83. *The Basic Strengths of Some* N-4-*Diphenylylamidines.*

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The basic strengths of a series of *N*-4-diphenylylamidines (p-Ph·C$_6$H$_4$·NH·CR:NH; R = alkyl, alicyclic and aryl groups) have been determined by potentiometric titration in 50% aqueous alcohol, and the results are discussed.

IT is becoming increasingly evident that an understanding of the relation between chemical constitution and anti-bacterial activity in any given series of compounds cannot be reached without an investigation of certain physico-chemical factors, notably the percentage of compound ionised at the physiological pH (7·2), the surface area of the molecule, and its partition between lipoid and aqueous phases (Albert, Rubbo, *et al.*, *Brit. J. Exptl. Path.*, 1945, **26**, 160; 1949, **30**, 159). Albert *et al.* (*locc. cit.*) were able to demonstate in the case of the acridine anti-bacterials that a pK_a of about 7·8 at 20° was a prerequisite for high bacteriostatic activity, and that this resided mainly in the cations; anions and undissociated molecules had little activity.

In view of the known antituberculous activity of 4-aminodiphenyl and β-naphthylamine (Erlenmeyer *et al.*, *Helv. Chim. Acta*, 1945, **28**, 1406; 1947, **30**, 2058; Doub and Youmans, *Amer. Rev. Tuberc.*, 1950, **61**, 407), which are both weak bases (pK_a 4·27 and 4·3 respectively at 25°; Hall and Sprinkle, *J. Amer. Chem. Soc.*, 1932, **54**, 3472; Farmer and Warth, *J.*, 1904, 1726), a series of *N*-4-diphenylylamidines p-Ph·C$_6$H$_4$·NH·CR:NH was prepared (Bauer and Cymerman, *J.*, 1950, 1826) and the determination of the ionisation constants of the 12 bases involved is reported herein.

Method.—pK_a values were obtained by potentiometric titration, using the procedure of Albert and Goldacre (*J.*, 1946, 706) with some modifications. Since the bases concerned are insoluble in water, they were titrated by running 50% aqueous-ethanolic N/20-hydrochloric acid into a solution of the base (3—25 mg., *ca.* 0·0001 mole) in 50 c.c. of 50% aqueous alcohol. Carbon dioxide-free distilled water and absolute alcohol were used as solvents. The solution was contained in a water-jacketed (20° ± 1°) beaker containing the glass and the calomel electrode supplied with the Leeds and Northrup Universal pH meter. The titration was carried out in a nitrogen atmosphere, a rapid stream of the gas being introduced directly below the microburette and serving as an efficient stirrer. The pH meter was checked against buffer solutions at pH 4·0, 7·1, and 9·2. All titrations were carried out in duplicate at 20° ± 1°; it has been shown (Hall and Sprinkle, *loc. cit.*; Albert and Goldacre, *loc. cit.*) that the temperature coefficient of basic strength in both aqueous and 50% alcoholic solution is of the order −0·01 to −0·03 unit per degree, and would thus not affect the experimental accuracy in these determinations.

Results.—The amidines being strong bases gave good end-points represented by a steep drop in the smooth curve relating pH to the quantity of acid added.

Calculations were carried out by using equation (1) which takes into account the effect of hydroxyl ion; in the low concentrations used this correction becomes appreciable at pH values exceeding 9. When thus corrected, pK_a values showing a mean deviation of from ±0·04 to 0·06 unit were obtained.

$$\mathrm{p}K_a = \mathrm{pH} - \log\frac{[\mathrm{B}] - [\mathrm{OH}^-]}{[\mathrm{BH}^+] + [\mathrm{OH}^-]} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

A typical result (for *N*-4-diphenylylhexanamidine) is as follows:

% neutralised	19	25	32	38	44	51	57	63	70	76	82	89
pK_a	9·31	9·28	9·29	9·30	9·29	9·28	9·24	9·26	9·26	9·26	9·24	9·24

In one case, for *N*-4-diphenylylheptadecanamidine, solubility was exceedingly low. The effect of 50% alcohol on ionisation of bases is known to be a depression of basic strength by 0·5—1·0 unit from the pK_a measured in water (Mizutani, *Z. physikal. Chem.*, 1925, **118**, 327; Hall and Sprinkle, *loc. cit.*) and it is assumed (Dippy, *Chem. Reviews*, 1939, **25**, 151; Bennett and Glasstone, *J.*, 1935, 1821) that a series preserves the same order of basicity in dilute alcohol as in water. Since the relation between pK_a and percentage of ethanol is a smooth curve, the value of pK_a for the heptadecanamidine in 50% alcoholic solution could be deduced by extrapolation from the results obtained for the compound in 80, 70, and 60% alcoholic solution. Low solubility, however, did not permit carrying out the potentiometric titration in 70% and 60% alcoholic solution; only the value in 80% ethanol could be obtained. The pK_a was therefore determined in both 80% and 50% alcoholic solution by measurement of the pH at the exact half-neutralisation point. The results are collected in the Table 1.

TABLE 1. *Ionisation of* N-4-*diphenylylamidines*, *p*-Ph·C_6H_4·NH·CR:NH (I), *in* 50% *alcohol at* 20° ± 1°.

R	pK_a	R	pK_a
(*a*) Me	9·26	(*c*) Ph	8·10
	9·17[1]	*p*-Ethoxyphenyl	8·25
n-C_5H_{11}	9·26	3 : 4-Dimethoxyphenyl	8·21
n-C_7H_{15}	9·14	*p*-Chlorophenyl	7·60
n-$C_{16}H_{33}$	9·06[1]	*p*-Carbethoxyphenyl	7·22
	9·12[2]		
	9·17[3]		
(*b*) *cyclo*Hexyl	9·20		
*cyclo*Pent-1-enyl	8·66		
*cyclo*Hex-1-enyl	8·85		

[1] In 80% alcohol by potentiometric titration. [2] In 80% alcohol from half-neutralisation point. [3] In 50% alcohol from half-neutralisation point.

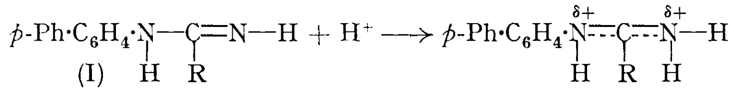
TABLE 2. *Ionisation of primary aromatic amines at* 20° ± 1°.

Substance	pK_a in 50% ethanol	pK_a in water	ΔpK_a
Aniline	4·33 ± 0·05	4·65[1]	0·32
2-Aminodiphenyl	3·39 ± 0·05	3·84[1]	0·45
3-Aminodiphenyl	3·97 ± 0·05	—	—
4-Aminodiphenyl	4·05 ± 0·05	4·34[1]	0·29

[1] Hall and Sprinkle, *loc. cit.*

The basic strengths of four related primary aromatic amines, *viz.*, aniline, and 2-, 3-, and 4-aminodiphenyl, were also determined in 50% alcoholic solution, and the results are recorded in Table 2, together with the results of Hall and Sprinkle (*loc. cit.*) for 3 of these amines in aqueous solution. It is seen that ΔpK_a lies between 0·29 and 0·45.

Discussion.—Addition of the proton may be written as in equation (2); there is a charge distribution in the cation but, although δ+ is used twice, it is not true to say that δ+ at the one centre equals δ+ at the other, although of course the sum equals the charge



$$p\text{-Ph}\cdot C_6H_4\cdot\underset{\displaystyle H}{\underset{|}{N}}-\underset{\displaystyle R}{\underset{|}{C}}=N-H + H^+ \longrightarrow p\text{-Ph}\cdot C_6H_4\cdot\underset{\displaystyle H}{\underset{|}{\overset{\delta+}{N}}}\cdots\underset{\displaystyle R}{\underset{|}{C}}\cdots\underset{\displaystyle H}{\underset{|}{\overset{\delta+}{N}}}-H \quad . \; . \; . \quad (2)$$

(I)

on a proton. Amidines, having two equivalent structures contributing to the amidinium ion, will therefore possess high basic strengths; thus acetamidine and benzamidine have pK_a 12·52 (Schwarzenbach and Lutz, *Helv. Chim. Acta*, 1940, **23**, 1162) and 11·6 (Albert, Goldacre, and Phillips, *J.*, 1948, 2241) at 20° respectively. The basicity of a series of substituted benzamidines has been determined potentiometrically by Lorz and Baltzly (*J. Amer. Chem. Soc.*, 1949, **71**, 3992) by titrating solutions of their hydrochlorides in 50% methanol with 0·1N-sodium hydroxide.

All the amidines examined in the present work are moderately strong bases; the differences observed are explicable on existing theory. In compounds of series (*a*) (I; R = alkyl), in which R is a group with a —*I* effect, the ionisation potential of the nitrogen atom is decreased and thus the basic strength of the parent compound (I; R = H) should be exceeded by the substituted compounds, as is shown, *e.g.*, by the greater basic strength of *n*-alkylamines compared with ammonia (Hall and Sprinkle, *loc. cit.*). Unfortunately the compound (I; R = H) could not be obtained. In the series (I; R = *n*-alkyl) it is known that the -*I* effect increases as the length of the *n*-alkyl chain increases, *e.g.*, *n*-amyl is more strongly —*I* than methyl but, that although this second-order inductive effect is relayed along the chain of carbon atoms, it is weaker than the primary inductive effect and is rapidly attenuated by about two carbon atoms in a *n*-alkyl chain. Thus while the pK_a of ammonia is 9·27 at 25°, the values for the five *n*-alkylamines from methyl to *n*-amyl all fall within the narrow range 10·62 ± 0·05 (Hall and Sprinkle, *loc. cit.*), and undecylamine, dodecylamine, and hexadecylamine all have pK_a 10·7 at 25° (Hoerr, McCorkle, and Ralston, *J. Amer. Chem. Soc.*, 1943, **65**, 328). In the same way, the pK_a values for the compounds (I; R = CH_3, *n*-C_5H_{11}, *n*-C_7H_{15}, and *n*-$C_{16}H_{33}$) all fall within the range 9·20 ± 0·06. Compounds of series (*b*) (I; R = alicyclic) show the olefinic groups to have a +*E* effect as expected, and the *cyclo*hexyl group is seen to have aliphatic character.

Series (*c*) (I; R = aryl) exhibits a +*E* effect due to the aryl group, together with the effect of the substituent attached to the phenyl group. Alkoxy-substituents are classified (Dewar, "Electronic Theory of Organic Chemistry," Oxford, 1948) as showing a −*E* effect and this is consistent with the results quoted for the ethoxy- and the dimethoxy-compound. The pK_a's of the other compounds are consistent with −*E* and +*I* effects of the chloro-group, the former being the greater, and with +*E* and +*I* effects of the carbethoxy-group.

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