 is the experimental value for thiobenzoic acid.⁴⁵ The results

⁴⁴ R. W. Taft and I. C. Lewis, *J. Amer. Chem. Soc.*, 1958, **80**, 2436.

⁴⁵ G. B. Barlin and D. D. Perrin, unpublished results.

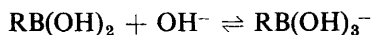
for heterocyclic acids suggests that similar considerations apply to these systems.

However, the (acidic) pK values⁴⁶ of six tripyridylmethanols, $(C_5H_4N)_3COH$, fit (within 0.5 pH unit) the equation,

$$pK = 22.0 - 4.3 \Sigma\sigma$$

where the σ constants for ring nitrogens are taken from Table 14. From the above discussion a ρ value of about unity would be expected. The difference probably stems from the overlap of π -orbitals of each of the three pyridine rings joined to the same carbon atom, thereby reducing the effective distance of the hydroxyl group from the aromatic nuclei.

The apparently anomalous value, $\rho = 2.15$, for arylboronic acids in 25% ethanol,¹⁹ falls into line with prediction if, as has been suggested by McDaniel and Brown⁴⁷ (for a different reason), the ionisation process is



That the Taft parameter, ρ^* , for aliphatic systems also depends mainly on distance from the reaction centre is indicated by the ρ^* values for the dissociation of the following types of acid in water, RNH_3^+ (3.14⁴⁸), RSH (3.50^{18,31}), and ROH (~ 3.9 ³¹), and also for $RCH_2 \cdot NH_3^+$ (1.13) and RCO_2H (1.62). The attenuation factor of 0.36 (= 1/2.8) for each additional carbon atom in the chain is also very similar to the factor for ρ values in aromatic systems.

By analogy with the dissociation of the cations of primary amines, the ρ^* value for the acid dissociation of amides would be expected to be about 3.1. The σ^* constants from Table 10 being used with, as reference, the acidic pK (15.1) of acetamide,⁴⁹ this suggests that the equation

$$pK = 22.0 - 3.1 \Sigma\sigma^*$$

might afford an approximate pK value for any amide, R_1CONHR_2 , for which the σ^* constants of R_1CO and R_2 are known. The few experimental results available for testing this relation are collected in Table 19. The poorer fit for succinimide than for glutarimide may be due to greater ring-strain in the former.

Carbon acids, R_3CH , would also be expected to have ρ^* values of about 3.5 ± 0.4 , and results for substituted ethyl acetoacetates⁵⁰ support this. Five compounds of the type, $CH_3 \cdot COCH(R) \cdot CO_2C_2H_5$ (containing less than 0.4% enolic form), have pK values fitted within ± 0.17 pH unit by the equation

$$pK = 12.59 - 3.44 \sigma^*$$

⁴⁶ J. P. Wibaut and P. P. H. L. Otto, *Rec. Trav. chim.*, 1958, **77**, 1048.

⁴⁷ D. H. McDaniel and H. C. Brown, *J. Amer. Chem. Soc.*, 1955, **77**, 3756.

⁴⁸ H. K. Hall, *J. Amer. Chem. Soc.*, 1957, **79**, 5441.

⁴⁹ G. E. K. Branch and J. O. Clayton, *J. Amer. Chem. Soc.*, 1928, **50**, 1680.

⁵⁰ P. Rumpf and R. Reynaud, *Compt. rend.*, 1960, **250**, 1501.

TABLE 19. *Experimental and predicted pK values for amides and imides.*

Compound	pK	
	Calc. ^a	Found
Benzamide	13.4	14–15 ^b
Glutarimide	11.8 ^c	11.43 ^d
Succinimide	11.8 ^c	9.62 ^e
CF ₃ ·CO·NH·C ₆ H ₅	8.7	9.54 ^f
N-Cyanoacetamide	5.7 ^g	4 ^h
Phthalimide	8.4 ⁱ	7.4 ^h , 8.3 ^j

^aFrom $pK = 22.0 - 3.1 \Sigma\sigma^*$. ^bG. E. K. Branch and J. O. Clayton, *J. Amer. Chem. Soc.*, 1928, **50**, 1680. ^cCH₃·CO·NH·COCH₃ being taken as a model for calculation. ^dG. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162. ^eH. F. Walton and A. A. Schilt, *J. Amer. Chem. Soc.*, 1952, **74**, 4995. ^fP. M. Mader, *J. Amer. Chem. Soc.*, 1965, **87**, 3191. ^g $\sigma^* = 3.61$ being taken for -CN. ^hG. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry", Prentice-Hall, Inc., New York, 1941, p. 268. ⁱC₆H₅·CO·NH·COC₆H₅ being taken as a model for calculation. ^jL. F. Fieser and M. Fieser, "Advanced Organic Chemistry", Reinhold Publ. Corp., New York, 1961, p. 503.

by use of Taft σ^* constants from Table 10 (R varied from Bu^o to Ph.) By replacing CH₃CO by CH₃, and CO₂C₂H₅ (= CO₂CH₃) by NO₂, the acidic pK of nitroethane is predicted to be 9.4. The experimental value⁵¹ is 8.5. On the other hand, a qualitative correlation, but not a straight-line relation, is found between pK values⁵² and σ^* for a similar group of substituted acetylacetones (in their keto-forms).

From the foregoing discussion, a good prediction of a pK value can be expected if the pK value of a compound of the same structure, but lacking one or two of the substituent groups, is taken as reference, and the effects of these substituents on the pK value are then calculated using the appropriate Hammett or Taft equation. Improvement of the simple methods set out above must await more detailed studies of cases where calculations fail.

In the examples so far discussed, ρ^* values relate only to the transmission of effects along a saturated chain. The presence of a double or a triple bond in the chain should lead to an increase in ρ^* value for an ionisation reaction. For the enolic forms of four acetylacetones CH₃COCR=C(OH)-CH₃ (R = H,⁴⁹ Me,⁵³ SO₂Me,⁵³ and Ph⁵²), the equation

$$pK = 9.25 - 1.78 \sigma^*$$

fits the experimental values (range 2.7 to 9.50) within ± 0.2 pH unit. This value of ρ^* is about the same as for formic acid (1.62), although, on the basis of the number of carbon atoms in the chain between substituent and reaction centre, the value should have been near to that for acetic acid (0.73). The same grouping, R-C=C-OH, also occurs in 3-substituted-2-

⁵¹ D. Turnbull and S. H. Maron, *J. Amer. Chem. Soc.*, 1943, **65**, 212.

⁵² P. Rumpf and R. La Riviere, *Compt. rend.*, 1957, **244**, 902.

⁵³ G. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, 1944, **27**, 1701.

hydroxyl-1,4-naphthaquinones, and the plot of experimental pK values⁵⁴ for eight of these compounds against σ^* gives a line of comparable slope, namely

$$pK = 5.16 - 1.40 \sigma^*$$

(This line reproduces the experimental pK values, which range between 2.49 and 5.30, to within ± 0.3 pH unit.) In both cases, the slopes of the lines suggest that there is a substantially complete transfer of an inductive effect across a carbon-carbon double bond, as against about 36% for a carbon-carbon single bond.

⁵⁴ M. G. Ettliger, *J. Amer. Chem. Soc.*, 1950, 72, 3085.