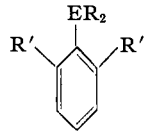
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Steric Strain as a Factor in the Ionization Constants of *Ortho* Substituted Aromatic Amines and Phosphines[1,2]

BY HERBERT C. BROWN AND ARNO CAHN[3]

Introduction

According to present concepts the relative strengths of aromatic bases of the type



(where E is either nitrogen or phosphorus and R and R′ are either alkyl or hydrogen) should be functions of (1) the inductive and hyperconjugative effects of the groups R and R′, (2) resonance involving the atom E and the ring, and (3) steric inhibition of resonance.

Unfortunately, the observed behavior of such *ortho* substituted aromatic bases cannot be accounted for in terms of these effects. This difficulty led Bennett and Mosses[4] to invoke an unusual −I effect of the *ortho* alkyl groups and Thomson[5] to propose that resonance cannot be a very important factor in determining the strength of aromatic bases.[6]

Previous papers in this series have demonstrated that steric strain is an important factor in the strength of bases, when such bases are compared with trimethylboron and similar reference acids.[7] It is here proposed that the peculiar effects of *ortho* substituents on the strength of aniline bases are easily understandable in terms of the steric strain concept. It is considered that there is an increase in steric strain accompanying addition of the proton to the atom E with resulting transformation of the atom from its trivalent configuration in the free base to the bulkier tetrahedral configuration in the onium ion. With addition of this fourth factor, to the three previously mentioned, the observed variations in base strength of aromatic bases accompanying changes in R′, R and E are readily explicable without major changes in current concepts.[4,5]

Discussion

Effect of Ortho Substitution in Aniline.— Values for the base strengths of aniline and the toluidines are given in Table I.[8] The introduction of a methyl group into the *meta* or *para* positions of aniline brings about a moderate increase in base strength. However, the presence of one methyl group in the *ortho* position results in a decrease in base strength. Moreover, a second *ortho* substituent results in an even greater drop in the value of *pKa* (Table II). The opposite effects of *ortho* substitution, and *meta* and *para* substitution, are clearly indicated in Fig. 1.

TABLE I

BASE STRENGTHS[8a] IN AQUEOUS SOLUTION AT 25°

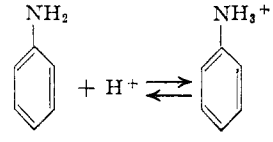
Base	*pKa*
Aniline	4.58
o-Toluidine	4.39
m-Toluidine	4.69
p-Toluidine	5.12

TABLE II

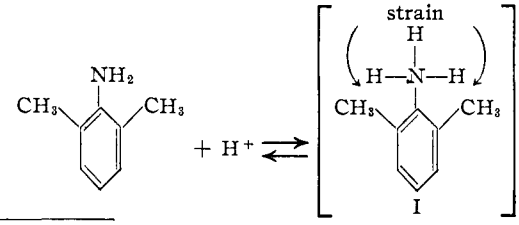
BASE STRENGTHS[8c] IN 50% ETHANOL AT 25°

Base	*pKa*
Aniline	4.25
o-Toluidine	3.98
m-2-Xylidine	3.42
m-4-Xylidine	4.61
m-5-Xylidine	4.48
p-Xylidine	4.17

Although an unusual −I effect of the ortho methyl group has been utilized[4] to explain the drop in strength, steric strain appears to offer a simpler interpretation. Consider the equilibrium



In the anilinium ion, the nitrogen atom has changed from the trivalent to the tetravalent configuration with dimensions roughly comparable to those of a methyl group. A group in the *ortho*



(1) Studies in Stereochemistry. XVII.

(2) Included in a paper presented in the symposium, "Acid-Base Reactions in Organic Chemistry," at the Atlantic City Meeting of the American Chemical Society, Sept. 21, 1949.

(3) Research Fellow at Purdue University, 1948–1950, under a contract with the Office of Naval Research for the study of "Steric Strains in Chemical Reactions."

(4) Bennett and Mosses, *J. Chem. Soc.*, 2367 (1930).

(5) Thomson, *ibid.*, 113 (1946).

(6) Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 136 *et seq.*

(7) Brown, THIS JOURNAL, **67**, 374, 378 (1945).

(8) Values of the base dissociation constants for aromatic bases are abundant in the literature of the past forty years. The values cited in this paper are taken from (a) Hall and Sprinkle, THIS JOURNAL, **54**, 3469 (1932); (b) Davies and Addis, *J. Chem. Soc.*, 1622 (1937); (c) Thomson, *ibid.*, 1113 (1946).

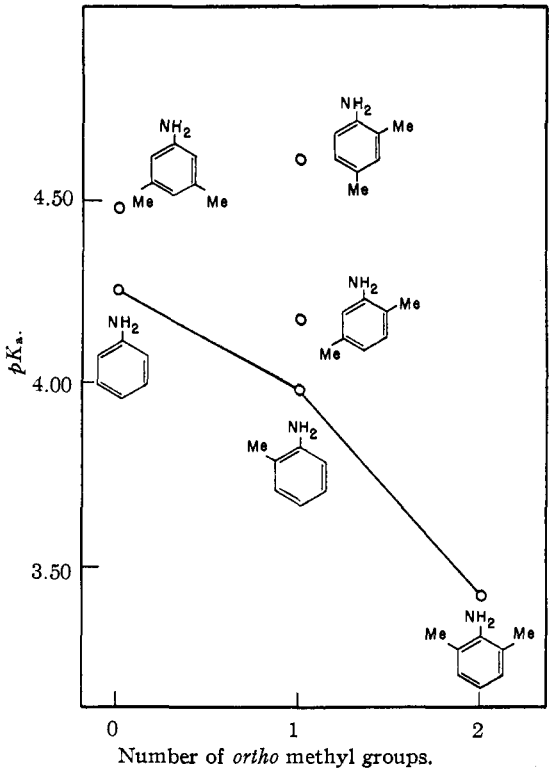
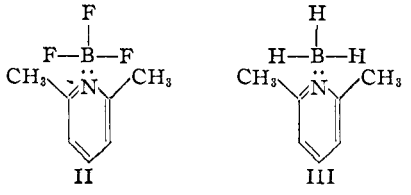


Fig. 1.—Effect of methyl ring substituents on the strength of aniline bases.

position with large steric requirements would conflict with the steric requirements of the $-NH_3^+$ group. The resulting steric strain would oppose the formation of the ammonium ion and decrease the apparent strength of the base.

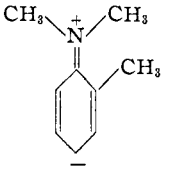
There is independent evidence that steric strains are appreciable in a molecule such as I. Thus, 2,6-lutidine-boron trifluoride,[9] II, is much more highly dissociated than the corresponding pyridine derivative. The steric requirements of



II III

the $-BF_3$ group are only slightly larger than those of the $-NH_3^+$ group. Moreover, preliminary experiments with 2,6-lutidine-borine, III, also indicate the presence of steric strains,[10] and this molecule is isosteric with the ammonium ion, I, with closely similar molecular dimensions. It should also be pointed out that the $-NH_3^+$ group must be strongly solvated in solution and stabilized by such solvation. Steric strain involving the solvating molecules and the *ortho* methyl groups would reduce the extent of solvation and further tend to shift the equilibrium between the free base and its ion toward the left.

Effect of *Ortho* Substitution in Dimethylaniline.—Steric inhibition of resonance accounts successfully for the relatively high base strength of dimethyl-*o*-toluidine.[6] According to this interpretation, crowding by the *ortho* methyl group prevents the dimethylamino group from assuming a position coplanar with the ring. Accordingly, the resonance contribution of structures, such as



IV

IV, is diminished, and the strength of the base is thereby increased.

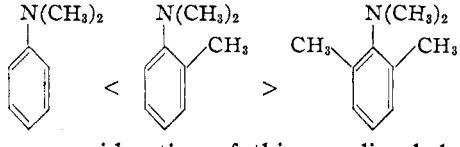
On the basis of this picture, one would expect a steady increase in base strength in going from dimethylaniline to dimethyl-*o*-toluidine to dimethyl-*m*-2-xylidine. However, this prediction is not confirmed by the data in Table III.

TABLE III

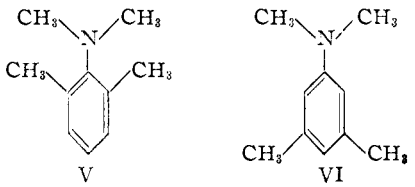
BASE STRENGTHS[8c] IN 50% ETHANOL AT 25°

Base	*pKa*
Dimethylaniline	4.26
Dimethyl-*o*-toluidine	5.07
Dimethyl-*m*-2-xylidine	4.69
Dimethyl-*m*-4-xylidine	5.28
Dimethyl-*m*-5-xylidine	4.48
Dimethyl-*p*-xylidine	5.19

These values are plotted in Fig. 2. From the data, the surprising order of *pKa* values is seen to be



From a consideration of this peculiar behavior, Thomson[5] was led to the conclusion that resonance cannot be of such determining importance on the value of the base strength as has been previously assumed. He further supports his argument by calling attention to the small difference in *pKa* between dimethyl-*m*-2-xylidine, V, and dimethyl-*m*-5-xylidine, VI. In the former, the inhibition of resonance should be at a maximum, while in the latter no inhibition of resonance would be anticipated. Yet, the *pKa* values differ by only 0.21 unit.



V VI

(9) Brown, Schlesinger and Cardon, THIS JOURNAL, **64**, 325 (1942). See especially footnote 23 in this reference.

(10) Unpublished work of H. C. Brown.

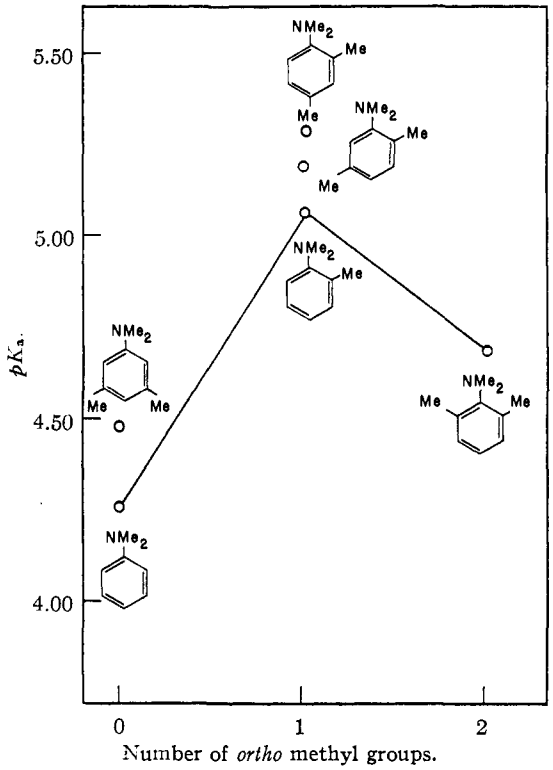


Fig. 2.—Effect of methyl ring substituents on the strength of dimethylaniline bases.

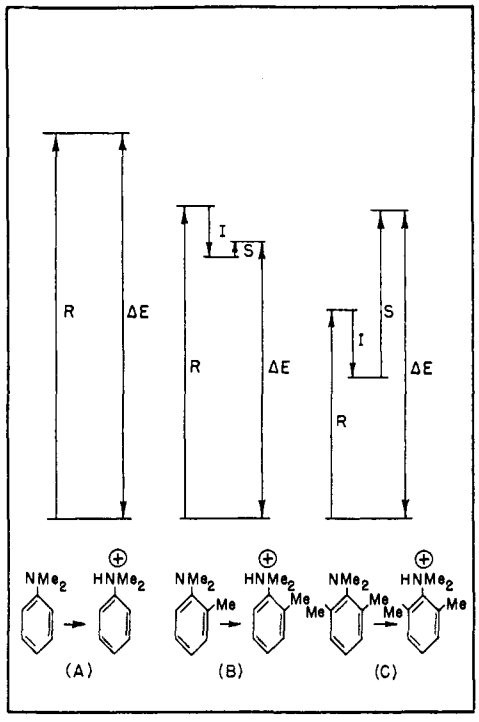


Fig. 3.—Schematic representation of energy change, ΔE, accompanying the conversion of an aniline base into its anilinium ion. The components of ΔE considered are: resonance (R), inductive effect (I), and steric strain (S).

Again, a consideration of steric strain permits these data to be interpreted without doing violence to generally accepted concepts of the importance of resonance as a factor in the strength of aromatic bases and the effect of *ortho* substituents in damping such resonance.

The addition of a proton to dimethylaniline will destroy resonance involving the nitrogen atom of the amino group and the aromatic ring. Steric inhibition of resonance will not be involved, nor will steric strain of the type under consideration here.

Resonance in dimethyl-*o*-toluidine is somewhat less than in the parent tertiary amine because of the damping effect of the *ortho* substituent. Addition of a proton will, therefore, involve a smaller loss of resonance energy (R-I, Fig. 3). However, the total energy change is increased by a small rise in steric strain accompanying the formation of the ammonium ion. The net effect is that the base strength of dimethyl-*o*-toluidine is increased somewhat, but not to the extent that would have occurred in the absence of steric strain.

Finally, in dimethyl-*m*-2-xylidine, resonance is reduced further by the more severe damping resulting from the presence of the two *ortho* methyl substituents. However, steric strain here becomes a major factor. The net result is a large energy change which is reflected in a small value of *pKa*.

The argument may be clarified by the schematic representation in Fig. 3.

Not only does this concept of steric strain permit a reasonable interpretation of the surprising effect of the second *ortho* substituent in dimethyl-*m*-2-xylidine, but it permits a number of predictions.

As the bulk of the *ortho* substituents is increased, as in the series Me, Et, *i*-Pr, *t*-Bu, the base strength should first increase as the resonance is increasingly damped, but should then decrease. This decrease should become more and more severe as the larger steric requirements of the *ortho* substituent result in larger steric strains.[11]

As the bulk of the substituents attached to nitrogen is increased, the effect of steric strain should be magnified. There should be observed a sharp increase in base strength at first, due to damping of resonance, followed by an even sharper decrease as steric strains become important.[12]

Finally, a change in the basic atom from the

(11) NOTE ADDED TO PROOF.—Important evidence supporting this prediction has been obtained by Dr. B. M. Wepster of the Delft Technical University, Delft, Holland. In a private communication, which he has generously permitted the authors to quote, Dr. Wepster reports $pKa = 3.78$ for *o*-*t*-butylaniline in water at 25°, and $pKa = 4.32$ for *o*-*t*-butyldimethylaniline in 50% ethanol at 25°.

(12) NOTE ADDED TO PROOF.—Vexleaschi, *Compt. rend.*, **228**, 1655 (1949), reports $pKa = 7.10$ for N-*t*-butylaniline in water at 19°. In this case the large alkyl group on nitrogen has apparently brought about a marked inhibition of resonance and the base weakening effect of steric strain has not yet become an important factor.

small nitrogen to the larger phosphorus atom should tend to reduce both the damping and the steric strain. The larger phosphorus atom moves the groups attached to it away from the ring and reduces the steric conflict between those groups and the *ortho* substituents. It may, therefore, be concluded that more and larger *ortho* substituents would be required to bring about appreciable steric inhibition of resonance and that steric strains would be relatively unimportant until the bulk of the substituents became very large.

Unfortunately, data in the literature are not sufficient to test these predictions fully. What data are available, however, appear to be in full agreement with these conclusions.

Effect of Nitrogen Substitution in N-Alkylanilines.—Pertinent data illustrating the effect of substitution on the nitrogen atom are listed in Table IV.

TABLE IV

BASE STRENGTHS[8a] (*pKa*) IN AQUEOUS SOLUTION AT 25°

Base	R = H	Me	Et	*n*-Pr
C_6H_5NHR	4.58	4.85	5.11	5.02
$C_6H_5NR_2$	4.58	5.06	6.56	5.59

For both series shown the effect of the alkyl substituent in increasing the base strength is in the order: H < Me < Et > *n*-Pr.[13]

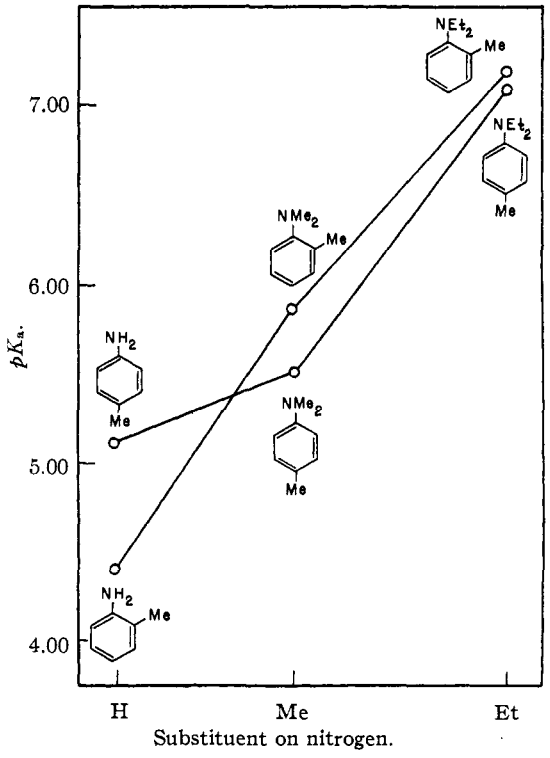


Fig. 4.—Effect of increased size of nitrogen substituents on the strength of aniline bases.

(13) This peculiar order is also observed in the normal amines RNH_2 and in the carboxylic acids RCOOH. This phenomenon will be the subject of a paper now under preparation with Dr. M. D. Taylor.

In view of the marked polar effects of the normal alkyl groups on base strength, the effect of increasing bulk of the substituents attached to nitrogen is best studied by comparing the corresponding *pKa* values for the *o*- and *p*-toluidine derivatives.

TABLE V

BASE STRENGTHS[8a] (*pKa*) IN AQUEOUS SOLUTION AT 25°

Base	R = H	Me	Et
p-$MeC_6H_4NR_2$	5.12	5.50	7.09
o-$MeC_6H_4NR_2$	4.39	5.86	7.18

The values of the *p*-toluidine series follow those of the unsubstituted series of Table IV. Again a small increase from *p*-toluidine to dimethyl-*p*-toluidine is followed by a large increase to diethyl-*p*-toluidine (Fig. 4).

The increased steric strain resulting from the presence of ethyl groups instead of methyl groups is realized by comparing the last two columns. The value of *pKa* for dimethyl-*o*-toluidine is 0.36 unit greater than for dimethyl-*p*-toluidine. The larger ethyl groups should be even more effective in damping resonance, yet the value of *pKa* for diethyl-*o*-toluidine is but very slightly higher than that for the *para* derivative. According to the interpretation advanced in this paper, the increasing steric strain has more than compensated for the effect of increased resonance inhibition.

Effect of Increasing Size of the Donor Atom.—As was pointed out, increasing size of the donor atom moves the substituents attached to that atom away from the ring, out of range of the *ortho* substituents. More and larger substituents should be required to cause appreciable

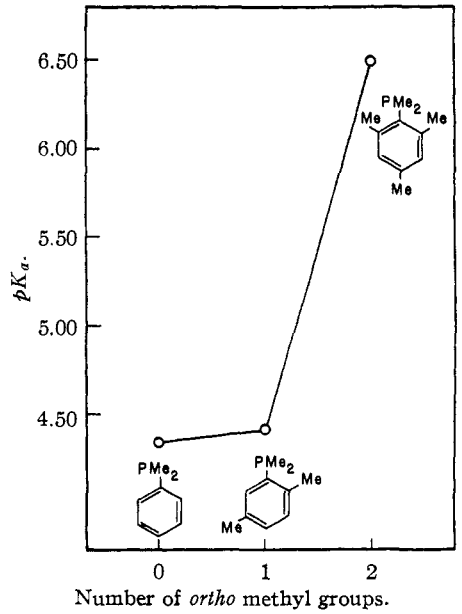


Fig. 5.—Effect of methyl ring substituents on the strength of aromatic phosphine bases.

resonance damping. Steric strain should become important only with unusually bulky substituents.

These conclusions are supported by data on the base strengths of phosphines, reported by Davies and Addis.[8b]

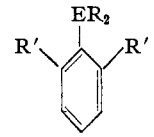
The introduction of a single *ortho* substituent into dimethylphenylphosphine leads to a relatively minor increase in base strength. However, two *ortho* substituents lead to a sharp increase in strength (Fig. 5), in marked contrast to the effect of a second *ortho* substituent in the dimethylaniline series (Fig. 2). In terms of the steric strain hypothesis, steric inhibition of resonance has become appreciable only with the second *ortho* methyl group; steric strain has not yet become significant.

Conclusion

A rigorous quantitative test of the importance of steric strains on the ionization constants of *ortho* substituted aromatic bases will require considerable additional data on compounds in which the number and bulk of alkyl groups attached to the donor atoms and to the *ortho* positions are varied in a systematic manner. It is hoped that such data will be forthcoming. However, even the relatively meager data now available are in good agreement with the steric strain interpretation. This suggests that steric strain should be considered as an important factor in the strength of aromatic bases. Steric strain in conjunction with current ideas concerning the factors affecting the strength of aromatic bases, permits a reasonable interpretation of all available data on the strength of such bases.

Summary

Currently the relative strengths of aromatic bases of the type



where R and R′ are hydrogen or alkyl groups and E is either nitrogen or phosphorus, are attributed to the operation of three major factors: (1) the inductive and hyperconjugative effects of the groups R and R′, (2) resonance involving the atom E and the ring, and (3) steric inhibition of resonance. It has, however, not been possible to account for the behavior of a number of *ortho* substituted amines and phosphines in terms of these factors. Consideration of steric strains resulting from the change in the steric requirements of the $-ER_2$ group accompanying its conversion into the onium ion, $-ER_2H^+$, permits a simple interpretation of outstanding discrepancies. It is suggested that steric strain be added as a fourth important factor in the strengths of *ortho* substituted aromatic bases.

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[CONTRIBUTION FROM MEDICAL DEPARTMENT FIELD RESEARCH LABORATORY, U. S. ARMY]

A Microelectrophoretic and Microionophoretic Technique[1]

BY E. L. DURRUM

In performing electrophoretic and ionophoretic separations, several investigators have utilized an electrical potential applied across various packing materials intended to stabilize migrating boundaries by preventing convection currents in the electrolytes employed. Strain[1a] combined ionophoresis with chromatographic adsorption in the conventional Tswett adsorption column and mentioned utilizing columns filled with cotton for this purpose. Coolidge[2] was able to separate protein constituents in a column packed with ground glass wool across which a potential was applied. Consden, Gordon and Martin[3] described an ionophoretic technique suitable for the separation of certain amino acids which was carried out in silica jelly slabs made up with various buffers. These investigators utilized paper pulp to reinforce the mechanical strength of the silica jelly slabs employed. They also reported an experiment in which their trough was filled with "paper powder saturated with liquids to be analyzed" but abandoned this variation of their method because current densities optimum for their purpose could not be employed. Butler and Stephen[4] have utilized asbestos fiber packed in a segmented polystyrene plastic tube and reported separating glycine from glycylglycine at *p*H 9.3 in this apparatus. None of the above processes was adapted to the separation of small quantities of material.

Recently, Haugaard and Kroner[5] applied electrical potentials across paper partition chromatographs during their development with phenol. They wove thin, flat, metallic electrodes into the edges of the paper which had first been treated with phosphate buffer solution and then dried prior to development with phenol. They reported that the degree of separation of basic and acidic amino acids attainable by paper partition

(1) Presented before the American Chemical Society, Division of Biological Chemistry, March 29, 1949, in San Francisco, California.

(1a) Strain, THIS JOURNAL, **61**, 1292 (1939).

(2) Coolidge, *J. Biol. Chem.*, **127**, 551 (1939).

(3) Consden, Gordon and Martin, *Biochem. J.*, **40**, 33 (1946).

(4) Butler and Stephen, *Nature*, **160**, 469 (1947).

(5) Haugaard and Kroner, THIS JOURNAL, **70**, 2135 (1948).