The Strengths of Some Organic Bases.

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The basic strengths of twenty-nine organic amines have been determined by potentiometric titration in 50% aqueous alcohol, and the results are discussed.

The percentage of a compound ionised at the physiological pH (7·2) is an important factor in deciding its biological activity (cf. Albert, Rubbo, *et al.*, *Brit. J. Exp. Path.*, 1945, **26**, 160; 1949, **30**, 159). Ionisation constants have now been determined for a series of organic bases exhibiting tuberculostatic activity.

The pK_a values were obtained by potentiometric titration of the base in 50% aqueous alcohol with N/20-hydrochloric acid; in some cases (compounds 24, 25, and 26, Table 4) the hydrochloride of the base was titrated with N/20-sodium hydroxide. The concentration of the base was *ca.* 0·002M and the procedure was that of Carswell, Cymerman, and Lyons (*J.*, 1952, 430).

The effect of 50% alcohol on the ionisation of organic bases has been discussed by many authors (cf. Carswell *et al.*, *loc. cit.*) and it is assumed that the pK_a values of a related series of bases will have the same order in dilute alcohol as in water.

The pK_a values of some primary aromatic amines, determined in 50% alcohol, are given in Table 1. Most of these are structurally related to aniline or 4-aminodiphenyl. The possibility of mesomeric interaction between the lone pair of the uncharged nitrogen atom in a primary aromatic amine increases with the number of fused aromatic rings; this would be expected to enhance the stability of the un-ionised form, and hence decrease the basic strength. The addition of fused benzene rings to aniline decreases the pK_a, the effect of each additional ring becoming less with increasing number of rings (see Nos. 16, 17, 1, and 2 in Table 1).

Table 1. *Ionisation in* 50% *alcohol at* 20°.

No.	Compound	pK_a	No.	Compound	pK_a
1	9-Aminophenanthrene	3·57	10	2-Aminodibenzofuran	3·54
2	2-Aminochrysene	3·42	11	2-Aminofluorenone	2·67
3	4-Aminodiphenylamine	5·24	12	4 : 4′-Diaminodiphenyl disulphide	3·53
4	4-Aminodiphenylmethane	4·54	13	4 : 4′-Diaminodiphenyl sulphone	2·28
5	4-Aminodiphenyl ether	4·44	14	*p-cyclo*Hexylaniline	4·71
6	4-Aminodiphenyl sulphide	3·30	15	*N*-Phenyl-β-naphthylamine	2·84
7	4-Aminodiphenyl sulphone	2·47	16	Aniline	4·33 [1]
8	2-Aminofluorene	4·36	17	β-Naphthylamine	3·8 [2]
9	2-Aminodibenzothiophen	3·80	18	4-Aminodiphenyl	4·05 [1]

[1] Carswell, Cymerman, and Lyons, *loc. cit.* [2] Value estimated from ΔpK_a from aniline to β-naphthylamine *in water* (Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3472).

Compounds 3—7 are *p*-substituted anilines, and the substituents Ph·NH, Ph·CH_2, PhO, H, PhS, and Ph·SO_2 provide dissociation constants which decrease in this order, compatible with our knowledge of the electronic displacements effected by these groups.

Although both –O– and –S– have $+I$ and $-E$ effects, yet oxygen is known to be base-strengthening and sulphur base-weakening when substituted in the *p*-position in aniline and phenol (Table 2). The explanation offered is that in the case of –O– the $-E$ effect is much stronger than the $+I$ effect, and the net result is base-strengthening, while in the case of –S–, despite the slight decrease (Table 3) in the $+I$ effect, the magnitude of the decrease in the $-E$ effect (Baddeley, *J.*, 1950, 663) is such that the net result is base-weakening. In the case of compounds 5 and 6 (Table 1), their pK_a's follow the above order. The pK_a's of the phenoxy- and the phenylthio-compound (Nos. 5 and 6) are lower than those of their methoxy- and methylthio-analogues (Table 2), in agreement with the $+E$ effect of the aryl, and the electron-releasing effect of the alkyl group. Baker, Barrett, and Tweed

(*J.*, 1952, 2831) showed, however, that in the case of the *p*-methoxy- and *p*-methylthiobenzoic acid the overall effect was electron-releasing in *both* cases, both acids being weaker than benzoic acid in spite of a similar large decrease of the $-E$ effect in passing from oxygen to sulphur.

Compounds 8—11 can be considered as derivatives of 4-aminodiphenyl with a substituent –X– *meta* to the amino-group (I; X = CH_2, S, O, and CO respectively); their dissociation constants decrease in this order. The thiophen is seen to be a stronger base than the furan derivative, in agreement with the fact that the $+I$ effect of oxygen is greater than that of sulphur (Table 3). However, in the case of both phenols and anilines, the *m*-methoxy-compounds have higher pK_a's than the *m*-methylthio-analogues (Table 2), which is in the opposite order to their $+I$ effects. The explanation of this anomaly may be similar to that offered (Dippy and Lewis, *J.*, 1936, 644) in the case of *m*-halogenobenzoic acids,

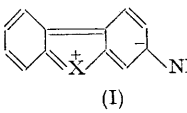

(I)

TABLE 2. *Ionisation* (pK_a *values*) *of substituted phenols and anilines* * *in water at* 25°.

R	*p*-MeO	H	*p*-MeS	*m*-MeO	*m*-MeS	*p*-$MeSO_2$
R·C_6H_4·OH	10·20	9·98	9·53	9·65	9·53	7·83
R·C_6H_4·NH_2	5·25	4·58	4·40	4·20	4·05	1·48

* Hall and Sprinkle, *loc. cit.*; Bordwell and Cooper, *J. Amer. Chem. Soc.*, 1952, **74**, 1058.

TABLE 3. *Ionisation of substituted acetic acids* * *in water at* 25°.

R	H	MeS	MeO	EtS	EtO
R·CH_2·CO_2H	4·75	3·72	3·53	3·74	3·60

* Palomaa, *Chem. Zentr.*, 1912, **2**, 596; Larsson, *Ber.*, 1930, **63**, *B*, 1347; Ramberg, *Ber.*, 1907, **40**, 2588.

where it is postulated that the effect of a mesomeric displacement to the *o*-position is relayed to the adjacent carbon atom by an inductive mechanism. In compounds 9 and 10, however, the observed values are in the expected order of their inductive effects, *m*-RO>RS>H (where X = H is No. 18). Baker, Barrett, and Tweed (*loc. cit.*) found that the acid strength in the *meta*-substituted benzoic acids decreased in the same order. The electromeric effects ($-E$) of oxygen and sulphur being in the order O>S (Baddeley, *loc. cit.*), any mesomeric interaction according to formula (I) would tend to increase the basicity of the furan (No. 10) more than that of the thiophen derivative (No. 9). Since the former is the weaker base, inductive effects appear to predominate and mesomeric interaction must be negligible.

Compounds 12 and 13 show $-SO_2-$ to be more strongly electron-attracting than –S·S–.

N-Phenyl-β-naphthylamine (No. 15) is an appreciably stronger base than diphenylamine (pK_a in water 0·85; Hall and Sprinkle, *loc. cit.*). This at first seems to contradict the results (above) relating increasing number of fused rings to a decrease in pK_a. However,

TABLE 4. *Ionisation of heterocyclic and aliphatic amines in* 50% *alcohol at* 20°.

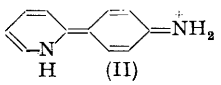
No.	Compound	pK_a
19	4-Amino-2-methylquinoline	9·06 [1]
20	7-Amino-2 : 4-dimethyl-1 : 8-naphthyridine [2]	6·67
21	9-Amino-3-methylphenanthridine [3]	7·04
22	9-Amino-1 : 3-dimethylphenanthridine [3]	7·38
23	9-Amino-5 : 6 : 7 : 8-tetrahydro-3 : 4-benzophenanthridine [3]	6·60
24	9-Amino-5 : 6 : 7 : 8-tetrahydrophenanthridine [3]	7·40
25	2-Amino-4-phenylthiazole	4·06
26	*p*-2-Pyridylaniline	4·77
27	*p*-Piperidinoaniline	6·56
28	4-2′-Diethylaminoethoxydiphenyl [4]	8·30
29	*N*′-4′-Diphenylyl-*NN*-diethylethylenediamine [4]	8·30
30	*N*-4′-Diphenylyl-2-morpholinoethylamine [4]	6·03
31	4-*p*′-Methoxybenzylaminodiphenyl [4]	3·52 [5]
32	4-*p*′-Methoxybenzylideneaminodiphenyl [4]	4·00 [5]

[1] Albert, Goldacre, and Phillips (*J.*, 1948, 2240) give pK_a 9·44 in water at 20°. [2] Source: Bernstein, Stearns, Shaw, and Lott, *J. Amer. Chem. Soc.*, 1947, **69**, 1151. [3] Source: Hollingsworth and Petrow, *J.*, 1948, 1537. [4] Source: Bauer, Cymerman, and Sheldon, *J.*, 1951, 2342. [5] In 66% alcohol.

whereas the symmetrical diphenylamine resonates between equivalent structures which confer extra stability on the un-ionised form, the unsymmetrical *N*-phenyl-β-naphthylamine, although resonating between a greater number of structures, is less stabilised as the structures are not equivalent.

The heterocyclic bases shown in Table 4 are related to 2- or 4-aminopyridine. From resonance considerations (Albert, Goldacre, and Phillips, *loc. cit.*) the heterocyclic nitrogen is the stronger basic centre of the system. The naphthyridine, No. 20, an example of a heterocyclic base with two nitrogen atoms in adjacent rings, is slightly weaker than the related 2-aminoquinoline.

2-Amino-4-phenylthiazole (No. 25) shows the base-weakening effect of the phenyl group as a substituent; 2-aminothiazole has pK_a 5·39 in water at 20° (*idem, ibid.*). This change is similar to the drop in pK_a from aniline to 4-aminodiphenyl (Table 1) but of greater magnitude. *p*-2-Pyridylaniline (No. 26) is a vinylogue of 2-aminopyridine, so that the ring nitrogen atom is the stronger basic centre of the molecule; the yellow colour of the ion can be taken as supporting evidence for the structure (II).



(II)

In compounds 28 and 29 the effects of the 4-diphenylylamino- and the 4-diphenylyloxy-group are either not transmitted through a saturated two-carbon chain or are of the same magnitude.

The ΔpK_a (2·27) between Nos. 29 and 30 is identical with that (2·28 in water at 25°) between diethylamine and morpholine (Hall and Sprinkle, *loc. cit.*; Ingram and Luder, *J. Amer. Chem. Soc.*, 1942, **64**, 3043).

Compound 32 is a Schiff's base; no pK_a determinations on compounds of this type have, to our knowledge, been carried out. No abnormality was observed in the determination, and the titration curves were smooth, giving a pK_a almost identical with that of 4-aminodiphenyl. The possibility that instantaneous hydrolysis to the parent amine had occurred was excluded by a parallel experiment, in which the Schiff's base was recovered unchanged from the titration. The increased pK_a of No. 32, compared with No. 31, may be due to relaying of the base-strengthening (−*E*) effect of the methoxy-group to the nitrogen atom.

Experimental.—A solution of 4-*p'*-methoxybenzylideneaminodiphenyl (0·050 g.) in 66% alcohol (200 c.c.) was titrated with one equivalent of N/20-hydrochloric acid at 20°, and the solution poured into ice-water (450 c.c.) and basified to pH 8—9 with 2N-sodium hydroxide at 0°. Extraction with chloroform and evaporation of the washed (water) and dried (K_2CO_3) extracts gave unchanged Schiff's base (0·042 g.), m. p. 158—162° (from methanol), undepressed on admixture with an authentic sample.

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