Proximity Effects in the Interpretation of the Basic Strengths of Primary Aromatic Amines.

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The basic strengths of some aniline derivatives with methyl substituents in the ring have been determined by a combination of ultra-violet spectrophotometry and pH measurements, and the values compared with those obtained by other methods. The substituent effect is additive except when two substituents, or a substituent and the basic group, are vicinal. Explanations of the departures from additivity are attempted in terms of electromeric, inductive, and spatial effects. Steric hindrance involving the amino-group is known to be absent. Steric strain in, and steric hindrance to solvation of, the anilinium ions appear to play, at most, only a minor rôle in influencing basic strength.

An investigation of the dissociation constants of a series of tumour-inhibitory and carcinogenic *trans*-aminostilbene derivatives necessitated a study of the variations in base strength of some ring-substituted methyl derivatives of aniline. Although values for a number of these bases have been reported (see Table 1), the dissociation constants of aniline, the

toluidines, mesidine, and five of the six isomeric xylidines have been determined under identical conditions, in order to enable reliable comparisons to be made.

The present work has a bearing on the complex " *ortho*-effect " (Hofmann, *Ber.*, 1872, **5**, 704; Kehrmann, *Ber.*, 1888, **21**, 3315; Meyer, *Ber.*, 1894. **27**, 510; Lapworth and Manske, *J.*, 1928, 539; Bennett and Mosses, *J.*, 1930, 2364; Dippy, *Chem. Reviews*, 1939, **25**, 151) for primary aromatic amines, and qualitative assessment of the effects of more than one alkyl substituent in the aniline ring is attempted.

EXPERIMENTAL

Purification of Bases.—A commercial sample of the base was poured into 18% hydrochloric acid, and the resulting precipitate was dissolved by heat. The solution was allowed to cool without refrigeration during 1—2 hr. and the crystals were collected and washed with small quantities of 18% hydrochloric acid. The wet hydrochloride was dissolved in water, and the solution rendered alkaline with 40% aqueous sodium hydroxide, cooled, and extracted with ether. The combined extracts were washed with water, dried, and filtered. After removal of the ether, the residual oil was roughly fractionated at atmospheric pressure; a small middle fraction was collected for determination of the pK_a value. In each case a colourless oil or solid resulted.

Spectrophotometric Determination of the Degree of Ionisation (α).—About 0·2 ml. of oil or 0·18 g. of solid base was dissolved immediately after distillation in 20 ml. of M-hydrochloric acid and the whole diluted to 100 ml.; 25 ml. of this solution were further diluted with water to 100 ml., this solution being suitable for spectrophotometric measurement in 1-cm. cells. A knowledge of the exact concentration of base was not required. A solution of the free base in 0·05M-sodium hydroxide was prepared similarly by diluting 2·5 ml. of the concentrated solution to 100 ml. (the base absorbs more strongly than the ion). Two solutions of the same total base concentration as for the alkaline solution were prepared in sodium acetate–hydrochloric acid buffers of ionic strength 0·05, chosen to give pH values such that the degree of ionisation, α, lay in the range 40—60%. The solutions of the ion, base, and their mixtures were examined in a Beckman spectrophotometer at a series of wave-lengths in the region 260—300 mμ where the extinction coefficients of ion and base differ most. Optical densities were corrected for any imbalance in light absorption of the blank and solution cells when both were filled with the appropriate solvent. Similar techniques have been used for the visible region by Brode (*J. Amer. Chem. Soc.*, 1924, **46**, 581) and for the ultra-violet region by, *inter al.*, Flexser, Hammett, and Dingwall (*ibid.*, 1935, **57**, 2103; cf. Clark, " The Determination of Hydrogen Ions," Mac-Millan and Co., Oxford, 1928, 3rd Edn., p. 154; Beale and Liberman, *J.*, 1950, 2287).

If, in one of the buffer solutions, α is the degree of ionisation, and D the observed optical density at a given wave-length, then

$$D = \varepsilon_0 lc\alpha + \varepsilon_b lc(1 - \alpha) \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where ε_0 and ε_b are respectively the molar extinction coefficients of the ion and of the base, c is the molar concentration, and l the cell-length in cm. If c and l are kept constant, equation (1) may be written

$$D = D_0\alpha + D_b(1 - \alpha) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where D_0 and D_b are the observed optical densities of ion and base at concentration c. In the present work D_0 was obtained by dividing the observed optical density of the ion solution by ten to allow for the concentration differences mentioned above. It follows from equation (2) that :

$$\alpha = (D - D_b)/(D_0 - D_b) \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

The mean value of α was calculated from determinations at a series of wave-lengths. The spread of the values served as a useful index of the purity of the base and of the success of the experiment. Thus in a typical good experiment the value of α was 0·597 with a standard deviation for 12 wave-lengths of 0·002. A further mean value of α was calculated similarly from the results for the second ion–base solution. The values of α thus obtained were substituted in equation (5) below, giving two values for pK_a. These usually agreed to within 0·04 pK unit.

The pH values of the buffer solutions were determined with a " Doran " pH meter and a calomel half-cell and glass electrode, with automatic temperature compensation. The standard buffer solution was 0·05M-potassium hydrogen phthalate [pH 4·01 $\pm$ 0·01 at 25°; " pH Scale."

British Standard (1950) 1647, Brit. Stand. Instn., London; "Standardisation of pH Measurements made with the Glass Electrode," Letter Circular LC993, Nat. Bur. Standards, Washington, D.C., 1950).

No attempt was made rigidly to control the temperature of the solutions, but measurements were made in a room kept at $25° \pm 1°$. The lamp housing of the spectrophotometer was water-cooled, the water flowing at such a rate that no heating or cooling of the cell-compartment occurred. Solutions were adjusted to $25°$ before measurement.

Calculation of the pK_a Value.—For the base B and its conjugate acid BH$^+$ it follows from the equilibrium BH$^+$ $\rightleftharpoons$ B $+$ H$^+$ that, in terms of activities,

$$K_a = a_{\rm B} \cdot a_{\rm H^+}/a_{\rm BH^+} = c_{\rm B} \cdot a_{\rm H^+}/c_{\rm BH^+} \cdot f_{\rm BH^+} \quad \cdots \quad (4)$$

on the assumption that, at ionic strength $I = 0.05$, $f_{\rm B}$, the activity coefficient of the base, is unity. Putting the measured pH $= -\log a_{\rm H^+}$, we have from (4):

$$pK_a = {\rm pH} + \log_{10} \alpha/(1-\alpha) + \log_{10} f_{\rm BH^+} \quad \cdots \quad (5)$$

The pK_a' values recorded in Table 1 were obtained by omitting the last term in equation (5). To evaluate the rational activity coefficient $f_{\rm BH^+}$, the approximation was made that the effective diameter (a_i') of the hydrated ion was 6 Å, as has been computed for the benzoate and similar ions (Kielland, *J. Amer. Chem. Soc.*, 1937, **59**, 1675). To a sufficient degree of accuracy, f_+ is then given by :

$$\log_{10} f_{\rm BH^+} = (-0.5\sqrt{I})/(1 + 2\sqrt{I})$$

which gives the value $\log_{10} f_{\rm BH^+} = -0.08$ when $I = 0.05$.

Results.—These are given in Table 1. The limits quoted are not standard deviations, but represent the spread of results which were considered reliable, as calculated from the spread in

TABLE 1. pK_a *values of aromatic bases in aqueous media at* $25°$.

Base	Present work		Lit.	Ref.[‡]
	pK_a' [*]	pK_a		
Aniline	4.67 ± 0.02	4.59 ± 0.02	4.58	1
	4.61 ± 0.02 [†]	4.57 ± 0.02	4.64 ± 0.05	2
			4.66	3
o-Toluidine	4.50 ± 0.02	4.42 ± 0.02	$4.39, 4.5$	1, 4
m-Toluidine	4.81 ± 0.02	4.73 ± 0.02	$4.69, 4.8$	1, 4
p-Toluidine	5.16 ± 0.02	5.08 ± 0.02	$5.07, 5.1$	1, 4
2 : 3-Xylidine	4.78 ± 0.02	4.70 ± 0.02	4.64 ± 0.05	5
2 : 4-Xylidine	4.97 ± 0.02	4.89 ± 0.02	5.0	4
2 : 5-Xylidine	4.61 ± 0.02	4.53 ± 0.02	4.6	4
2 : 6-Xylidine	4.03 ± 0.03	3.95 ± 0.03	4.1	4
3 : 4-Xylidine	5.25 ± 0.02	5.17 ± 0.02	5.22 ± 0.05	5
3 : 5-Xylidine	—	—	4.9	4
Mesidine	4.46 ± 0.05	4.38 ± 0.05	—	—

* Unless otherwise indicated, pK_a' values were determined at ionic strength $I = 0.05$. † $I = 0.01$.
‡ 1, Hall and Sprinkle, *loc. cit.*; 2, Flexser, Hammett, and Dingwall, *loc. cit.*; 3, Landolt–Börnstein, "Tabellen"; 4, Golumbic and Goldbach, *loc. cit.*; 5, Kieffer and Rumpf, *Compt. rend.*, 1950, **230**, 2302.

α mentioned above. Concordance of results was satisfactory except for mesidine which appeared to be somewhat unstable. There is satisfactory agreement with Hall and Sprinkle's measurements (*ibid.*, 1932, **54**, 3469) of the e.m.f. of concentration cells containing the half-neutralised base. Golumbic and Goldbach (*ibid.*, 1951, **73**, 3966) employed a partition method, no correction being made for activities, and our results for pK_a' are in fair agreement with theirs.

DISCUSSION

In the aniline molecule, the nitrogen atom possesses a lone-pair orbital which projects in a direction approximately perpendicular to the plane of the ring but slightly away from it since the bonds from the nitrogen atom are tetrahedrally disposed. However, the lone-pair electron cloud will be statistically symmetrical about a plane through the N–C bond perpendicular to the plane of the ring. The effect of substituents in the ring may be regarded as producing change in the electron density in the lone-pair orbital or in its immediate vicinity and in some cases distorting the symmetry of the orbital. The distor-

tion should be greatest in *ortho*-substituted anilines. The present concept envisages that any effect which shifts negative charge towards the nitrogen atom will enhance its proton-attracting power, and hence the strength of the base, by increasing the electron density in the lone-pair orbital : further, any effect which distorts the orbital will reduce the strength of the base, distortion being concomitant with partial neutralisation of the electronic charge around the nitrogen atom by the substituent.

The following qualitative effects of substitution have to be considered as influencing the pK_a values of primary aniline bases : (i) the mesomeric (M) and inductive (I_R) effects of the substituent relayed through the bonds of the ring and of the substituent; (ii) the bulk effect (B_S) of substituents causing hindrance to approach or recession of the protons; (iii) the combination effect (C) of more than one substituent; (iv) a direct spatial effect (E) due to interaction between the electron clouds of the amino-group and of the substituent; and (v) steric hindrance to solvation (S) of the anilinium ion.

Since only methyl groups are considered here, effects (i) are positive, and negative charge will flow towards the nitrogen atom. Thus these effects alone will be base-strengthening. The effect B_S is difficult to assess, for in the equilibrium between base and ion it is not clear whether hindrances to approach and recession of the protons differ in magnitude. The assumption is made that the two hindrances are approximately equal and that B_S is small. Effect C is considered later. The spatial effect E is of greatest importance when the alkyl group is *ortho* to the amino-group; it is then part of the well-known " *ortho*-effect." E is considered to be interrelated with the $+M$ and $+I_R$ effects. As a result of the latter, the hydrogen atoms of the methyl group in, for example, *o*-toluidine, are slightly positively charged, and it is suggested that electrostatic interaction may then occur between the partially unscreened nuclei of the methyl-hydrogen atoms and the lone-pair orbital, causing distortion and reduced electron density around the nitrogen atom.

From Table 1, it is seen that the expected $+M$ and $+I$ effects of methyl lead to an enhancement of basic strength for *m*- and *p*-toluidine. The greater basic strength of the latter emphasises the marked $+M$ effect when the methyl group is in conjugation with the amino-group. For *o*-toluidine, which shows the " *ortho*-effect," the reduction in basic strength relative to aniline may be ascribed to effect E or S, or to both, when pK_a values in aqueous media are considered. Values obtained in non-aqueous media (Bell and Bayles, *J.*, 1952, 1518) indicate that *o*-toluidine is a somewhat stronger base than aniline, these authors ascribing the lowered basic strength in water to the results of hydrogen bonding between amine cation and solvent molecules. However, the same argument should be applicable to *N*-methyl-*o*-toluidine which, in both aqueous and non-aqueous media (Hall and Sprinkle, *loc. cit.*; Bell and Bayles, *loc. cit.*), is a weaker base than *N*-methylaniline. This suggests strongly that there is no steric hindrance to maximum conjugation of the methylamino-group with the ring and that the *N*-methyl and the *o*-methyl group are oriented away from each other. There is a regular and consistent reduction in basic strengths in aqueous solution on introduction of an *o*-methyl group into aniline and its *N*-methyl and *N*-ethyl derivatives (Hall and Sprinkle, *loc. cit.*), whereas the behaviour in non-aqueous solutions is irregular. These results indicate, therefore, that although an *o*-methyl group may be causing some hindrance to ion solvation the effect on the pK_a values of *ortho*-substituted bases is not likely to be of major importance. This effect is considered further in the discussion on disubstituted bases which follows.

In order to assess the changes (ΔpK_a) in pK_a caused by introduction into the ring of more than one methyl substituent, Table 2 was constructed as follows. From Table 1, the ΔpK_a on introduction of *o*-methyl into aniline was shown to be :

$$\Delta pK_a = pK_2 - pK_1 = 4.42 - 4.58 = -0.16$$

Similarly, for a *m*-methyl group $\Delta pK_a = +0.15$ and for a *p*-methyl group $\Delta pK_a = +0.60$. On the assumption for the moment that the effects are additive, pK_a values are calculated and compared with the experimental values. For example the pK_a(calc.) for 3 : 4-xylidine is given by :

$$pK_a \text{ (}p\text{-toluidine)} + \text{increment due to the 3-Me group} = 5.08 + 0.15 = 5.23$$

The results thus obtained are summarized in Table 2, with the limits of error.

TABLE 2. *Comparison of calculated and experimental* pK_a *values for xylidines and mesidine.*

Base	Calc. pK_a	Obs. pK_a	δpK_a (obs. − calc.)
2 : 3-Xylidine	4·57 ± 0·035	4·70 ± 0·02	+0·13 ± 0·04
2 : 4- ,, ...	4·92 ± 0·035	4·89 ± 0·02	−0·03 ± 0·04
2 : 5- ,, ...	4·57 ± 0·035	4·53 ± 0·02	−0·04 ± 0·04
2 : 6- ,, ...	4·26 ± 0·035	3·95 ± 0·03	−0·31 ± 0·045
3 : 4- ,, ...	5·23 ± 0·035	5·17 ± 0·02	−0·06 ± 0·04
Mesidine	4·45 ± 0·04	4·38 ± 0·05	−0·07 ± 0·065

The largest diversion from additivity occurs with 2 : 6-xylidine, where the pK_a value is lowered by much more than twice the decrement caused by one *o*-methyl group. A model indicates lack of hindrance in this xylidine in keeping with the marked pK_a reduction. It must be that, as a result of the symmetry of the electron cloud about the N–C axis each methyl group is able to interact more strongly with the lone-pair orbital because of the presence of the other. This indicates some kind of electrostatic interaction, the magnitude of which is in inverse proportion to some power function of the distance between the centres of gravity of the interacting charges. A similar effect is noted in mesidine, where the observed and the calculated values are not significantly different. The normal " *ortho* " decrement in pK_a is found for both 2 : 4- and 2 : 5-xylidine, the close agreement between calculated and experimental values indicating no appreciable interaction between methyl groups when these are *meta* or *para* to each other. When the methyl groups are *ortho* to each other as in 3 : 4-xylidine, a slight departure from additivity is indicated. Since the base is somewhat weaker than expected, there must be some mutual restriction of electron flow from the methyl groups into the ring; small though this effect is in 3 : 4-xylidine its importance in 2 : 3-xylidine is clear, since this base is markedly stronger than expected.

The marked difference in behaviour between 2 : 5- and 2 : 3-methyl derivatives of benzene compounds of the type PhR has been noted recently by van Helden, Verkade, and Wepster (*Rec. Trav. chim.*, 1954, **73**, 39) when R = NO_2 and by Dippy, Hughes, and Laxton (*J.*, 1954, 1470) when R = CO_2H. In both these cases a methyl or an alkyl group *ortho* to R causes hindrance to mesomerism with the ring, and introduction of a 3-methyl group has the apparent effect of increasing the size of the 2-substituent—a result interpretable in terms of a reduction in mesomeric interaction between R and the ring. As pointed out by van Helden *et al.* (*loc. cit.*), in addition to repulsion between vicinal methyl groups, some hindrance to rotational freedom of the methyl groups may be a further complication.

In the present case, where R = NH_2, no steric interaction occurs with the 2-methyl group, as is shown clearly by van Helden *et al.* (*loc. cit.*), so that the situation is simplified to that extent. In 2 : 3-xylidine, interaction between the methyl groups could have the following results : closer approach of the methyl to the amino-group would enhance the *E* effect and, concomitantly, the *S* effect, both factors causing reduction in basic strength. Since, however, the reverse occurs, the dominant factor must be the restraint of positive-charge flow from the methyl groups into the ring. Whether this is due to distortion of the C_{Me}–C_{ar} bonds or to restrictive orientation of the methyl groups, or to both, it is not yet possible to decide.

Finally, the explanation of the phenomenon given by Brown and Cahn (*J. Amer. Chem. Soc.*, 1950, **72**, 2939) must be considered. These authors propose that the reduction in pK_a caused by an *o*-methyl group is the result of steric strain, the larger steric requirements of the ion favouring dissociation to the free base. There is also the further concept of Evans, Watson, and Williams (*J.*, 1939, 1348) in which the *ortho*-effect is regarded as a transition-state phenomenon. In view of these hypotheses it is important to consider whether the *ortho*-effect is present in the molecule in its normal ground state, *i.e.*, when not undergoing reaction with an electrophilic reagent. Evidence from dipole moments should indicate the presence or absence of the effects under such conditions. Ingham and Hampson (*J.*, 1939, 981) found that the moments of aminodurene and mesidine are about 0·13 D lower than that of aniline (1·53 D). Since, contrary to Ingham and Hampson's explanation, steric hindrance is considered to be absent in these compounds, the result is ascribed, as

already suggested in somewhat similar terms by Watson (*Ann. Reports*, 1939, **36**, 219), to electrostatic interaction which restricts charge flow from the nitrogen atom into the benzene ring. In order to test the possibility of steric strain in the *o*-toluidinium ion, a model was constructed in which the $-NH_3^+$ group was represented, for want of an appropriate N atom, by a methyl group. The latter has a van der Waals radius of 2·0 Å, which is larger than that of the crystal radius of NH_4^+ (1·48 Å; Pauling, " Nature of the Chemical Bond," Cornell Univ. Press, 1954, pp. 189, 350). It seems unlikely, therefore, that the $-NH_3^+$ group will have a radius larger than that of methyl. By using this group in the model, it is possible to orient the methyl groups so as to avoid steric strain, although independent rotational freedom of the groups is restricted. This may, of course, be tantamount to the existence of a repulsion between groups, for which, as already seen, there is some evidence; but, particularly with the smaller $-NH_3^+$ group, it is unlikely that the overall strain in the ion will be large. If such strain be appreciable, it is difficult to account for the enhanced basic strength of 2 : 3-xylidine, since introduction of a 3-methyl group into *o*-toluidine would not be expected to reduce strain in the ion; rather it would tend to increase it.

Given that the present interpretations are valid, then, in the absence of steric hindrance in these compounds, the spatial E effect of *o*-methyl appears to play an important part in the " *ortho* "-phenomenon. If, on the other hand, hindrance to the ionising group occurs, as is now considered to be the case with the *ortho*-substituted benzoic acids (Dippy, Hughes, and Laxton, *loc. cit.*), this appears to be the dominant effect. The difference in behaviour between the benzoic acids and the anilines is clearly shown in the case of the 2 : 5- and 2 : 4-dimethyl derivatives. Whereas the ΔpK_a values for the 2 : 5-derivatives are additive (when calculated as above), the behaviour of the 2 : 4-derivatives is different. While the ΔpK_a for 2 : 4-xylidine is as expected, 2 : 4-dimethylbenzoic acid is weaker than calculated as above. Dippy *et al.* (*loc. cit.*) consider this to be due to an increase in double-bond character of the linkage between carboxyl and ring on substitution of a 4-methyl group into *o*-toluic acid (CO_2H at 1). This must mean that the angle of rotation of the carboxyl group about its linkage with the ring is less than in *o*-toluic acid.

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