PREDICTION OF THE STRENGTHS OF ORGANIC BASES

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THIS review sets out methods for predicting the approximate thermodynamic pK_a values, in water, of organic bases. With small changes, the same methods should also be applicable to organic acids. Extant compilations of published ionization constants in water, which include 1056 organic acids[1] and 3790 organic bases,[2] cover only a small fraction of known substances in these classes. For the numerous compounds where pK measurements have not been (or cannot be) made, estimates of acidic or basic strength are often required by organic chemists and biochemists.

Many examples of the importance of this information could be given. To obtain spectra of essentially pure ionic species, measurements must be made at pH values at least two units away from pK values.* Again, apparently baffling changes in products obtained under slightly different conditions of pH can sometimes be interpreted in terms of the ionic species undergoing reaction. This is also true of changes in physical properties, such as solubility and extraction by solvents, which govern conditions for the isolation of substances. At a more sophisticated level, comparison of measured and predicted pK values frequently allows a choice to be made between alternative structures for a given compound. Allied to this are applications of pK values to the investigations of equilibria between tautomeric species. Also, a knowledge of the fraction ionized can be valuable to workers concerned with the effects of substances under physiological conditions.[3] Again, an estimated pK value is useful in discussing the properties of a postulated reaction intermediate which is not available for direct measurement. Finally, for the physical-organic chemist, such ionization reactions provide probably the simplest reversible systems for studying and interpreting the effects of molecular structure on chemical reactions.

Throughout this review, the strength of a base will be expressed in terms of the pK_a ($= -\log K_a$) value of its conjugate acid. That is, for the equilibrium, $BH^+ \rightleftharpoons B + H^+$,

$$K_a = (B)(H^+)/(BH^+),$$

where the parentheses denote activities and all species are solvated. Except where stated, all pK_a values are taken from reference 2: they have been

* There are numerous instances in the literature where spectral comparisons are invalidated because this condition is not met.

[1] Kortüm, Vogel, and Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution", Butterworths, London, 1961.

[2] Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution", *Pure and Appl. Chem.*, in the press.

[3] See, *e.g.*, Albert, *Pharmacol. Rev.*, 1952, **4**, 136.

reduced to a common temperature (arbitrarily selected as 20°), by using the approximate relations:[4]

$$-\mathrm{d}(\mathrm{p}K_a)/\mathrm{d}T = (\mathrm{p}K_a - 0{\cdot}9)/T, \text{ for monocations,}$$

and $$-\mathrm{d}(\mathrm{p}K_a)/\mathrm{d}T = \mathrm{p}K_a/T, \text{ for dications.}$$

Qualitatively, the factors which influence ionization constants are well understood[5,6]. These factors also provide the basis of the three main methods for quantitatively predicting pK values, namely:

(1) Prediction from other physical quantities.

(2) Analogy with other substances of known pK_a.

(3) Consideration of effects of substituents on substances of known pK_a.

1. Prediction from other physical properties

The free energy, $\Delta G°$, of ionization is directly related to the pK_a value, thus:

$$\Delta G° = 2{\cdot}303\boldsymbol{RT}.\mathrm{p}K_a$$

In principle, free energies of ionization reactions, and hence pK_a values, should be calculable from thermodynamic cycles involving the formation of gas ions, followed by their solvation. In practice, the uncertainties in the appropriate energy terms are so great as to vitiate any such attempts. Nevertheless, this approach predicts that pK_a values of different substances will fall in the same order in different solvents, so long as solvation effects do not vary widely for the bases examined. Thus, Hall[7] used titrations of bases in glacial acetic acid to obtain estimates of their pK_a values in water: in general, predictions were within about $\pm$ 0·1 pH unit of the directly measured values. This method is unsatisfactory with mixed solvents, mainly because of differential solvation: the solvent sheath around the organic species is different from the bulk phase and varies with the solute. For example, there is no general correlation between apparent pK_a values in 4:1 methylcellosolve–water (for which extensive collections are available[8]) and pK_a values in water.

Many difficulties beset the quantitative study, by theoretical chemical methods, of the basic strengths of nitrogen heterocycles.[9] Recently,[10]

[4] Perrin, *Austral. J. Chem.*, 1964, **17**, 484.

[5] Brown, McDaniel, and Häfliger, "Determination of Organic Structures by Physical Methods", ed. Braude and Nachod, Academic Press, New York, 1955, ch. 14.

[6] Albert, "Physical Methods in Heterocyclic Chemistry", Vol. I, ed. Katritzky, Academic Press, New York, 1963, ch. 1.

[7] Hall, *J. Amer. Chem. Soc.*, 1930, **52**, 5115.

[8] Simon, Lyssy, Moriköfer, and Heilbronner, "Zusammenstellung von scheinbaren Dissoziationskonstanten im Lösungsmittelsystem Methylcellosolve/Wasser", Juris-Verlag, Zürich, 1959; Sommer and Simon, *ibid.*, Vol. II, Juris-Verlag, Zürich, 1961.

[9] See, *e.g.*, Pullman and Pullman, "Les Théories Electroniques de la Chimie Organique", Masson, Paris, 1952, p. 328.

[10] Nakajima and Pullman, *J. Chim. phys.*, 1958, **55**, 793.

however, a correlation has been noted between ionization potentials for electrons on ring-nitrogen atoms (as calculated by a self-consistent molecular field method) and pK_a values. A good straight-line relation between pK_a and calculated ionization potential was found for methylpyridines, but the predictive value of the method is poor. Different lines are required, for example, for aminopyridines, aminoquinolines, and aminoacridines, probably because of differences in solvation energies. Moreover, individual values show a scatter exceeding $\pm$ 1 pH unit about the mean straight lines. Conversely, for the diazines the line passes through the point for quinazoline, although it has been clearly established[11] that the measured pK_a value is a composite one involving, predominantly, a covalently hydrated cation and an "anhydrous" neutral molecule. (The true pK_a of quinazoline lies at least 2 pH units below this value.[11]) This theoretical approach has been extended to purine,[12] pyrimidine and purine bases,[13] and aminoacridines[14] but, for the present purpose, it appears to be inferior to the empirical methods described below.

Similarly, correlations between the relative free energies of ionization of aromatic[15] and *N*-heteroaromatic[16] amines and the π-electron changes accompanying protonation are usually poor because of variations in steric factors, σ-bond energy changes, and solvation effects. A linear relation, confirming theoretical predictions, has been reported between the basic pK values of aromatic aldehydes and a^2, where a is the coefficient of the atomic orbital of the aldehyde carbon atom in the non-bonding molecular orbital.[17]

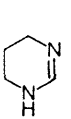
2. Analogy with other substances of known pK_a

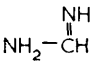
In saturated systems, inductive effects fall off rapidly with distance, so that only atoms which are near-neighbours to basic centres exert a significant effect on the observed pK_a values. This enables the prediction to be made that the pK_a values of primary and secondary aliphatic alkylamines for which the alkyl groups are ethyl or greater will be close to those of ethylamine (10·81 at 20°) and diethylamine (11·09), respectively. The observed range for 31 of 33 reasonably reliable values for primary amines up to docosylamine is 10·77 $\pm$ 0·2, while for 13 of 14 secondary amines up to dioctadecylamine it is 11·15 $\pm$ 0·2.

The same principle suggests the near-equivalence of two alkyl substituents and an unstrained ring. Thus, cyclic amines such as pyrrolidine have pK_a values not very different from diethylamine (11·34 $\pm$ 0·2 for 9 recorded polymethyleneimines and *C*-alkyl derivatives, 11·09 for diethyl-

[11] Albert, Armarego, and Spinner, *J.*, 1961, 2689, 5267.
[12] Pullman, *Tetrahedron Letters*, 1963, 231.
[13] Veillard and Pullman, *J. Theoret. Biol.*, 1963, **4**, 37.
[14] Pullman, *Compt. rend.*, 1962, **255**, 3255.
[15] Hush, *J.*, 1953, 684.
[16] Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 275.
[17] Cuthbertson and Pettit, *J. Amer. Chem. Soc.*, 1963, **85**, 741.

amine), and their *N*-alkyl derivatives are comparable with aliphatic tertiary amines. This similarity is also found for quinuclidine (10·71), which is bicyclic about the nitrogen, and 1-ethylpiperidine (10·55). In the same way, 1,4,5,6-tetrahydropyrimidine (I) (pK_a 13·0) is analogous to formamidine (II) (pK_a 12·6). The high pK values of these two bases are due to an


(I)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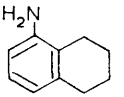
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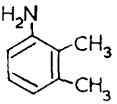
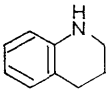

(IV)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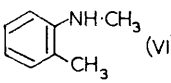

(VI)

amidinium-type resonance involving two equivalent structures in the cation.

Similarly, ionizing aromatic and heterocyclic systems bearing saturated rings can be compared with the corresponding simpler dialkyl structure: for example, 5-amino-1,2,3,4-tetrahydronaphthalene (III) (pK_a 4·42) with 2,3-dimethylaniline (IV) (pK_a 4·77); and 1,2,3,4-tetrahydroquinoline (V) (pK_a 5·03) with *N*,2-dimethylaniline (VI) (pK_a 4·62).

3. Consideration of effects of substituents on substances of known pK_a

A reasonable estimate of the pK_a of a substituted organic base can usually be obtained by considering the ways in which substituents are likely to modify the known pK_a values of related substances. In general, a substituent that stabilises a cation more than a base will increase the ease of ionization, and hence raise pK_a, whereas if the neutral molecule is preferentially stabilised the substituent is base-weakening. The principal ways in which substituents can affect pK values are:

(*a*) *Inductive and Field Effects.*—These are due to dipoles and electrical charges in the molecule. The inductive effect is transmitted along chemical bonds, while the field effect operates through space or, in solutions, through the solvent or the low-dielectric cavity provided by organic solutes. A group which, on insertion into a molecule in place of a hydrogen atom, increases the electron density at other points in a molecule has an electron-donating ($+I$) effect and is base-strengthening. Conversely, an electron-withdrawing ($-I$) effect leads to base-weakening. These effects can be understood in terms of the electrical work required to transfer a proton from the solution to the most basic centre of the molecule. Inductive effects probably fall off rapidly with distance in saturated hydrocarbons, and less rapidly in unsaturated systems (because of the greater mobility of π- than of σ-electrons).

(*b*) *Resonance Effects.*—These arise from the existence in the base or the cation of low-energy molecular orbitals, leading to π-electron delocalisa-

tion and the ready transmission of effects over unsaturated, especially aromatic and heteroaromatic, systems. The electron-donating ($+R$) and -withdrawing ($-R$) resonance effects of substituents need not operate in the same directions as their inductive effects. Where a group has opposite signs for its R and I effects, the overall result will depend on its location in the molecule. For example, resonance effects in *meta*-positions of aromatic molecules are slight, so that the inductive effect is the important one, whereas, in *para*-positions, the R effect is often significant. Resonance effects are also important in *ortho*-substituted aromatic bases, but the strengths of such bases are further modified by steric factors. The inductive and resonance effects of the more common substituents are summarised in Table 1.

TABLE 1. *Inductive and resonance effects of common substituents.*

Effect	Examples
$+I$ (base-strengthening)	O^-, NH^-, alkyl
$-I$ (base-weakening)*	SO_2R, NH_3^+, CF_3, NO_2, —CN, F, Cl, Br, CO_2H, CO_2R, I, COR, OR, SR, Ph, NR_2
$+R$ (base-strengthening)	F, Cl, Br, I, OH, OR, NH_2, NR_2, NH·CO·R, O^-,NH^-, Me, alkyl
$-R$ (base-weakening)	NO_2, —CN, CO_2H, CO_2R, $CO{\cdot}NH_2$, Ph, CO·R, SO_2·R

*Approximately in decreasing order.

pK_a values are very sensitive to factors which modify the free-energy difference between cation and neutral molecule: each incremental change of 1·3 kcal. mole^{-1} alters the pK by 1 pH unit. The favourable energy changes resulting from the considerable charge delocalisation in the cations of guanidines and amidines makes these bases much stronger than the primary amines. The same type of amidinium resonance in the cation of imidazole probably explains why imidazole is a much stronger base than pyrrole. This effect is also found in heteroparaffinic and partially reduced heteroaromatic systems where there is an imino-group alpha to a ring >NH group. It leads to higher pK_a values.

(*c*) *Steric Factors.*—These may be of two types. Primary steric hindrance to protonation may be important where there are bulky groups round a basic centre. The change in configuration at the nitrogen atom on protonation leads to greater internal strain in the cation than in the neutral molecule, and hence is base-weakening.[18] Secondary steric effects may be either base-weakening, if there is steric hindrance to solvation, or base-strengthening, if there is steric inhibition of resonance in the neutral molecule. The lower basic strength of 2,6- dimethylaniline (pK_a 3·98) than of aniline (4·69) and 2,5- dimethylaniline (4·61) is probably an example of the first effect, whereas the increase in basic strength of *NN*-diethylaniline (pK_a 6·65) relative to *NN*-dimethylaniline (pK_a 5·18) may be due to the second of these effects.[5]

[18] For further discussion, see ref. 5, and Taft, in "Steric Effects in Organic Chemistry", John Wiley and Sons, Inc., New York, N.Y. 1956, ch. 13.

Similarly, steric hindrance to solvation on cation formation, in this case from neighbouring hydrogen atoms on the annelated benzene rings, probably accounts for the weakness, relative to aniline, of 9-anthrylamine (pK_a 2·7), 1-aminotriphenylene (pK_a 2·75), 4-aminophenanthrene (pK_a 3·3), and similar *peri-* and *meso*-substituted aromatic amines.

(*d*) *Statistical Considerations.*—When a base contains n groups which have equal probabilities of accepting a proton, the observed pK_{a1} will be greater by log n, for statistical reasons, than the pK_a of the corresponding univalent base. This is a direct consequence of mass-action equilibria: there are n ways in which a proton can add but, once added, only one way in which it can be lost. Conversely, for a symmetrical diacidic base, the observed (numerically smaller) pK_{a2} will be less by log 2 because there is only one way in which a proton can be added to the monocation, but two ways in which it can be lost from the dication.

(*e*) *Tautomerism, including Zwitterion Formation.*—Proton migrations within molecule such as 2- and 4-hydroxypyridine can give rise to cyclic amide types of structures. Also, in amphoteric molecules where the pK_a value of the basic group is greater than, or near to, the pK_a value of the acidic group, zwitterion formation can occur. In both these examples, pK_a values of individual tautomeric forms can differ considerably from one another.

(*f*) *Solvation Effects.*—Solvation is an important factor in stabilising a cation in aqueous solution, both by suitable orientation of water molecules around the basic centre and by hydrogen-bonding of type, $\geqslant N^+—H\cdots OH_2$, between water molecules and hydrogen atoms attached to the basic centre. This stabilisation will vary with the available space around the basic centre: for example, it should be less for pyridine than for aniline. Similar steric effects of substituents were discussed in section (*c*). Also, diminishing the number of hydrogen atoms available for bonding should decrease basic strength. The weakness of tertiary amines relative to secondary amines has been attributed to this effect.[19]

(*g*) *Internal Hydrogen Bonding.*—This may be base-weakening or base-strengthening, depending on whether it is more important in the neutral molecule or in the cation. For example, the amino-group in 8-aminoquinoline, by hydrogen bonding to the ring-nitrogen atom, renders more difficult the protonation of the ring-nitrogen atom of the neutral molecule and, hence, lowers the pK_a value.

(*h*) *Steroisomerism.*—Pairs of geometrical or conformational isomers frequently have different pK_a values, especially when other ionic groups are present, as, for example, in dication or dianion formation. Qualitatively, the differences are generally those to be expected from electrostatic re-

[19] Trotman-Dickenson, *J.*, 1949, 1293; Hall, *J. Amer. Chem. Soc.*, 1957, **79**, 5441.

pulsions, so that the second amino-group of a *cis*-diamine is a weaker base than its *trans*-isomer.

Methods of estimating the net effects of (additional) substituents on pK_a values of aromatic, heterocyclic, and aliphatic-alicyclic compounds are discussed separately in the next three sections. A selection of reference compounds is given in Table 2.

TABLE 2. *Representative* pK_a *values of organic bases at* 20°.

Base	pK_a	Base	pK_a
Pyrrole	−3·80	Typical tertiary alkylamine	10·5
Indole	−2·3	Typical primary alkylamine	10·77
Tetrahydrofuran	−2·1	Ethylamine	10·81
Urea	0·1	Typical secondary alkylamine	11·15
4-Pyrone	0·1	Piperidine	11·28
Diphenylamine	0·77	Acetamidine	~12·4
Pyrimidine	1·23	Guanidine	~13·6
Aniline	4·69		
Quinoline	4·92		
Pyridine	5·23		
Isoquinoline	5·42		

Aromatic Bases

The effects of structural changes on chemical reactions and equilibria can often be expressed as the sum of independent inductive, resonance, and steric contributions. Of these three, usually only the first two are important in *meta*- and *para*-substituted aromatic compounds. In such compounds, linear additive relations for the free-energy changes in many kinetic and equilibrium processes are found if a set of constant values is assigned to the substituent groups.[20]

This empirical observation is expressed in the Hammett equation,[21]

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

where k_0 is the rate constant (or the equilibrium constant) for the unsubstituted aromatic compound, and k is the corresponding value for the substituent to which the constant, σ, relates. These σ values are compounded of resonance and inductive effects which may reinforce or oppose each other. Whereas σ is characteristic of the compound containing the substituent, ρ is a property of the particular reaction and the conditions under which it is carried out (for example, Hammett's original σ scale was based on the standard, $\rho = 1$, for the ionization of benzoic acids in water at 25°). The Hammett equation (and later refinements of it) seem, at present, to offer the best prospects for the prediction of pK_a values of aromatic and hetero-

[20] For a recent review of linear free-energy relations, see Wells, *Chem. Rev.*, 1963, **63**, 171.

[21] Hammett, "Physical Organic Chemistry", McGraw-Hill, New York, 1940, ch. 7; *Chem. Rev.*, 1935, **17**, 125.

aromatic bases. For this reason, Table 3 lists Hammett σ constants for many of the more common substituents, based mainly on ionization

TABLE 3. *Substituent constants for the Hammett equation.*

Substituent	σ_{meta}	σ_{para}	Substituent	σ_{meta}	σ_{para}
H	0	0	OH	0·12*	−0·37*
$B(OH)_2$	0·01	0·45	O^-	−0·71	−0·52
Me	−0·07	−0·17	OMe	0·12	−0·27
Et	−0·07*	−0·15	OEt	0·1*	−0·24*
Pr^n	−0·05†	−0·13	OPr^n	0·1*	−0·25*
Pr^i	−0·07†	−0·15	OPr^i	0·1*	−0·45*
Bu^n	−0·07†	−0·16	OBu^n	0·1*	−0·32
Bu^i		−0·12	OC_5H_{11}	0·1*	−0·34
CHMeEt		−0·12	$O{\cdot}[CH_2]_5{\cdot}CHMe_2$		−0·27
Bu^t	−0·10*	−0·20	$O{\cdot}CH_2Ph$		−0·42
CH_2Bu^i		−0·23	OPh	0·25*	−0·32*
CMe_2Et		−0·19	3,4-$O{\cdot}CH_2{\cdot}O$-		−0·16
CH_2Cl		0·18	$O{\cdot}CF_3$	0·36¶	0·32¶
$CH_2{\cdot}CN$		0·01	OAc	0·39*	0·31*
$CH_2{\cdot}CH_2{\cdot}CO_2H$	−0·03	−0·07	F	0·34	0·06
CH=CHPh	0·14		$SiMe_3$	−0·04*	−0·07*
3,4-$[CH_2]_3$ (fused ring)		−0·26	$SiEt_3$		0·0*
3,4-$[CH_2]_4$ (fused ring)		−0·48	PO_3H^-	0·2*	0·26*
Ph	0·06*	0·01*	SH	0·25*	0·15*
3,4-$[CH]_4$ (β-naphthyl)		0·04*	SMe	0·15*	0·00*
$CH_2{\cdot}SiMe_3$	−0·16*	−0·21*	SEt		0·03*
CHO	0·36	0·22 (0·99)‡	SPr^i		0·07*
CF_3	0·43*	0·54* (0·74)	SMe_2^+	1·00*	0·90*
CO_2H	0·37*	0·45*	$SO{\cdot}Me$	0·52*	0·49*
CO_2^-	−0·1*	0·0*	$SO_2{\cdot}Me$	0·60*	0·72* (1·14)
CO_2Me	0·32	0·44‖ (0·75)	$SO_2{\cdot}NH_2$	0·46*	0·57* (0·80)
CO_2Et	0·37*	0·45* (0·72)	SO_3^-	0·05*	0·09*
$CO{\cdot}NH_2$	0·28	0·36†	-SCN		0·52*
Ac	0·38*	0·50* (0·81)	SAc	0·39*	0·44*
Bz	0·34§	0·46 (0·83)	$S{\cdot}CF_3$	0·35¶	0·38¶
-CN	0·56*	0·66* (1·00)	Cl	0·37	0·23
NH_2	−0·16	−0·66	$GeMe_3$		0·0*
NHMe	−0·30	−0·84*	$GeEt_3$		0·0*

TABLE 3.—*continued*

Substituent	σ_{meta}	σ_{para}	Substituent	σ_{meta}	σ_{para}
NHEt	−0·24	−0·61†	AsO_3H^-		−0·02
$NHBu^n$	−0·34	−0·51†	SeMe	0·1*	0·0*
NMe_2	−0·21	−0·83*	-SeCN		0·66
NH_3^+	0·63	(0·56)	Br	0·39	0·23
NH_2Me^+	0·96		$SnMe_3$		0·0*
NMe_3^+	0·88*	0·82*	$SnEt_3$		0·0*
NH_2Et^+	0·96		I	0·35	0·18*
NHAc	0·21*	0·00*	IO_2	0·70*	0·76*
NHBz	0·22	0·08			
$NH{\cdot}NH_2$	−0·02	−0·55			
NH·OH	−0·04	−0·34			
N=NPh		0·64			
NO_2	0·71	0·78			
		(1·26)			
NO		0·12			

*McDaniel and Brown, *J. Org. Chem.*, 1958, **23**, 420. Unless otherwise indicated, all other values are from Jaffé, *Chem. Rev.*, 1953, **53**, 191. †Charton, *J. Org. Chem.*, 1963, **28**, 3121. ‡Values in parentheses are those needed to fit experimental results for aniline. §White, Schlitt and Gwynn, *J. Org. Chem.*, 1961, **26**, 3613. ¶Yagupolskii and Yagupolskaya, *Doklady, Akad. Nauk S.S.S.R.*, 1960, **134**, 1381. ||Charton and Meislich, *J. Amer. Chem. Soc.*, 1958, **80**, 5940.

constants for benzoic acids. Negative σ constants indicate electron-donation (base-strengthening), whereas positive σ constants imply electron-withdrawal (and hence, base-weakening).

Once the regression line of pK_a on σ-constants has been obtained for a family of aromatic bases, so that ρ is known, the pK_a of any member of this group can be predicted by summing the σ constants for all of the substituents and inserting the total into the Hammett equation.

Where effects are essentially inductive, as for all *meta*- and some *para*-substituents, σ values seem to be true constants, leading to good linear relations for many different reactions and equilibria. Taft and his collaborators[22] called these constants σ° values, and Wepster and his collaborators[23] designated them as σ^n. However, where a *para*-substituent can contribute significantly to "through-resonance"* in the molecule (as in groups such as NO_2, OH, and NH_2), σ values are not constant but vary for different reactions. Attempts have been made to allow for resonance effects by introducing new, σ^-, values for electron-withdrawing substituents conjugated with electron-donating side chains, and σ^+ values where electron-donating substituents are conjugated with electron-withdrawing side chains. Their use for quantitative prediction is limited to the class of reaction for which they have been obtained. Taft, *et al.*[22] endeavoured to

* That is, the effect is transmitted readily from one end of the molecule to the other.

[22] Taft and Lewis, *J. Amer. Chem. Soc.*, 1959, **81**, 5343; Taft, Ehrenson, Lewis, and Glick, *J. Amer. Chem. Soc.*, 1959, **81**, 5352; Taft, *J. Phys., Chem.* 1960, **64**, 1803, 1805, and papers cited therein.

[23] Van Bekkum, Verkade and Wepster, *Rec. Trav. chim.*, 1959, **78**, 815.

separate σ constants into their inductive (σ_I) and mesomeric (σ_R) components, whereas Jaffé[24] originally assumed that substituent effects are due to polarisation of π-electrons. For the present purpose, it is convenient in those cases where *para*-substituents have variable σ constants to obtain the σ values from pK measurements on simple bases and then use them in estimating the pK values of related multi-substituted bases.

No true σ constants can be obtained for *ortho*-substituents, mainly because of variable steric and conjugative effects for the same groups in different reactions. Nevertheless, according to the additivity principle, apparent σ_{ortho} constants (valid only for the reaction conditions under which they are determined) can be used satisfactorily in conjunction with σ_{meta} and σ_{para} constants for prediction. Some of these values, obtained from pK_a determinations on *ortho*-substituted anilines, are listed in Table 4.

TABLE 4. *Apparent σ constants for* ortho-*substituents in anilines.*

Substituent	σ_{ortho}	Substituent	σ_{ortho}
Me	0·10	OMe	0·00
Et	0·05	OEt	0·02
Pr^i	0·03	F	0·47
NH_2	0·00	Cl	0·67
NH_3^+	1·23		
NO_2	1·72	Br	0·71
OH	−0·09	I	0·70

Effects due to two *ortho*-substituents may not be additive (for example, the pK_a value of *o*-methylaniline does not lie midway between those of 2,6-dimethylaniline and aniline), because of steric hindrance to conjugation or to solvation.

With the exceptions given in parentheses in Table 3 (which comprise *para*-substituents conducive to "through-resonance"), published values of σ constants reproduce experimental pK values of anilines substituted in one or more *meta*- or *para*-positions, when the equation

$$pK_a = 4{\cdot}57 - 2{\cdot}81\ (\Sigma\sigma)$$

is used. Agreement is usually within $\pm$ 0·2 pH unit. Extension, by using Table 4, to include *ortho*-substituents, also leads to reasonable predictions, as shown by the representative values given in Table 5. The use of Tables 3, 4, and 5 and the above equation is illustrated by the example of 2,4-dichloro-6-nitroaniline:

$$\begin{aligned} \text{predicted } pK_a &= 4{\cdot}57 - 2{\cdot}81\ (\sigma_{ortho}Cl + \sigma_{para}Cl + \sigma_{ortho}NO_2) \\ &= 4{\cdot}57 - 2{\cdot}81\ (0{\cdot}67 + 0{\cdot}23 + 1{\cdot}72) \\ &= -2{\cdot}8\ (\text{measured } pK_a = -3{\cdot}3) \end{aligned}$$

If X denotes any substituent for which a σ constant is given in Table 3,

[24] Jaffé, *J. Chem. Phys.*, 1952, **20**, 279, 778; *J. Amer. Chem. Soc.*, 1954, **76**, 4261, 5843; 1955, **77**, 274.

σ constants for the groups XY-, where Y may be O, S, NH, CO, or *o*-, *m*-, or *p*-phenylene, can be estimated from the equation, $\sigma_{XY} = a\sigma_X + b$, where a and b are empirical constants.[25] The constants, a and b, are found graphically by using pairs of X and XY- for which experimental values are known. This relation is probably most useful when the substituent leads to instability of the base. For example, σ can be obtained for the group, COCl, by taking X = Cl and Y = CO.

Substitution of hydrogen of the amino-group of aniline changes both the σ and the ρ value. However, except for *NN*-dimethylaniline, there are insufficient reliable results to enable the new values of these parameters to be obtained.

TABLE 5. pK_a *values of some substituted anilines predicted from the constants in Tables* 3 *and* 4.

Derivative	Predicted pK	Observed pK
2,4,6-$(NO_2)_3$	−8·6	−9·4
2,4-$(NO_2)_2$	−3·8	−4·5
2,4-Cl_2-6-NO_2	−2·8	−3·3
4-Cl-2-NO_2	−0·91	−1·11
3-OMe-5-NO_2	2·24	2·13
3,5-$(OMe)_2$	3·83	3·87
3-Br-4-Me	3·95	4·06
2,6-Me_2	4·01	3·97
2,3,5,6-Me_4	4·40	4·36
2,3-Me_2	4·49	4·77
2-OH-4,5-Me_2	5·50	5·26

TABLE 6. *Dependance of* pK_a *at* 20° *on* $\Sigma\sigma$.

Class	Equation
Anilines	$pK_a = 4{\cdot}57 - 2{\cdot}81\Sigma\sigma$
α-Naphthylamines*	$pK_a = 3{\cdot}90 - 2{\cdot}81\Sigma\sigma$
β-Naphthylamines†	$pK_a = 4{\cdot}35 - 2{\cdot}81\Sigma\sigma$
NN-Dimethylanilines	$pK_a = 5{\cdot}13 - 3{\cdot}46\Sigma\sigma$
Pyridines	$pK_a = 5{\cdot}25 - 5{\cdot}90\Sigma\sigma$
Quinolines*	$pK_a = 4{\cdot}90 - 5{\cdot}90\Sigma\sigma$
Isoquinolines‡	$pK_a = 5{\cdot}40 - 5{\cdot}90\Sigma\sigma$

*2-, 3-, and 4-Substituted. †3- and 4-Substituted; fails for 1- and 3-NO_2. ‡1-, 3-, and 4-Substituted.

Naphthylamines can be regarded as substituted anilines, the substituent being an annelated benzene ring which has a σ value of 0·24 and 0·08, respectively, for α- and β-naphthylamine. Using these values, substituted naphthylamines are adequately described by the equation for anilines in Table 6. Results for α-naphthylamines are given in Table 7. Because resonance effects in substituted anilines and substituted β-naphthylamines are not the same, pK_a values of the latter, predicted from σ values for the

[25] Charton, *J. Org. Chem.*, 1963, **28**, 3121.

aniline series, are somewhat lower for substituents with $-R$ effects and somewhat higher for substituents with $+R$ effects.[26] These deviations are usually less than $\pm$ 0·2 pH unit. However, agreement is poor when there is a nitro-group *ortho* to the amino-group, possibly owing to hydrogen bonding.

Similarly, biphenylamines are predictable as anilines containing a phenyl substituent.

TABLE 7. *Comparison of predicted* and experimental* pK_a *values for some* α*-naphthylamines at* 20°.

Substituent	Predicted pK_a	Observed pK_a
2-NO_2	−0·9	−1·7
4-NO_2	0·36	0·54
3-NO_2	1·90	2·09
3-CN	2·33	2·28
3-Br	2·80	2·70
3-Cl	2·86	2·72
3-I	2·92	2·85
3-CO_2Me	3·00	3·16
4-Br	3·25	3·25
3-OMe	3·56	3·30
3-OH	3·57	3·34
3-Me	4·10	4·01
3,4-$(OH)_2$	4·60	~4·47
4-NH_2	6·05†	5·87

*From the equation in Table 6 and the σ constants in Tables 3 and 4. †Corrected for statistical factor.

The Hammett relation can also be used for bases which protonate on atoms other than nitrogen. Thus, the pK_a values of substituted acetophenones are given (usually within $\pm$ 0·2 unit) by the equation

$$pK_a = -6{\cdot}0 - 2{\cdot}6\sigma.$$

The limited experimental data suggest that the pK_a values of substituted benzaldehydes lie along a line of comparable slope. The strengths of substituted benzoic acids as bases are well represented by the equation

$$pK_a = -7{\cdot}26 - 1{\cdot}2\sigma.$$

Heterocyclic bases

If the 3- and the 4-position in pyridine are taken as corresponding to *meta-* and *para*-substitution, respectively, in aniline, a roughly linear plot is obtained for pK_a of pyridines against σ constants of anilines.

This was first pointed out by Jaffé and Doak.[27] Bryson[28] found that the

[26] Bryson, *J. Amer. Chem. Soc.*, 1960, **82**, 4862.
[27] Jaffé and Doak, *J. Amer. Chem. Soc.*, 1955, 77, 4441.
[28] Bryson, *J. Amer. Chem. Soc.*, 1960, **82**, 4871.

data were slightly better represented by drawing two lines, one through results for substituents with $+R$ effects, the other through results for substituents with $-R$ effects. He has also shown that in *meta*-substituted anilines and naphthylamines, and analogous pyridines and quinolines, the inductive parts (σ_I) for the σ values of the substituents are roughly the same.

Once again, anomalies are found with such substituents as OH, CHO, and NO_2 when they occupy position 4 (in these cases, use of the modified σ values of Table 3 does not bring the points into line). For steric and other reasons, the σ_{ortho} constants for aniline would not be expected to apply to pyridine, and Table 8 lists the values that need to be assigned to bring

TABLE 8. *Apparent σ constants from experimental* pK *values of simple pyridine derivatives.*

Substituent	σ_{ortho}	σ_{para}
Me	−0·13	
Et	−0·13	
Pr^n	−0·14	
Pr^i	−0·11	
Bu^t	−0·10	
CH_2Ph	0·02	
$CH_2{\cdot}NH_2Me^+$	0·39	
$CH_2{\cdot}CH_2{\cdot}NH_3^+$	0·25	
CHO	0·23	0·99
CO_2^-	−0·03	
CO_2Me	0·51	
CO_2Et		0·72
NH_2	−0·27	
NO_2		1·26
OH	0·76	0·35
OMe	0·34	−0·21
SH		0·65
SMe	0·28	−0·12
Cl	0·79	
I	0·58	

results for the simpler pyridine derivatives into line. Agreement between predicted and experimental pK_a values for multisubstituted pyridines is comparable with that obtained in the aniline series.

Just as naphthylamine can be looked upon as aniline substituted in two positions by annelation of a benzene ring, quinoline and isoquinoline are derivatives of pyridine. Table 9 shows how σ constants for pyridine predict the pK_a values of substituted quinolines and isoquinolines (positions 1 and 3 in the latter being taken as equivalent).

Insufficient experimental results are available to permit useful tabulation of σ constants for substituents in positions 5, 6, 7, and 8 of naphthylamines, quinoline, and isoquinoline. Nor does there appear to be any simple way of relating σ constants for a substituent at different locations in such mole-

TABLE 9. *Predicted and experimental* pK_a *values of substituted quinolines and isoquinolines at* 20°.

Quinoline	Predicted*	Obsd.	Isoquinoline†	Predicted	Obsd.
3-NO_2	0·7	1·03	4-NO_2	1·2	1·36
CO_2Me	1·9	1·77	4-Br	3·1	3·35
3-Br	2·6	2·72	1-OMe	3·4	3·01
2-OMe	2·9	3·16	3-SMe	3·8	3·37
3-SMe	3·0	3·84	1-SMe	3·8	3·89
2-SMe	3·3	3·67	4-OH	4·7	4·78
3-SH	3·4	2·29	3-Me	6·2	~5·64
4-Cl	3·5	3·77	4-NH_2	6·3	6·26
3-OH	4·2	4·28	1-NH_2	7·0	7·59
3-NH_2	5·0	4·91	3-NH_2	7·0	7·59
2-CO_2^-	5·1	4·95			
3-Me	5·3	5·17			
2-Me	5·7	5·83			
4-Me	5·9	5·67			
2-NH_2	6·5	7·30			
4-OMe	6·5	6·63			
4-NH_2	8·8	9·13			

*From $pK_a = 4{\cdot}90 - 5{\cdot}90\,\Sigma\sigma$, with σ constants from Tables 3 and 8. †From $pK_a = 5{\cdot}40 - 5{\cdot}90\,\Sigma\sigma$.

cules. However, if the σ constants for substituents in these positions in quinoline and α-naphthylamine are the same, the equations in Table 6 lead to the relation:

$$(pK_a)^{\text{subst.}}_{\text{quin.}} = 2{\cdot}1(pK_a)^{\text{subst.}}_{\text{naphth.}} - 3{\cdot}1$$

Similarly, for substituted isoquinolines and β-naphthylamines,

$$(pK_a)^{\text{subst.}}_{\text{isoquin.}} = 2{\cdot}1(pK_a)^{\text{subst.}}_{\text{naphth.}} - 3{\cdot}7$$

Where the pK_a of either the quinoline or the naphthylamine derivative is known, these equations enable the pK_a of the other member of the pair to be predicted. In general, agreement with experimental values is within about ± 0·3 pH unit. Thus, from 5-amino-1-naphthylamine, with pK_a 4·21, the predicted pK_a of 5-aminoquinoline is 5·7 (found 5·42). Similarly, from 7-amino-2-naphthylamine, pK_a 4·66, the pK_a of 7-aminoisoquinoline is predicted to be 6·1 (found 6·19).

Prediction of basic pK_a values for pyrroles, indoles, indolizines, and other π-excessive *N*-heteroaromatic compounds is difficult because protonation can occur on different sites. For example, in pyrrole, protonation on an α-*carbon atom* is preferred and an α-methyl group directs the proton to the opposite α-position, whereas β-methyl substitution favours the adjacent α-site.[29] Correlations have been found between changes in pK_a and

[29] Chiang and Whipple, *J. Amer. Chem. Soc.*, 1963, **85**, 2763.

nuclear magnetic resonance chemical shifts on protonation of methylpyrroles.[29] Protonation on a carbon atom (position 3) has also been suggested to explain the anomalously high pK_a values of 1,2-dialkylpyrrolines.[30] In the absence of the 1-alkyl group, the usual base-weakening effect of an unsaturated carbon–carbon bond is observed.

Where two or more potentially basic centres are present in a molecule it is necessary to decide which is the site to which the proton adds. In some cases this is straightforward. For example, in 3-2′-dimethylaminoethylpyridine the pK_a of 8·99 is clearly for the exocyclic nitrogen (compare trimethylamine pK_a 9·91, and the base-weakening, $-I$, effect of the pyridyl group), whereas the pK_a of 4·36 is for the pyridine nitrogen (compare pK_a~5·6 predicted for 3-ethylpyridine, which would be lowered by the protonated dimethylamino-group). Similar arguments show that the pK_a of 9·70 for 4-dimethylaminopyridine is for the ring-nitrogen atom (compare pK_a ~ 10, predicted from $\sigma_{para} = -0{\cdot}83$ for the dimethylamino-group). Protonation of amino-derivatives of nitrogen-heteroaromatic compounds usually involves a ring-nitrogen atom.[31] Often, however, and particularly when two or more ring-nitrogen atoms are involved, it is necessary to argue by analogy with simpler bases. Thus, 1,6- and 1,7-naphthyridine are aza-derivatives of both quinoline (pK_a 4·92) and isoquinoline (5·42), and it is likely that, because the latter is the stronger base, protonation occurs at the corresponding nitrogen atom (positions 6 and 7, respectively).

Several sites of protonation exist in purines. The predictability (within 0·3 pH unit) of pK values of $N_{(7)}$-, 8-, and $N_{(9)}$-methyl- and 8-aminopurines from the pK_a values for the corresponding benzimidazoles suggests that, in these cases, the site is in the imidazole ring. On the other hand, 2-hydroxylation of benzimidazole depresses the pK_a by more than 7 pH units, whereas in purine there is a slight elevation. This indicates that, in the latter and in other suitable compounds, protonation can also occur in the pyrimidine ring.

In aromatic polyaza-heterocycles, it is a useful approximation that the pK_a of a base can be taken to be the same as the pK_a of the corresponding monoaza-heterocycle in which all except the most basic of the nitrogen atoms is replaced by an aromatic carbon atom bearing a nitro-group. Thus 3-nitropyridine and pyrimidine are comparable (after allowance for statistical factor). This means that heteroaromatic ring-nitrogen atoms, if doubly bound, have much the same $-I$ and $-R$ effects as have nitro-groups. Examples are given in Table 10. This makes it possible to obtain rough estimates of pK_a values of substituted polyaza-heterocycles by comparison with the corresponding nitro-derivatives of pyridine, quinoline, or isoquinoline. Thus, the σ values in Tables 3 and 8, applied to 2,4-diamino-3-nitropyridine, lead to a predicted pK_a of 6.6 for 2,4-diamino-

[30] Adams and Mahan, *J. Amer. Chem. Soc.*, 1942, **64**, 2588.
[31] Osborn, Schofield, and Short, *J.*, 1956, 4191.

pyrimidine (found 7·23). Similarly, for 2-methylthiopyrimidine the predicted pK_a is —0·3 (corrected for the statistical factor) and the experimental value is 0·59 (see, however, p. 319).

TABLE 10. *Comparison of* pK_a *values of polyaza-heterocycles and related nitro-compounds at* 20°.

Polyaza-base	pK_a	Related NO_2-compound	pK_a
Pyrimidine	1·0*	3-nitropyridine	0·8
Quinazoline	~1·5†	4-nitroisoquinoline	1·3
1,5-Naphthyridine	2·50*	5-nitroquinoline	2·69
1,6-Naphthyridine	3·76‡	5-nitroisoquinoline	3·49
1,7-Naphthyridine	3·61‡	8-nitroisoquinoline	3·55
1,8-Naphthyridine	3·06*	8-nitroquinoline	2·55

*Corrected by a statistical factor of 0·30 (= log 2). †True pK_a; the customarily determined value, 3·5, is a composite one involving a covalently hydrated cation. ‡These naphthyridines are analogues of quinoline (pK 4·90) and also of isoquinoline (pK 5·40). They are assumed to protonate on the isoquinoline-nitrogen atom because this should be the more basic centre. The alternative analogues are, respectively, the weaker bases 6- (pK 2·72) and 7-nitroquinoline (2·40).

This generalisation does not apply satisfactorily to pyridazine and other bases in which there is a ring-nitrogen atom next to the basic nitrogen. Nor can it be used for imidazole or its aza-derivatives. Pyridazine (pK_a 2·24) would be expected, from the much greater base-weakening effect of an *ortho-* than of a *meta-* or *para-* ring-nitrogen atom (by analogy with nitro-groups), to be much weaker than pyrimidine (pK_a 1·3) or pyrazine (0·6). Bases such as cinnoline, phthalazine, and 3,4-benzocinnoline, derived from pyridazine by annelation of benzene rings, are also comparable in strength with pyridazine.

Aliphatic, alicyclic, and heteroparaffinic systems

The additivity of substituent effects in aliphatic systems enables σ^* values[32] to be assigned to individual groups. These σ^* values are analogous to Hammett's values for aromatic systems (except that, by definition, σ^* is zero for the methyl group whereas σ is zero for hydrogen, leading to a σ^* value of 0·49 for each hydrogen attached to nitrogen or phosphorus). Typical σ^* values, applicable to groups in primary amines, $R{\cdot}NH_2$, are given in Table 11. The pK_a values of aliphatic amines[33] and phosphines[34] at 25° are fitted by the equations:

$$\begin{aligned}
R{\cdot}NH_2 \quad & pK_a = 13{\cdot}23 - 3{\cdot}14\Sigma\sigma^* \\
RR'NH \quad & pK_a = 12{\cdot}13 - 3{\cdot}23\Sigma\sigma^* \\
RR'R''N \quad & pK_a = 9{\cdot}61 - 3{\cdot}30\Sigma\sigma^* \\
R{\cdot}PH_2 \quad & pK_a = 2{\cdot}46 - 2{\cdot}64\Sigma\sigma^* \\
RR'PH \quad & pK_a = 5{\cdot}13 - 2{\cdot}61\Sigma\sigma^* \\
RR'R''P \quad & pK_a = 7{\cdot}85 - 2{\cdot}67\Sigma\sigma^*
\end{aligned}$$

[32] Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 3120; 1953, **75**, 4231.
[33] Hall, *J. Amer. Chem. Soc.*, 1957, **79**, 5441.
[34] Henderson and Streuli, *J. Amer. Chem. Soc.*, 1960, **82**, 5791.

TABLE 11. *Taft σ* constants for aliphatic systems.*

R	σ*	R	σ*	R	σ*
Cl_3C	2·65	MeO_2C	2·00	$^+Me_3N{\cdot}CH_2$	1·90
MeO	1·81	Ac	1·65	HO	1·34
$Me{\cdot}SO_2{\cdot}CH_2$	1·32	$NC{\cdot}CH_2$	1·30	$Cl{\cdot}CH_2$	1·05
$CF_3{\cdot}CH_2$	0·92	$HC{\equiv}C{\cdot}CH_2$	0·76	NH_2	0·62
Ph	0·60	$Ac{\cdot}CH_2$	0·60	$HO{\cdot}CH_2$	0·555
$Me{\cdot}O{\cdot}CH_2$	0·52	$NO_2{\cdot}[CH_2]_2$	0·50	H	0·49
$Cl{\cdot}[CH_2]_2$	0·385	$Me{\cdot}CH{=}CH$	0·360	$CF_3{\cdot}[CH_2]_2$	0·32
$Ph{\cdot}CH_2$	0·215	$Me{\cdot}CH{=}CH{\cdot}CH_2$	0·13	$Ph{\cdot}[CH_2]_2$	0·08
Me	0	Et	−0·10	Pr^n	−0·115
Bu^n	−0·13	cyclo-C_6H_{11}	−0·15	Pr^i	−0·19
Bu^t	−0·30				

The σ* constant for the group $R{\cdot}CH_2$ is approximately 0·36 times σ* for the group R (Taft, "Steric Effects in Organic Chemistry", John Wiley and Sons, Inc., New York, N.Y., 1956, ch. 13, pp. 607—610).

The use of these equations and Table 11 is illustrated by the case of *N*-ethylbenzylamine:

$$\begin{aligned}\text{predicted } pK_a\ (25°) &= 12{\cdot}13 - 3{\cdot}23\ (\sigma^*Ph{\cdot}CH_2 + \sigma^*\ Et + \sigma^*H)\\ &= 12{\cdot}13 - 3{\cdot}23(0{\cdot}215 - 0{\cdot}10 + 0{\cdot}49)\\ &= 10{\cdot}16\ (\text{measured } pK_a = 9{\cdot}64)\end{aligned}$$

The primary, secondary, and tertiary amines lie on different lines, probably because the σ* value for hydrogen takes no account of hydrogen-bonding, in the cations,[19] by the hydrogen on the nitrogen atoms. The above equations apply only when steric and resonance effects are much smaller than the inductive effect: they fail, for example, with aniline because of π-bond interaction between the nitrogen atom and the benzene ring. In benzoquinuclidine, on the other hand, the phenyl group is constrained in such a position that only inductive effects are important. The σ* value of Ph is, therefore, applicable and, used in conjunction with Tables 2 and 11, leads to predicted pK_a value of 8·1 (experimental is 7·9). Setting $R = NH_2$ gives hydrazine and its derivatives: here again, predictions are satisfactory.

There are insufficient experimental values to test this relation in the imidazole series, but, with two exceptions, known pK_a values of 2-substituted benzimidazoles (ranging from 3·46 for protonated 2-aminomethyl to 6·29 for 2-isopropyl) are fitted within ± 0·2 pH unit by the equation: $pK_a = 6{\cdot}15 - 1{\cdot}4\sigma^*$. Exceptions are the 2-amino- and the 2-hydroxy-derivative: in both cases tautomerism is likely. Similarly, the pK_a values of nine 2-substituted benzimidazoles at 30° in 5% aqueous ethanol and 0·1M-sodium chloride[35] are fitted within ± 0·15 pH unit by the equation: $pK_a = 6{\cdot}01 - 0{\cdot}93\sigma^*$. Substituents in the aromatic ring have smaller effects on the pK_a values; (for example, $\Delta pK_a = 0{\cdot}20$ for 5-methoxybenzimidazole,[35] whereas for the 2-isomer a difference of about 1·7 would be expected.

[35] Rabiger and Joullié, *J. Org. Chem.*, 1964, **29**, 476.

An alternative approach is to assign a typical pK value to each class of amine and to tabulate substituent effects directly in terms of the changes that they produce in pK_a values. The pK_a of a substituted amine can then be predicted from the typical value and the sum of the ΔpK_a values for the various substituents.

The length and extent of branching of an alkyl side chain larger than methyl has very little effect on a pK_a value. Thus, for 24 of 30 typical primary aliphatic amines the range is 10·77 $\pm$ 0·05. For secondary and tertiary amines the typical values are 11·15 and (approximately) 10·5, respectively. Even with bulky alkyl groups the base-weakening steric effect does not usually outweigh the combined electronic effects. For purposes of prediction, the electronic and steric effects of all groups larger than methyl can be taken as approximately equal to those of an ethyl group. For example, the strength of di-t-butylamine (pK_a 11·22[36]) differs only slightly from that of diethylamine (pK_a 11·09). *N*-Methyl-substituted amines are generally weaker bases than corresponding higher homologues by about 0·2 pH unit for each methyl group directly attached to the nitrogen. For example, the pK_a of trimethylamine (9·90) is about 0·6 unit less than the average for tertiary amines.

When several substituents are present, their effects are roughly additive. Further, a substituent (such as OMe, NH_2, or Cl) exerts comparable effects on the pK_a values of primary, secondary, and tertiary bases provided it is at the same distance from the nitrogen atom. Substituent effects diminish with distance from the basic centre, suggested transmission factors ranging from 0·33 to 0·53 for each atom in the chain.[37] In this review we assume that the effect of a substituent is halved for each additional carbon atom. Values of ΔpK_a for some common substituents are given in Table 12. For predictive purposes (*e.g.*, in Tables 13, 14, and 15) we have used constants obtained from pK_a values of β-substituted amines: constants from α-substituted amines are sometimes anomalous.

Although ΔpK_a values usually parallel electronegativities of the groups, some exceptions are observed. Thus, SMe is more base-weakening than OMe, possibly because the latter is more effectively solvated, with consequent lower effectiveness of the C–O dipole. This is probably also the reason why OH, CO_2H and NH_2 are slightly less base-weakening than OMe, CO_2R, and NR_2, respectively.

It was formerly assumed[38] that the inductive effect of a non-ionised carboxyl group is identical with that of an alkoxycarbonyl group, but this has recently been shown to be not quite true,[39] the ester being slightly more base-weakening.

The base-weakening effect of a hydroxy-group separated from a primary

[36] Klages and Sitz, *Chem. Ber.*, 1963, **96**, 2394.
[37] McGowan, *J. Appl. Chem.*, 1960, **10**, 312.
[38] Ebert, *Z. phys. Chem.*, 1926, **121**, 385; Wegscheider, *Monatsh.*, 1895, **16**, 153; 1902, **23**, 287.
[39] Bryson, Davies, and Serjeant, *J. Amer. Chem. Soc.*, 1963, **85**, 1933.

TABLE 12. *Base-weakening ($-\Delta pK_a$) effects of substituents in aliphatic amines*[a].

Substituent	$-\Delta pK_a$ (b)	$-\Delta pK_a$ (c)	Substituent	$-\Delta pK_a$ (b)	$-\Delta pK_a$ (c)
$CH{=}CR_2$	~1·0	~0·5	NH_2		0·8
$C{\equiv}CR$	~2·0	~1·0	NHR, NR_2	~1·7	0·9
Ph[d]	1·4	0·8	NH_3^+, NR_3^+		3·6
—CN	5·8	3·0	NHAc		1·5
CO_2^-	0·8[e], −0·1[f]	−0·2	OH		1·1[g]
CO·R		1·6	OMe, OR		1·2
CO_2R	3·0	1·3	O·CO·R		~1·7
$CO{\cdot}NH_2$	2·8	1·1	SH		1·2
Cl		1·9	SR	~3·5	1·4
F		~1·6	$SiMe_3$	−0·4	−0·4

[a]Typical primary, secondary, and tertiary amines have pK_a values of 10·77, 11·15, and 10·5, respectively. Ring formation increases pK_a by 0·2, *N*-methylation decreases it by 0·2 relative to other *N*-alkylations. [b]On carbon next to basic centre. [c]Substituent two carbon atoms from the basic centre; this figure should be halved for each additional carbon atom between substituent and basic centre. [d]Other aromatic rings have similar values. [e]Adjacent to a primary or secondary amine. [f]Adjacent to a tertiary amine. [g]Variable, see text and examples in Table 14.

or secondary amine by two carbon atoms ranges between 0·4 and 1·2 pH units (cf. p. 316). This variation is probably due to hydrogen-bonding. A similar effect probably explains the pronounced base-weakening effect (about 0·8 unit) of a carboxylate anion in α-amino-acids. This pK_a lowering is not found in α-dialkylamino-acids (where hydrogen bonding is not possible), in *N*-methyliminodiacetic acid (predicted 10·5, found 10·1), or in β-amino-acids. In the last series, a very small base-strengthening is observed. On the other hand, carboxylic esters, carboxylic amides, and, probably, un-ionised carboxylic acids are invariably base-weakening. The constants given in Table 12 satisfactorily reproduce the pK_a values of amino-polycarboxylic acids. Examples include iminodiacetic acid (predicted 9·6; found 9·1), *N'N'*-dimethylethylenediamine-*NN*-diacetic acid (predicted 9·8, 6·5; found 10·1, 6·1), ethylenediamine-*NNN'N'*-tetra-acetic acid (predicted 10·1, 6·8; found 11·0, 6·3, ethylenediamine-*NN'*-diacetic-*NN'*-dipropionic acid (predicted 10·2, 6·9; found 10·1, 6·0), and aspartic acid (predicted 10·2; found 10·2). The rather high experimental value for EDTA may be due to stabilisation of the cation by symmetrical bifurcated hydrogen-bonding.[40]

The use of Table 12 in predicting pK_a values is illustrated by the following examples. The pK_a of the base, $MeO{\cdot}CH_2{\cdot}CH_2{\cdot}N(CH_2{\cdot}CH_2Cl)_2$, is estimated by subtracting from 10·5 (the pK of a typical tertiary alkylamine) the amount of 1·2 pH units (for the OMe group two carbon atoms away) and a further 3·8 pH units (2 × 1·9, for chlorine, also two carbon atoms away). The predicted value, 5·5, agrees with the experimental value, 5·53. Where a substance has several basic centres it is necessary, also, to decide

[40] Chapman, Lloyd, and Prince, *J.*, 1963, 3645.

the sequence in which they are likely to be protonated. Table 13 summarises calculations for triethylenetetramine. Experimental and predicted values are in reasonable agreement.

TABLE 13. *Predicted* pK_a values for triethylenetetramine at 20°.*

$$\overset{1}{H_2N}\cdot[CH_2]_2\cdot\overset{2}{NH}\cdot[CH_2]_2\cdot\overset{3}{NH}\cdot[CH_2]_2\cdot\overset{4}{NH_2}$$

For assumed protonation on $N_{(1)}$ (or $N_{(4)}$):

(i) Typical value for primary amine	10·77	
(ii) Effect of NHR group, 2 carbons distant	−0·9	
(iii) Effect of NHR group, 4 carbons and 1 nitrogen away	−0·11	= 10·0
(iv) Statistical factor†	+0·3	

A similar type of calculation, beginning with a secondary amine value of 11·15, predicts that for protonation on $N_{(2)}$ or $N_{(3)}$ the pK_a value would be 9·6. The figures suggest that the initial protonation is predominantly on the terminal nitrogen atoms.

For the dication protonated on $N_{(1)}$ and $N_{(4)}$:

(i) + (ii) + (iii), above	9·76	
(v) Effect of NH_3^+ group at opposite end	−0·06	= 9·4
(vi) Statistical factor†	−0·3	

For protonation on $N_{(2)}$ and $N_{(4)}$ the predicted pK = 8·9

Further protonation (on $N_{(2)}$) gives a trication:

(vii) Typical value for secondary amine	11·15	
(viii) Effect of $-NH_3^+$ group ($N_{(1)}$)	−3·6	
(ix) Effect of $-NH_3^+$ group ($N_{(4)}$)	−0·45	= 6·5
(ii) + (iv), above	−0·6	

The tetracation is predicted, from (vi) + (vii) + (viii) + (ix) − 3·6 (the last term is for effect of protonated $N_{(2)}$), to have pK_a = 3·2.

Summary

	pK_{a1}	pK_{a2}	pK_{a3}	pK_{a4}
Predicted	10·0	9·4	6·5	3·2
Observed	9·9	9·3	6·7	3·3

*From data in Table 12. †See section on statistical considerations.

Aromatic compounds with an amino- or substituted amino-group in a side chain are conveniently considered as substituted alkylamines. Table 12 shows that a phenyl group has about the same inductive effect as an amino-group. The inductive effects of many substituted phenyl groups and other aromatic systems do not differ substantially from that of a phenyl group provided they are two or more carbon atoms away from the basic centre.

Polymethyleneimines such as pyrrolidine and piperidine can be regarded as dialkylamines, and their pK_a values confirm this view. Thus, 9 out of 10 heteroparaffinic compounds including azetidine, pyrrolidine, piperidine, hexahydroazepine and some *C*-alkyl derivatives have pK_a values in the range 11·34 ± 0·2. The increase of about 0·2 unit over the typical value for acyclic secondary amines (11·15) may arise from constraint of two of the bonds to the nitrogen (because of ring formation), leading to improved

solvation of the cation. A similar increase is noted when open-chain tertiary amines (typical value 10·5) are compared with *N*-alkylpolymethyleneimines (typical value 10·7), so that a ΔpK_a value of 0·2 is added to allow for ring formation when typical values of open-chain secondary and tertiary amines are used to predict the pK_a values of cyclic amines. The factor becomes about 0·3 unit when all three bonds to nitrogen are concerned in ring formation. As in the open-chain amines, *N*-methyl compounds have lower basic strengths than *N*-ethyl or higher homologues (typical value for *N*-methylpolymethyleneimine, 10·4).

In these cyclic bases, substituent effects can be treated in much the same way as for the open-chain analogues. However, it might be desirable to distinguish between substituent effects transmitted by a true inductive process and those transmitted as direct field effects. If the former effect were the more important, the open-chain analogue of morpholine (VII) would be a dialkyl derivative (VIII) of diethanolamine. If a direct field effect predominated, the appropriate analogue would be a dialkyl derivative (IX) of ethanolamine. In practice, the oxygen atom in morpholine

(VII)

$RO{\cdot}CH_2{\cdot}CH_2{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}OR$ (VIII)

$RO{\cdot}CH_2{\cdot}CH_2{\cdot}NHR$ (IX)

(pK_a 8·45) has about the same base-weakening effect as would be expected for both of the oxygen atoms of the diether (VIII) (predicted pK_a 8·75; compare predicted pK_a of 9·95 for IX; R = Et).

This appears to favour an interpretation in terms of inductive effect. However, the oxygen and the nitrogen atom in morpholine are held in closer proximity to each other than, on average, is likely in the open-chain analogues (VIII) and (IX), so that a greater direct field effect of the oxygen atom is to be expected in morpholine. Also, in such molecules, the distinction between inductive and field effects may be somewhat artificial. Eucken[41] suggested that the magnitude of an electrostatic interaction varies inversely with the dielectric constant. Whereas the bulk dielectric constant of water is about 80, values between 1 and 5 are more appropriate to organic molecules, so that the transmission of electrostatic effects through the "low-dielectric cavity" of the latter should be favoured. Thus Bowden[42] has concluded that in a σ-bonded molecule the apparent inductive effect along its chain is due primarily to such a preferred transmission of a field effect. (In π-bonded structures, on the other hand, true inductive effects may also have to be considered.[42]) Hence, our assumption that transmission in cyclic saturated molecules is predominantly through chains is not necessarily in conflict with current views regarding the importance of field effects.[42,43]

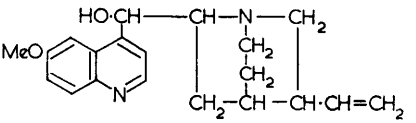
[41] Eucken, *Angew. Chem.*, 1932, **45**, 203.
[42] Bowden, *Canad. J. Chem.*, 1963, **41**, 2781.
[43] Dewar and Grisdale, *J. Amer. Chem. Soc.*, 1962, **84**, 3539, 3541, 3546, 3548.

Some representative examples of pK_a values, predicted as indicated in Table 13 on this assumption, are given in Tables 14 and 15. This assumption overestimates the effect of a substituent when one or more positive charges are involved or when numerous small inductive effects operate along several paths in a relatively small molecular volume. The former is

TABLE 14. *Predicted* and experimental basic* pK_a *values for some natural products at* 20°

Substance	Predicted	Obsd.	Substance	Predicted	Obsd.
Atropine¶	8·8	~10·0	Cysteine	8·8	8·3
Cocaine¶	7·2	~ 8·5	Glutamic acid	10·2	10·11
Codeine	8·4	8·33	Glycylglycine	8·0	8·39
Dihydrocodeine	8·9	8·87	Lysyl-lysine	7·5,	7·64§,
Ephedrine	9·1	9·68		10·0†,	10·20§,
Hyoscine¶	6·4	~7·6		10·8‡	11·18§
Quinine	8·4	8·34	Ornithine	9·1†,	8·82,
Strychnine	7·1	8·4		10·6‡	10·92
Tropine	9·4	10·49	Phenylalanine	9·2	9·35
			Proline	10·55	10·78
			Sarcosine	10·15	10·32
			Serine	8·9	9·35

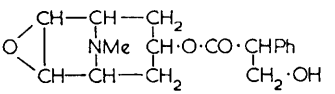
Worked example 1: Quinine, non-aromatic nitrogen.



pK_a of simple tertiary alkylamine	10·5
Effect of ring formation	0·3
Effect of OH, 2 carbons away	−1·1
Effect of arom. system, 2 carbons away	−0·8
Effect of $CH{=}CH_2$, 2 carbons away	−0·5

Predicted pK_a 8·4
Obsd. pK_a 8·34

Worked example 2: Hyoscine.



pK_a of simple tertiary alkylamine	10·5
Effect of ring formation	0·2
Effect of *N*-methyl	−0·2
Effect of OR, 2 carbons away (two paths)	−2·4
Effect of O·CO·R, 3 carbons away (two paths)	−1·7

Predicted pK_a 6·4
Obsd. pK_a ~7·6

*From data in Table 12. †Amino acid N. ‡Terminal N. §"Practical" constant, for LL configuration, I=0·1 (NaCl). ¶Hyoscine, atropine, and cocaine form cations in which the added proton might be expected to be hydrogen-bonded to an oxygen atom in the molecule. All these compounds are about 1·2 pK units stronger than predicted, indicating that a low ΔpK_a value for the oxygen-bearing substituent is applicable (cf. p. 313).

TABLE 15. *Predicted* and observed* pK_a *values for some heteroparaffins at* 20°.

Substance	Predicted	Obsd.
1,4-Diazacycloheptane, pK_{a1}	10·3	10·4
pK_{a2}	5·7	6·7
Morpholine	8·9	8·45
4-2′-Aminoethylmorpholine, pK_{a1}	9·6	9·45
pK_{a2} (ring)	4·7	4·8
4-(2-Benzylcarbonylphenethyl)morpholine	5·9	6·2
4-(3-Cyano-3,3-diphenylpropyl)morpholine	6·0	6·13
4-Ethylmorpholine	8·3	7·9
Piperazine, pK_{a1}	9·8	9·82
pK_{a2}	3·9	5·7
1-Methyl-3,3-diphenylpiperidine	8·5	8·65
Tetrahydro-1,4-thiazine	8·6	9·0

Worked example: 4-2′-aminoethylmorpholine

pK_{a1} (*side-chain* NH_2):

pK_a of simple primary alkylamine	10·77	
Effect of NR_2 group, 2 carbons away	−0·9	Predicted pK_a 9·6
Effect of OR group, 5 atoms away but transmitted by two paths	−0·3	Obsd. pK_a 9·45

If the first proton had been assumed to go on the ring nitrogen atom the predicted pK_{a1} would have been 8·1. Therefore, initial protonation is almost exclusively on the side-chain NH_2.

pK_{a2} (*ring nitrogen atom*):

pK_a of simple tertiary alkylamine	10·5	
Effect of ring formation	0·2	Predicted pK_a 4·7
Effect of NH_3^+, 2 carbons away	−3·6	Obsd. pK_a 4·8
Effect of OR, 2 carbons away but transmitted through two paths	−2·4	

*From data in Table 12.

exemplified by the second pK_a value of piperazine, and the latter by strychnine (Table 14).

The pK_a value of aziridine (8·15) is abnormally low for a secondary amine. So is that of 1-ethylaziridine (8·03) for a tertiary amine. The low values are probably due to the severe ring strain in these substances.

Prediction based on analogy and also on substituent effects

Even when a base does not fall within the groups discussed in the preceding section, its pK_a value can sometimes be predicted by using analogies with structurally similar compounds of known pK. It is assumed that the changes in pK arising from a given substituent are roughly constant for the two series being compared. In Table 16, pK_a values of aminoacridines are predicted from the known pK_a values of acridine, quinoline, and aminoquinolines.

TABLE 16. *Predicted* pK_a values of aminoacridines at* 20°.

Acridine	Corresp. quinoline	ΔpK†	Predicted	Obsd.
1-NH_2	5-NH_2	0·52	6·1	6·00
2-NH_2	6-NH_2	0·69	6·3	5·84
3-NH_2	7-NH_2	1·71	7·3	8·00
4-NH_2	8-NH_2	−0·95	4·6	4·36
9-NH_2	4-NH_2	4·23	9·8	9·95

*From effect of substituent on pK_a of quinoline + pK_a of acridine (5·58). †Amount by which substituent raises the pK_a of quinoline (4·90).

In a similar manner, pK_a values of substituted pyridazines can be estimated from the pK_a of pyridazine by using the same σ constants as for pyridine and assuming that protonation occurs on whichever nitrogen is the more strongly basic as determined by the substituents. (A statistical factor must also be included when the two nitrogen atoms have very similar basic strengths, as for example, when substitution is symmetrical). The results, shown in Table 17, are reasonable except for 3-amino-derivatives:

TABLE 17. *Predicted* pK_a values of pyridazines at* 20°.

Pyridazine†	Predicted	Obsd.	Pyridazine	Predicted	Obsd.
3,6-$(OMe)_2$	1·5	1·61	2,4-Me_2	3·5	~4·1
3-OMe	1·9	2·48	4-OMe	3·5	3·70
3-SMe	1·9‡	2·26	3-NH_2	3·5	~5·2
4-SMe	2·6	3·24	3-NH_2-6-Me	3·9	5·29
4-Me	2·9	2·92	3,4,6-Me_3	4·1	~4·8
3,6-Me_2	3·4	~4·0	4-NH_2	5·8	6·65

*From the pK_a of pyridazine and σ constants for substituted pyridines. †pK_a = 2·24. ‡σ_{ortho} for SMe is taken to be the same as for OMe.

amidinium-type resonance in the cation may be responsible for the poor agreement in this case

In heteroaromatic systems the effect of annelating benzene rings rarely produces pK changes of as much as 1 pH unit. Examples include (i) pyridine to quinoline, isoquinoline, acridine, 5,6-, 5,7-, and 7,8-benzoquinoline, and phenanthridine, (ii) pyridazine to cinnoline, phthalazine, and 3,4-benzocinnoline, and (iii) pyrazine to quinoxaline and phenazine.

Because of the rapid attenuation of substituent effects across increasing numbers of aromatic rings, 1,10-phenanthroline should have a pK_a value not very different from quinoline, if allowance is made for the statistical factor of 0·30 (predicted pK_a 5·2; found 4·83). Similarly, for a symmetrically substituted derivative such as 2,9-dimethyl-1,10-phenanthroline the analogue is the 2-substituted quinoline (predicted 6·0; found 6·2). For unsymmetrical substitution, the pyridine ring containing the more effectively base-weakening groups can be ignored. This rough generalisation is least satisfactory when substituents have strong inductive effects.

Apparent failures of predictions

Notwithstanding the agreements in Table 10 between pK_a values of polyaza-heterocycles and the related nitro-compounds, predicted and experimental values for some polyazanaphthalenes can be widely different (Table 18). These differences, which also persist in many of the derivatives, are due to covalent hydration, mainly of the cation, so that the experimental pK_a values are composite ones.[44] Large differences in absorption spectra of cations and neutral molecules can sometimes be used to detect whether this effect is operating. If the carbon atom to which a hydroxyl group becomes bound on covalent hydration carries an alkyl group, the extent of hydration is markedly reduced. The pK_a value is then closer to expectation and this often leads to the apparent anomaly of a large base-weakening effect produced by an alkyl substituent.

TABLE 18. *Some apparent failures* of predictions based on equating nitro-groups and ring-nitrogen atoms.*

Polyazanaphthalene	Predicted pK_a	Apparent pK_a
Quinazoline	1·3	3·46
1,3,5-Triazanaphthalene	0·2	4·11
1,3,7-Triazanaphthalene	1·6	4·70
1,3,8-Triazanaphthalene	0·4	3·85
1,4,6-Triazanaphthalene	1·7	4·60
Pteridine	−2·5	4·05
1,4,5,8-Tetraazanaphthalene	−3·5	2·47

*Owing to preferential covalent hydration of the cations.

Inspection of Tables 3 and 8 shows that, whereas the apparent σ_{ortho} constants, and also the σ_{para} constants, for OH and OMe are almost the same in the aniline series, they are quite different in the pyridine series. Similar variations are shown by mercapto- and methylthio-groups. They are due to the ability of 2- and 4-hydroxy- and -mercapto-pyridines and other heterocyclic bases to exist in tautomeric (*e.g.*, "pyridone") forms in which the mobile hydrogen atom of the neutral molecule is attached to the ring-nitrogen atom. The protonation behaviour of these tautomers is quantitatively different from the true hydroxy- or mercapto-bases, and the Hammett equation cannot be applied to their derivatives. The α-tautomers are essentially cyclic amides and thioamides, and are weak bases. Typical cyclic amides have pK_a values in the range −2 to +1 (compare acetamide −0·6 and benzamide −2·2). The corresponding sulphur compounds are weaker bases by a further 1—2 pH units.

Tautomerism (involving imine formation) is also possible in α- and γ-heterocyclic amines. The pairs of tautomers have widely differing pK_a values. For example, the pK_a value of 4-aminopteridine is 3·56, and this figure is only slightly affected by *C*- or exocyclic *N*-methylation. However,

[44] Albert, Armarego, and Perrin, "Advances in Heterocyclic Chemistry," Vol. 3, ed. Katritzky, Academic Press, New York, in the press.

methylation on $N_{(1)}$ (which requires an imino-structure) increases the pK_a by about 6 units. The high pK_a values of imino-forms can be attributed to increased resonance in the cation; these bases are comparable in strength to amidines. The large increase in pK following O-methylation of urea also arises in a similar way.

Tautomerism is involved in zwitterion formation, which occurs in amphoteric substances when the pK_a of the basic group is comparable with, or greater than, the pK_a of the acidic group. The neutral species then has a protonated basic centre and an acidic group present as an anion. The cationic portion is strongly acid-strengthening and the anionic part is often slightly base-strengthening relative to hydrogen. When predicting the pK_a value of a basic centre where zwitterion formation is likely to occur, it is necessary to allow for the effect of an ionised acidic group, whereas an un-ionised group must be allowed for if the basic pK_a lies well below that of the acidic group.

The additivity method fails for tertiary bases with partially reduced ring systems, such as pyrroline and tetrahydropyridine, experimental values lying several pH units higher than predicted, especially if an $\alpha\beta$-double bond is present. Protonation on the carbon atom with double-bond migration to the nitrogen and α-carbon atom has been postulated.[30]