[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

A Quantitative Approach to the Ortho Effects of Halogen Substituents in Aromatic Systems[1,2]

BY DARL H. MCDANIEL[3,4] AND HERBERT C. BROWN

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The *ortho* effects of alkyl groups are now fairly well understood and they may be interpreted largely in terms of F-strain interactions and steric inhibition of resonance. The highly polar nature of the halogen substituents has made the attainment of a similar understanding of the *ortho* effects of these substituents more difficult. It is suggested that in their reaction with a proton the substituted pyridine bases provide a system which is largely free of such *ortho* effects as F-strain, steric inhibition of resonance and hydrogen bonding. Consequently, the substituted pyridine bases provide a nearly ideal reference system for the estimation of the purely polar contribution of *ortho* substituents. In this way it has been possible to arrive at a quantitative estimate of the direction and magnitude of the *ortho* effects of halogen substituents, as well as other substituents, in a number of aromatic systems. This quantitative estimate of the *ortho* effects permits an assessment of the relative contributions of such phenomena as F-strain, steric inhibition of resonance, and hydrogen bonding to the total *ortho* effect of substituents in a number of aromatic systems.

Almost as soon as quantitative data on the dissociation of aromatic acids and bases were available it was recognized that the effect of *ortho* substituents on the acid strength often differed greatly from the expected behavior. It has been common to attribute any peculiar effect of a substituent in the *ortho* position to an *ortho* or proximity effect,[5] these terms remaining free of any physical implications as to the precise nature of the interaction. That the *ortho* effect is a combination of many different types of interaction is now well recognized.[6]

The *ortho* effects of alkyl groups provide a relatively simple area for study. The absence of important resonance interactions and relatively small polar contributions of alkyl groups makes it possible to estimate the electrical contribution of such groups with considerable precision. Deviations from the predicted behavior can then be interpreted in terms of such concepts as steric inhibition of resonance, F-strain and, possibly, steric hindrance to solvation.

However, it has not been possible previously to estimate accurately the relative importance of electrical effects and specific *ortho* effects for strongly polar substituents. Consequently, it is usually not possible to state from the experimental data whether specific *ortho* effects are present and are playing any significant role in determining the behavior of the substituted compounds.

Branch and Calvin[7] have pointed out that the existence of *ortho* effects may be observed by the deviation from linearity of a plot of the logarithm of the dissociation constants of a substituted reference acid (such as the phenylboric acids) against other correspondingly substituted aromatic acids (such as phenols, benzoic acids, etc.). They point out, however, that this method shows only that an *ortho* effect exists, but not in which acid it exists nor whether it is acid strengthening or acid weakening. Only in the event that a reference system could be found free of *ortho* effects would it be possible to utilize such plots for the estimation of the magnitude and direction of *ortho* interactions.

In the pyridine system *ortho* substitution should be relatively free of the type of specific *ortho* interactions under discussion. Steric inhibition of resonance is impossible. The formation of a hydrogen bond is highly improbable with all but a few substituents. F-strain should be negligible with all but the most bulky substituents.[8] Finally, there is evidence that solvation effects and steric hindrance to solvation are relatively unimportant.[8,9]

It follows that the pyridine bases should provide a satisfactory reference system. Deviations from linearity between the pK_a values of substituted pyridine bases and those of the corresponding substituted aromatic acids and bases should provide a measure of the *ortho* effect of the substituent in the particular organic acid or base under consideration.[10] With a quantitative estimate of the effect available, it should be possible to make reasonable interpretations regarding the particular type of interaction involved. This approach will be applied

(1) Steric Effects in Displacement Reactions. VIII.

(2) Based upon a thesis submitted by Darl H. McDaniel in August, 1954, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) Research assistant at Purdue University, 1952–1953, on a National Science Foundation grant; Allied Chemical and Dye Corporation Fellow at Purdue University, 1953–1954.

(4) Department of Chemistry, University of Pittsburgh, Pittsburgh, Pa.

(5) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 204–207.

(6) For a review of the available data and theory see H. C. Brown, D. H. McDaniel and O. Häfliger, "Dissociation Constants," Chapter 14 in "Physical Methods of Structure Determination," edited by E. C. Nachod and E. A. Braude, Academic Press, Inc., New York, N. Y., in press.

(7) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1947, p. 258.

(8) H. C. Brown and P. N. Mihm, THIS JOURNAL, **77**, 1723 (1955).

(9) D. P. Craig, *J. Chem. Soc.*, 534 (1946). See also H. C. Brown and B. Kanner, THIS JOURNAL, **75**, 3865 (1953).

(10) It has been pointed out by one of the Referees that the taking of deviations from the linear free energy relationships as quantitative measures of steric effects assumes that the ratio of the inductive and resonance contributions to the total polar effect of the *ortho* substituent is the same in both the pyridine and the other aromatic system.

In the case of many substituents it has been found necessary to assign two different σ-values, the higher value to take account of resonance interactions between substituents located *para* to each other [see H. H. Jaffe, *Chem. Revs.*, **53**, 191 (1953)]. However, this has not proven necessary in the case of the alkyl and halo substituents, presumably because resonance interactions here are relatively small compared to the inductive contributions. If this is the case in the more remote 4- or *p*-position, then it is reasonable to expect that in the neighboring 2- or *o*-position, the inductive contributions of these substituents should far outweigh their resonance contributions. On this basis we believe that resonance contributions of the halo and alkyl substituents in the 2- or *o* positions are relatively small, and any error introduced by neglect of possible changes in the ratio of the inductive and resonance contributions of these substituents in the different aromatic systems should be quite minor.

in the following sections to the interpretation of the *ortho* effects of halogen and alkyl substituents.

Pyridine Bases, the Reference System.—The dissociation constants of the substituted pyridines are summarized in Table I. It should be noted that the strength of the 2-halopyridines roughly parallels that of the haloacetic acids and it may be safely assumed that the inductive effect is responsible for this order. Similarly, alkyl groups exhibit an effect which is in accord with the postulated polar effect of these groups.

TABLE I

pK_a VALUES OF SUBSTITUTED PYRIDINES IN AQUEOUS SOLUTION AT 25°

Pyridine XC_5H_4N		Position 2-	3-	4-
Hydrogen-		5.17[c]	5.17[c]	5.17[c]
Fluoro-		−0.44[b]	2.97[b]	
Chloro-		.72[b]	2.84[b]	
Bromo-		.90[b]	2.84[b]	
Iodo-		1.82[b]	3.25[b]	
Methyl-		5.97[c]	5.68[c]	6.02[c]
Ethyl-		5.97[c]	5.70[c]	6.02[c]
Isopropyl-		5.83[c]	5.72[c]	6.02[c]
t-Butyl-		5.76[c]	5.82[c]	5.99[c]
Phenyl-		4.55[f]	4.87[f]	5.38[f]
Acetyl-			3.18[e]	
Hydroxyl-		4.47[e]		
Amino-		6.68[a]	5.80[a]	8.96[a]
Carboxyl-	pK_1	1.08[d]	2.09[d]	1.82[d]
	pK_2	5.32[d]	4.75[d]	4.78[d]

[a] A. Alberts, R. Goldacre and J. Phillips, *J. Chem. Soc.*, 2240 (1948). The values have been corrected to 25° and zero ionic strength. [b] H. C. Brown and D. H. McDaniel, THIS JOURNAL, **77**, 3752 (1955). [c] H. C. Brown and X. R. Mihm, *ibid.*, 1723 (1955). [d] R. F. Evans, E. F. G. Herington and W. Kynaston, *Trans. Faraday Soc.*, **49**, 1284 (1953). [e] N. F. Hall and M. R. Sprinkle, THIS JOURNAL, **54**, 3469 (1932). The value for 2-hydroxypyridine is calculated assuming additivity from the pK_a value of 2-hydroxy-3-ethylpyridine. [f] P. Krumholz, *ibid.*, **73**, 3487 (1951); estimated from the reported values in 20% aqueous ethanol.

On the other hand, a number of groups exhibit unusual effects which make it undesirable to include such substituents in this study. Such groups as $-NH_2$, $-NO_2$, $-CHO$, $-COCH_3$, $-CO_2CH_3$, $-CO_2H$ and $-OH$ will not be examined here because they may involve extra resonance in either the pyridine molecule or the pyridinium ion[11]; also, picolinic acid may involve hydrogen bonding[12] and 2-hydroxypyridine exists as a keto–enol tautomeric mixture.[13]

Fortunately, these difficulties do not appear to be a factor in the case of the halogen and alkyl substituents and the discussion will therefore be limited primarily to the nature and magnitude of the *ortho* effects involving these substituents.

Benzoic Acid.—Values for the dissociation constants of representative benzoic acids are listed in Table II.

(11) The large increase in basicity of 4-aminopyridine can be attributed to additional ionic resonance in the pyridinium ion; A. Alberts, "The Acridines, Their Preparation, Physical, Chemical and Biological Properties and Uses," Edward Arnold and Co., London, 1951.

(12) N. H. Cantwell and E. V. Brown, THIS JOURNAL, **74**, 5967 (1952).

(13) H. Sperker and H. Gawrosch, *Ber.*, **75**, 1338 (1942).

TABLE II

pK_a VALUES OF SUBSTITUTED BENZOIC ACIDS IN AQUEOUS SOLUTION AT 25°

Benzoic Acid $XC_6H_4CO_2H$	Position 2-	3-	4-
Hydrogen-	4.20[b]	4.20[b]	4.20[b]
Fluoro-	3.27[b]	3.87[b]	4.14[b]
Chloro-	2.94[b]	3.83[a,b]	3.99[a]
Bromo-	2.85[b]	3.81[a,b]	4.00[a]
Iodo-	2.86[b]	3.86[a]	
Methyl-	3.91[b]	4.24[a]	4.34[a]
Ethyl-	3.77[d]		4.35[b]
Isopropyl-			4.35[b]
t-Butyl-	3.46[c]	4.28[c]	4.40[b]
Phenyl-	3.46[b]		

[a] G. Briegleb and A. Bieber, *Z. Elektrochem.*, **55**, 2509 (1951). [b] J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939). [c] J. B. Shoesmith and A. Mackie, *J. Chem. Soc.*, 300 (1936). [d] "International Critical Tables," Vol. VI, McGraw-Hill Book Co., Inc., New York, N. Y., 1929, p. 259.

As mentioned earlier, the *ortho* effect of an alkyl group is discernible readily since the polar effect of these groups is quite small. For example, a *t*-butyl group in the 3- or 4-position of benzoic acid results in a relatively small change in the strength of the acid (Table II). In the 2-position a *t*-butyl group produces a marked *increase* in acid strength. Such an increase is, of course, opposite to the effect of the *t*-butyl group in the 4-position and contrary to the predicted polar effect of an alkyl group.

Several explanations of the *ortho* effect in the benzoic acids have been advanced.[14–16] The most satisfactory explanation of the *ortho* effect in the benzoic acids appears to be steric inhibition of resonance.[17] The same explanation has been applied to explain the difference in the *i*-factors of 2,4- and 2,6-dimethylbenzoic acids.[18]

In Fig. 1 is shown a plot of the pK_a values for the substituted benzoic acid *versus* the corresponding values for the pyridine bases. The deviations for the hydrocarbon groups are in the order *t*-Bu– > Ph– > Et– > Me–. This is the order that would be expected for deviations arising from steric inhibition of resonance and supports this interpretation.

The high polar characteristics of the halogen substituents render it difficult to demonstrate the presence of an *ortho* effect by the procedure applied to 2-*t*-butylbenzoic acid. Indeed, Jenkins has made calculations on the halogen substituted benzoic acids in an attempt to show that the magnitude of the constants could be accounted for solely in terms of the inductive effects of these substituents.[19] However, Fig. 1 reveals that the halogen substituents also exhibit a deviation which is in the order of the steric requirements of the individual halogens, I– > Br– > Cl– > F– (fluorine showing no deviation within experimental error).

The most logical explanation of the *ortho* effect in the halogen substituted benzoic acids also ap-

(14) B. Flürscheim, *J. Chem. Soc.*, **95**, 718 (1909).

(15) G. M. Bennett and A. N. Moses, *ibid.*, 2364 (1930).

(16) J. F. J. Dippy, D. P. Evans, J. J. Gordon, R. H. Lewis and H. B. Watson, *ibid.*, 1421 (1937).

(17) G. Baddeley, *Nature*, **144**, 444 (1939).

(18) M. S. Newman, THIS JOURNAL, **63**, 2431 (1941).

(19) H. O. Jenkins, *J. Chem. Soc.*, 640, 1137 (1939).

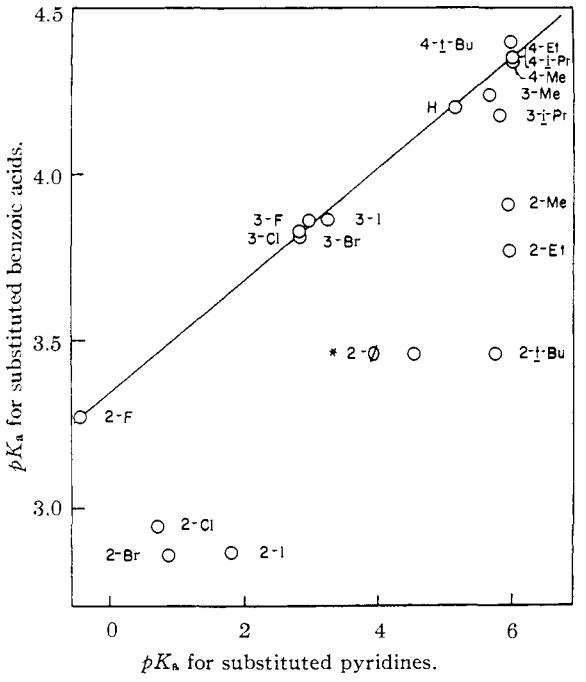


Fig. 1.—The relationship between the dissociation constants of the substituted benzoic acids and the substituted pyridines (*value estimated from other solvents).

pears to involve steric inhibition of resonance.[20] It should be noted that the observed magnitudes of the halogen deviations are in the opposite order of that which would be obtained if the hydrogen bonding of the *o*-halogen with the carboxyl group were important.[16]

The relationship represented in Fig. 1 permits a quantitative estimate to be made of the magnitude of the *ortho* effects in the benzoic acid system. In Table III are presented the *ortho* deviations along with the relative effect on the free energy of dissociation, calculated with aid of the relationship

$$\Delta\Delta F^\circ = -2.303RT\Delta pK_a$$

TABLE III

THE *ortho* EFFECT OF VARIOUS SUBSTITUENTS ON THE DISSOCIATION OF BENZOIC ACIDS

Substituent	ΔpK_a	$\Delta\Delta F^\circ$, kcal./mole
2-Fluoro-	0.0	0.0
2-Chloro-	− .52	.71
2-Bromo-	− .64	.87
2-Iodo-	− .79	1.08
2-Methyl-	− .44	0.60
2-Ethyl-	− .58	0.79
2-*t*-Butyl-	− .95	1.30
2-Phenyl-	− .65	0.89

Phenylboric Acids.—The phenylboric acids I bear a formal relationship to the benzoic acids II.

Data are available for the ionization of a number of substituted phenylboric acids[21] (Table IV).

(20) M. Crawford, *Nature*, **165**, 728 (1950), has adopted the same interpretation for *o*-chloro-, *o*-bromo- and *o*-iodobenzoic acid in accounting for the solubilities of the copper salts of these acids in mixed benzene–alcohol solvents.

(21) G. E. K. Branch, D. L. Yabroff and B. Bettman, THIS JOURNAL, **56**, 937 (1934).

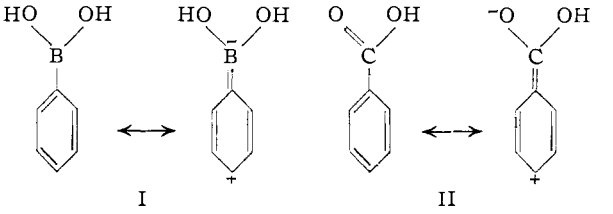


TABLE IV

pK_a VALUES OF SUBSTITUTED PHENYLBORIC ACIDS IN 25% ETHANOL AT 25°[a]

Phenylboric acid $XC_6H_4B(OH)_2$	Position 2-	3-	4-
Hydrogen-	9.71	9.71	9.71
Fluoro-		8.96	9.44
Chloro-	8.85	8.87	9.20
Bromo-		8.84	9.14
Methyl-	10.58	10.0	9.85

[a] Ref. 21. Values quoted by J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939).

It has been pointed out by Branch and Calvin[22] that resonance with the benzene ring has a greater acid-weakening effect in the phenylboric acids than in the benzoic acids. From this one might draw the conclusion that bulky *ortho* groups in phenylboric acid would cause an even greater acid-strengthening effect than in benzoic acid. However, the plot in Fig. 2 shows that the *ortho* effect of groups such as chloro or methyl is actually acid weakening.

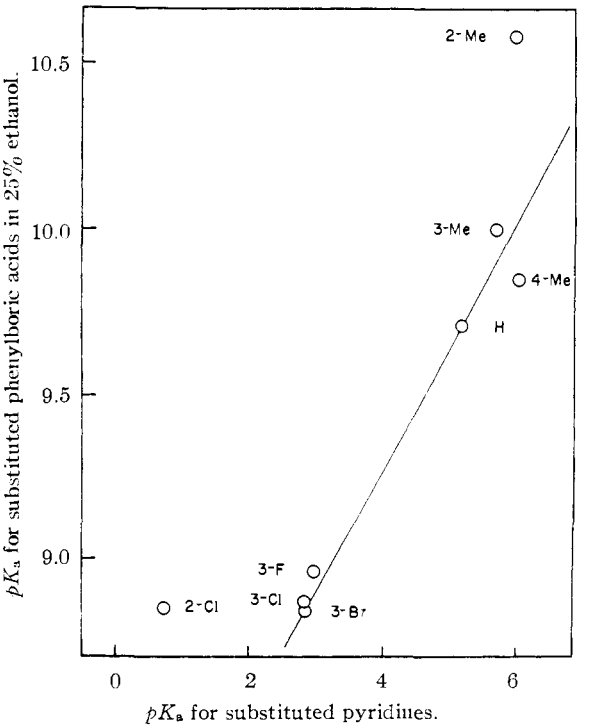


Fig. 2.—The relationship between the dissociation constants of the substituted phenylboric acids and the substituted pyridines.

This unexpected result suggests that the ionization reaction is not

(22) G. E. K. Branch and M. Calvin, ref. 7, pp. 243–244.

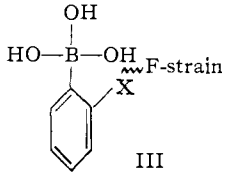
$$C_6H_5B(OH)(OH) + H_2O \rightleftharpoons C_6H_5B(OH)(O^-) + H_3O^+$$

but rather

$$C_6H_5B(OH)(OH) + 2H_2O \rightleftharpoons \left[C_6H_5B(OH)(OH)(OH)\right]^- + H_3O^+$$

It should be pointed out that the structure $H^+[B(OH)_4]^-$ has been proposed previously to account for the effect of polyhydroxy compounds on the strength of boric acid.[23]

The decrease in acid strength caused by *ortho* groups such as methyl or chloro is attributed to F-strain in the ion, $o\text{-}XC_6H_4B(OH)_3^-$ (III). Since resonance should be important in these compounds, it must be concluded that this factor outweighs the effect of steric inhibition of resonance.



III

That an acid-weakening effect is observed for *ortho* groups therefore may be taken as supporting evidence that the acidic character of the phenylboric acids and presumably of boric acid itself is due to the ability of boron to coördinate with a hydroxyl ion rather than to the loss of a proton from the parent acid.

Phenols.—Pertinent data on the strengths of substituted phenols are summarized in Table V.

TABLE V

pK_a VALUES OF SUBSTITUTED PHENOLS

Phenol XC_6H_4OH	In water at 25° Position 2-	3-	4-	In 48.9% ethanol at 20–22° Position 2-	3-	4-
Hydrogen-	9.95[e]	9.95[e]	9.95[e]	11.28[h]	11.28[h]	11.28[h]
Fluoro-	8.81[a]	9.28[a]	9.81[e]			
Chloro-	8.48[e]	9.02[g]	9.38[e]	9.95[g]	10.17[h]	10.60[h]
Bromo-	8.42[c]	9.11[d]	9.34[d]	8.89[g]	10.21[h]	10.50[h]
Iodo-		9.17[d]		10.02[g]	10.20[h]	10.41[h]
Methyl-	10.28[i]	10.08[b]	10.19[i]	11.55[g]	11.43[h]	11.61[h]
Ethyl-	10.2[c]	9.9[c]	10.0[c]			
Phenyl-	9.93[f]	9.59[f]	9.51[f]			
Acetyl-		9.19[b]	8.05[b]		10.43[h]	9.21[h]

[a] G. M. Bennett, A. L. Brooks and S. Glasstone, *J. Chem. Soc.*, 1821 (1935). [b] G. Bordwell and G. D. Cooper, THIS JOURNAL, **74**, 1058 (1952). [c] C. Golumbic, M. Orchin and S. Weller, *ibid.*, **71**, 2624 (1949). The values were determined at 28°. [d] H. H. Hodgson and R. Smith, *J. Chem. Soc.*, 263 (1939). [e] C. M. Judson and M. Kilpatrick, THIS JOURNAL, **71**, 3110 (1949). [f] F. Kieffer and P. Rumpf, *Compt. rend.*, **238**, 360 (1954). [g] Schwarzenbach and H. Egli, *Helv. Chim. Acta*, **17**, 1183 (1934). [h] G. Schwarzenbach and E. Rudin, *ibid.*, **22**, 360 (1939). [i] G. R. Sprengling and C. W. Lewis, THIS JOURNAL, **75**, 5709 (1953).

The plot of these pK_a values against those of the corresponding substituted pyridines is shown in Fig. 3. It will be observed that the alkyl groups show no deviations greater than the experimental uncertainty, whereas the *ortho* halo groups show a deviation F– > Cl– > Br–, I–, with bromine and iodine exhibiting almost normal behavior with respect to the line.

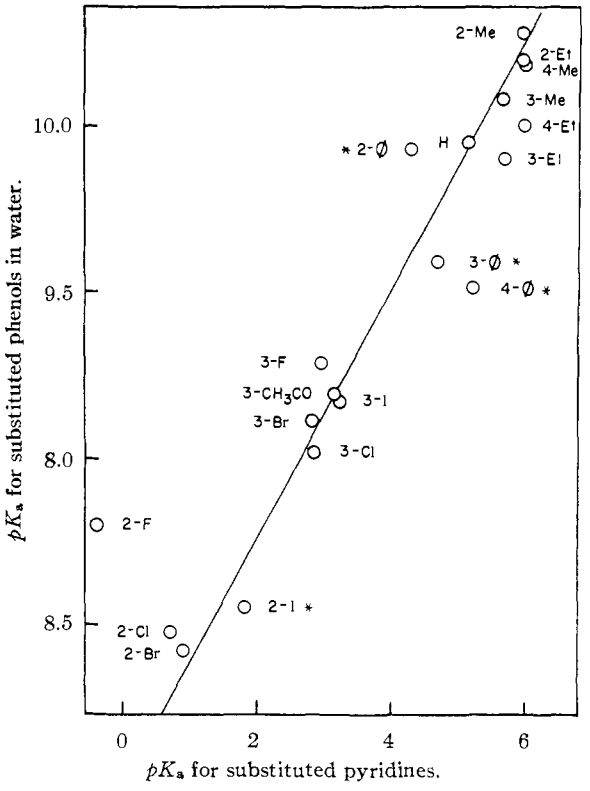
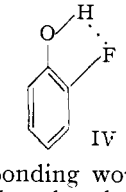


Fig. 3.—The relationship between the dissociation constants of the substituted phenols and the substituted pyridines (*value estimated from other solvents).

The normal behavior of the 2-alkyl groups suggests that neither steric inhibition of resonance nor F-strain can be a significant factor. Similarly, it does not appear that steric hindrance to solvation can be a factor with *ortho* groups of the magnitude being considered. Finally, the effect is largest with the 2-fluoro derivative, so that the *ortho* effect cannot have its origin in the steric requirements of the substituent.

It should be emphasized that the *ortho* effect under discussion is acid weakening. These results are readily explicable in terms of hydrogen bonding involving the *ortho* halogen substituent IV.



IV

Such hydrogen bonding would tend to stabilize the undissociated phenol and thus reduce the measured acid strength. Moreover, the order F– > Cl– > Br–, I– corresponds to the order anticipated for the relative importance of such hydrogen bonding. Hydrogen bonding has been shown to exist in *o*-chlorophenol in non-aqueous solvents from a study of the infrared absorption of the compound.[24] The above data suggest that such hydrogen bonding must persist even in aqueous solution.

(23) H. T. Macpherson and E. G. V. Percival, *J. Chem. Soc.*, 1920 (1937).

(24) O. R. Wulf and U. Liddell, THIS JOURNAL, **57**, 1464 (1935).

It may be further noted that such groups as -CHO and $-NO_2$ already have been reported to show hydrogen bonding with the -OH group,[25] and it has been shown that hydrogen bonding accounts for the increased strength of salicylic acid.[26] The second dissociation constant of this acid corresponds to the dissociation of the phenolic hydrogen and must therefore be correspondingly smaller.

The only *ortho* effect that we note with the phenols is one due to hydrogen bonding, alkyl groups exhibiting no appreciable deviations. This is contrary to a statement by Branch and Calvin that the methyl groups must show an acid-strengthening *ortho* effect which is attributed to a type of weak hydrogen bonding of the methyl group.[27]

With much bulkier alkyl groups, such as *t*-butyl, it appears that bulk steric effects of some kind become important. It has been suggested that the low apparent acidity of 2,4,6-tri-*t*-butylphenol and related compounds is due to steric hindrance to solvation of the ion.[28] However, in the absence of quantitative data on the dissociation constants of phenols of this kind, the present treatment cannot be applied and further discussion at this time appears undesirable.[29]

Thiophenols.—The dissociation constants of the substituted thiophenols in 48.95 vol. % ethanol at 20–22° are reported in Table VI.

Examination of the plot of the pK_a values for these substituted thiophenols *versus* those of the corresponding pyridines (Fig. 4) reveals that the *ortho* deviations appear quite similar to those already discussed for the phenols themselves. We may conclude therefore that the same factors control the *ortho* effect, that is, that substituents which may participate in hydrogen bonding will show an *ortho* effect.

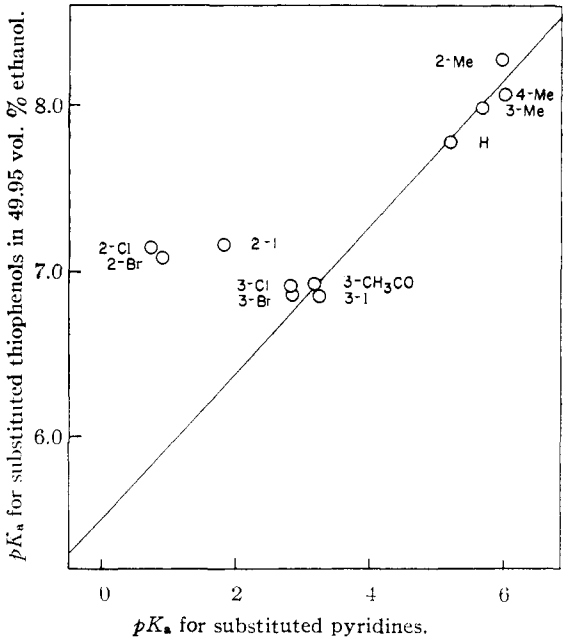


Fig. 4.—The relationship between the dissociation constants of the substituted thiophenols and the substituted pyridines.

TABLE VI

pK_a VALUES OF SUBSTITUTED THIOPHENOLS IN 48.9% ETHANOL AT 20–22°

Thiophenol XC_6H_4SH	Position 2-	3-	4-
Hydrogen-	7.78[b]	7.78[b]	7.78[b]
Chloro-	7.14[a]	6.85[b]	7.06[b]
Bromo-	7.08[a]	6.90[b]	7.00[b]
Iodo-	7.17[a]	6.85[b]	6.99[b]
Methyl-	8.28[a]	7.99[b]	8.07[b]
Acetyl-		6.93[b]	5.93[b]

[a] G. Schwarzenbach and H. Egli, *Helv. Chim. Acta*, **17**, 1183 (1934). [b] G. Schwarzenbach and E. Rudin, *ibid.*, **22**, 360 (1939).

It is of interest to compare the relative importance of the *ortho* effects in the two systems, phenol and thiophenol. Fortunately data are available for both of these systems under identical conditions, 20° and 48.45 vol. % ethanol. In Fig. 5 is shown a plot of the pK_a values for the substituted phenols in 48.9% ethanol against the pK_a values of the corresponding pyridines. The *ortho* effects of halogen substituents in phenol and thiophenol, estimated from the plots in Figs. 4 and 5, are summarized in Table VII.

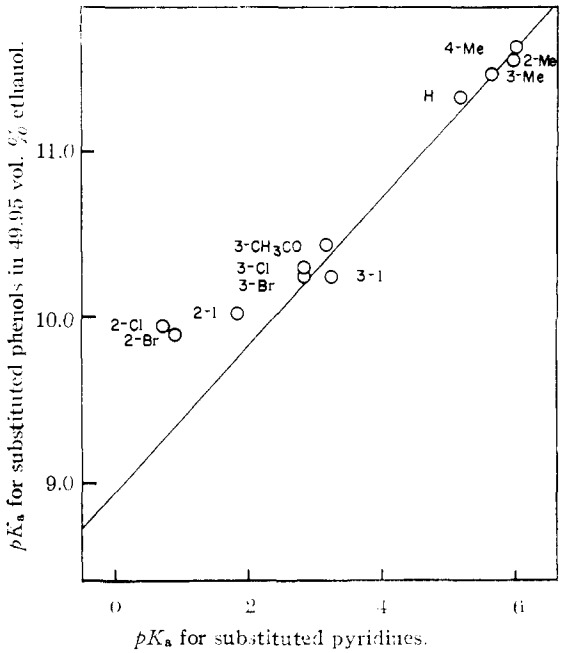


Fig. 5.—The relationship between the dissociation constants of the substituted phenols in 48.95 vol. % ethanol and the substituted pyridines.

The *ortho* deviation of the halogen derivatives in the thiophenol system is nearly twice that of the phenol system. The conclusion already has been reached that the *ortho* effect in these systems is due to hydrogen bonding. It follows that hydrogen bonding must be more important in the thiophenols than in the phenols.

(25) R. T. Arnold and J. Sprung, THIS JOURNAL, **61**, 2475 (1939).
(26) G. E. K. Branch and D. L. Yabroff, *ibid.*, **56**, 2568 (1934).
(27) G. E. K. Branch and M. Calvin, ref. 7, p. 264.
(28) P. D. Bartlett, *J. Chem. Ed.*, **30**, 22 (1953).
(29) We are presently undertaking a study of the dissociation constants of phenols with bulky *ortho* substituents in the hope of extending the present quantitative treatment to these compounds.

TABLE VII

THE *ortho* EFFECT OF HALOGEN SUBSTITUENTS IN PHENOLS AND THIOPHENOLS IN 48.95% ETHANOL

Substituent	Phenol ΔpK_a	Phenol $\Delta\Delta F^0$, kcal./mole	Thiophenol ΔpK_a	Thiophenol $\Delta\Delta F^0$, kcal./mole
2-Fluoro-		(−4.6)[a]		
2-Chloro-	0.72	−0.98	1.33	−1.82
2-Bromo-	.63	− .86	1.23	−1.68
2-Iodo-	.35	− .48	0.92	−1.26

[a] No data are available for the 2-fluoro derivatives in 48.95% ethanol. Estimated on basis that in water the *ortho* effect in 2-fluorophenol is 4.7 greater than that for 2-chlorophenol. See also discussion in footnote 32.

This startling conclusion is directly opposed to the widely accepted generalization regarding the relative tendency for oxygen and sulfur to participate in hydrogen bonding.[30] If the proposed explanation is at all reasonable, some explanation must be available for the apparent reversal in the usual strengths of hydrogen bonds involving sulfur as against oxygen.

It is suggested that the unusual behavior of the thiophenol derivatives is due to the smaller sulfur–hydrogen bond angle[31] and the larger size of the sulfur atom.[31] The smaller bond angle should favor hydrogen bonding, since it places the hydrogen in a more favorable position for bonding with the halogen. The larger size of the sulfur atom should result in some repulsion between the sulfur and halogen atoms, a repulsion which would be diminished by formation of the internal hydrogen bond.[32]

TABLE VIII

pK_a VALUES OF SUBSTITUTED ANILINES IN WATER AT 25°

Aniline $XC_6H_4NH_2$	Position 2-	3-	4-
Hydrogen-	4.58[d]	4.58[d]	4.58[d]
Fluoro-	2.96[a]	3.32[f]	4.52[f]
Chloro-	2.62[f]	3.32[f]	3.81[f]
Bromo-	2.60[c]	3.51[c]	3.91[c]
Iodo-	2.24[b]		
Methyl-	4.38[f]	4.67[f]	5.07[d,f]
t-Butyl-	3.78[g]		
Phenyl-	3.78[d]	4.18[e]	4.27[d]

[a] G. M. Bennett, G. L. Brooks and S. Glasstone, *J. Chem. Soc.*, 1821 (1935). [b] J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939). Corrected to water from another solvent. [c] N. F. Hall, THIS JOURNAL, **52**, 5115 (1930). [d] N. F. Hall and M. R. Sprinkle, *ibid.*, **54**, 3469 (1932). [e] F. Kieffer and P. Rumpf, *Compt. rend.*, **230**, 1874 (1950). Corrected to 25° from the value reported. [f] M. Kilpatrick and C. A. Arenberg, THIS JOURNAL, **75**, 3812 (1953), based upon 4.58 for aniline. [g] P. E. Verkade, B. M. Wepster and co-workers, private communication.

(30) See for example N. V. Sidgwick, "The Chemical Elements and Their Compounds," Vol. I, Oxford University Press, London, 1950, p. 28.

(31) L. Pauling, "The Nature of the Chemical Bond," Ind. 2nd, Cornell University Press, Ithaca, N. Y., 1940, pp. 79, 189.

(32) Both X-ray diffraction and electron diffraction studies indicate that in the *o*-dihalobenzenes, halogen being chlorine, bromine or iodine, the halogen atoms distort the normal bond angles due to their steric interactions; R. Schoppe and K. L. Wolf, *Z. ges. Naturw. Naturphilos. Gesch. Naturw. Med.*, **1**, 67 (1935); R. Schoppe, *ibid.*, **1**, 122 (1935); *C. A.*, **30**, 6253 (1936); S. B. Hendricks, L. R. Maxwell, V. L. Mosely and M. E. Jefferson, *J. Chem. Phys.*, **1**, 549 (1933). Since the steric requirements of sulfur are much larger than oxygen and quite similar to chlorine, similar steric interactions would be expected in the *o*-chloro-, *o*-bromo- and *o*-iodothiophenols. The steric interaction should be less in 2-fluorothiophenol and the estimate in Table VII therefore may be too high.

Anilines.—The pK_a values for the substituted anilines are summarized in Table VIII.

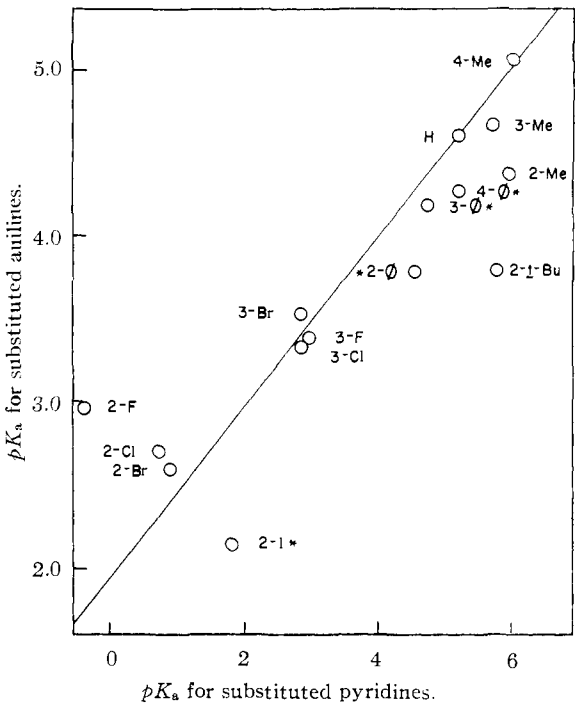


Fig. 6.—The relationship between the dissociation constants of the substituted anilines and the substituted pyridines (*value estimated from other solvents).

In the plot of these pK_a values *vs.* the pK_a values for the corresponding pyridine bases (Fig. 6) it is observed that all *ortho* alkyl groups decrease the base strength or, in terms of the anilinium ion, increase the acid strength. To account for this effect various explanations, such as an unusual inductive effect of *ortho* alkyl groups,[15] or hydrogen bonding with the *o*-methyl group,[16] have been proposed. However, the increased acid strength of the *ortho* alkyl substituted anilinium ions recently has been attributed to the increased strain in the *ortho* substituted anilinium ion as compared to the free base.[33] This explanation is rendered plausible by the homomorphic relationship of these anilinium ions V to the borine addition compounds of the corresponding pyridines VI, a system in which F-strain can be demonstrated to be present.

V VI

The magnitude of the *ortho* deviations are summarized in Table IX.

The relatively small difference between the effect of the methyl and *t*-butyl groups is unexpected. It may be that the *t*-butyl group causes some steric inhibition of resonance in the parent aniline base. This would result in a contribution which would

(33) H. C. Brown and A. Cahn, THIS JOURNAL, **72**, 2939 (1950).

TABLE IX

THE *ortho* EFFECT OF VARIOUS SUBSTITUENTS ON THE DISSOCIATION OF ANILINES

Substituent	ΔpK_a	$\Delta\Delta F^0$, kcal./mole
2-Fluoro-	1.23	−1.68
2-Chloro-	0.30	−0.41
2-Bromo-	.19	− .26
2-Iodo-	− .64	.87
2-Methyl-	− .63	.86
2-*t*-Butyl-	− .87	1.19
2-Phenyl-	− .50	0.63

tend to diminish the resultant increase in acidity of the anilinium ion.

The effects of the halogens are more complex than those of the alkyl groups. The 2-fluoro substituent causes a decrease in acidity of the anilinium ion, the 2-iodo group causes an increase. This suggests the operation of two factors, the effect of each of which must change in opposite orders as we go from fluorine to iodine. It is proposed that the two factors involved are hydrogen bonding of the anilinium hydrogens with the *o*-halogen, and F-strain of the type discussed for the *o*-methyl groups.

Hydrogen bonding should decrease in the order F− > Cl− > Br− > I−. As the importance of hydrogen bonding decreases, the size of the substituent increases, resulting in a growing contribution from F-strain. The deviation observed in 2-iodoaniline which is in the opposite order to that observed for 2-fluoroaniline, therefore is attributed to an F-strain effect which in the 2-iodoanilinium ion is sufficient to counterbalance any contribution from hydrogen bonding.

Steric hindrance of resonance in the free base conceivably could also be a factor. However, with the possible exception of 2-*t*-butylaniline discussed previously the data do not indicate that this factor is of significance in the compounds under consideration.

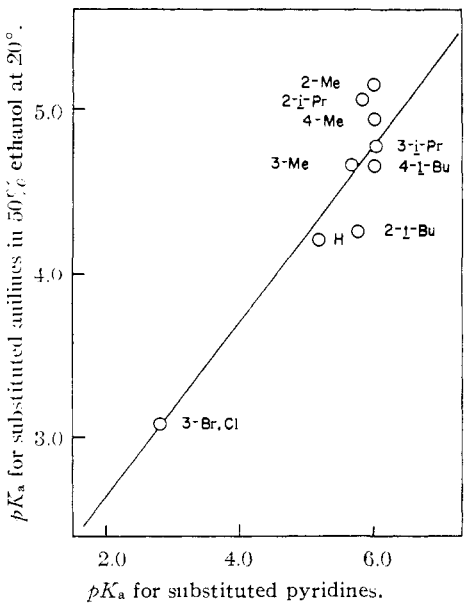


Fig. 7.—The relationship between the dissociation constants of the substituted dimethylanilines and the substituted pyridines.

Dimethylaniline.—Data on the dimethylanilines in 50% ethanol are given in Table X and a plot of these pK_a values against those for the correspondingly substituted pyridines are given in Fig. 7.

TABLE X

pK_a VALUES FOR SUBSTITUTED DIMETHYLANILINES IN 50% ETHANOL AT 20°

Dimethylaniline $XC_6H_4N(CH_3)_2$	Position 2-	3-	4-
Hydrogen-	4.21[c]	4.21[c]	4.21[c]
Chloro-		3.09[a]	3.33[c]
		3.08[a]	
Methyl-	5.15[d]	4.66[a]	4.94[a]
Isopropyl-	5.05[d]		4.77[b]
t-Butyl-	4.26[d]		4.65[b]

[a] R. A. Benkeser and H. R. Krysiak, THIS JOURNAL, **75**, 2421 (1953). [b] W. C. Davies, *J. Chem. Soc.*, 1865 (1938). [c] W. C. Davies and H. W. Addis, *ibid.*, 1622 (1937). [d] P. E. Verkade, B. M. Wepster and co-workers, private communication; values at 25°.

The estimated deviations are summarized in Table XI. It will be observed that in going from 2-methyl to 2-*t*-butyl there is a complete reversal in the direction of the deviation.

TABLE XI

THE *ortho* EFFECT OF ALKYL SUBSTITUENTS ON THE DISSOCIATION OF DIMETHYLANILINES

Substituent	ΔpK_a	$\Delta\Delta F^0$, kcal./mole
2-Methyl-	−0.39	0.53
2-Isopropyl-	− .37	.50
2-*t*-Butyl-	+ .37	− .50

The 2-methyl group decreases the acid strength of the dimethylanilinium ion, whereas the 2-*t*-butyl group increases the strength. Two factors must therefore be operating in opposition to each other as the size of the alkyl group is increased. Steric inhibition of resonance is much more important in the *ortho* substituted dimethylanilinium ions than in the parent anilinium ions, thereby accounting for the marked effect of the 2-methyl and 2-isopropyl groups in the dimethylanilinium series. As the size of the *ortho* alkyl group increases, F-strain in the corresponding dimethylanilinium ion increases, resulting in an increase in the acid strength.[34] In the case of the bulky 2-*t*-butyl substituent this F-strain effect must become larger than and actually overcome the acid-weakening effect of steric inhibition of resonance.[33]

With the possibilities for steric inhibition of resonance, F-strain and hydrogen bonding, the behavior of the 2-halodimethylanilines should be particularly interesting. Unfortunately, data are not now available on these compounds. However, one might make the following predictions: the deviation of all of these groups should be toward the acid-weakening side. That is, the pK_a values should be higher than that predicted from the linear relationship. Fluorine should deviate primarily due to hydrogen bond formation, with iodine deviating primarily due to the effect on steric inhibition of resonance, and chlorine and bromine should fall in

(34) The small difference in the effects of the isopropyl and methyl groups is attributed to the ability of the isopropyl group to reduce the effective strain by rotation so as to place the bulky portion of the groups in a direction away from the dimethylanilino group.

between. F-Strain should become a dominant factor only with reference acids having greater steric requirements than the proton.

Conclusions.—By using the alkyl and halo substituted pyridine bases as a reference system free of significant *ortho* effects, it has been possible to arrive at a quantitative measure of the *ortho* effects of these groups in other aromatic systems. In the case of the halogens, evidence has been advanced to support the conclusion that hydrogen bonding, steric inhibition of resonance and F-strain all contribute to the *ortho* effects in the acids and base examined. The important effects appear to be: 1, benzoic acids, steric inhibition of resonance; 2, phenylboric acids, F-strain in the anion complex; 3, phenols and thiophenols, hydrogen bonding; 4, anilines, hydrogen bonding and F-strain (in the anilinium ion); 5, dimethylanilines, no data available: hydrogen bonding (in the anilinium ion) and steric inhibition of resonance (in the free base) expected to be important.

Recently Taft[35] has made a brilliant attempt to extend the scope of the Hammett equation[36,37] to include *ortho* substituents. We shall not attempt to discuss Taft's treatment here, but we will comment on certain of his conclusions which bear on the subject matter of the present paper.

Taft finds that the ionization constants for the *ortho* substituted benzoic acids can be related linearly to the σ-values he has developed, that is, to what he calls the electron displacement parameter. From this observation he draws the conclusion that "the relative ionization of those benzoates listed (CH_3O–, CH_3–, C_6H_5–, Cl–, Br–, I–, O_2N–) are determined by polar effects of substituents and are not dependent to an appreciable degree upon steric factors." He also finds a linear relationship for the dissociation of *ortho* substituted anilines utilizing his σ-values.

From the treatment presented in the present paper, it would appear that the various types of *ortho* effects cannot be considered entirely negligible in comparison with the polar effects. Consequently, it would appear that Taft's σ-constants may represent a composite of a major contribution by the polar factor with relatively minor contributions by the different *ortho* effects. These σ-constants may be expected to operate satisfactory only in cases where the polar factor continues to dominate the situation. Taft has pointed out that his treatment may be expected to fail when steric effects are not nearly constant relative to polar effects.[35]

Many apparently erroneous interpretations of *ortho* effects have appeared in the literature, in part because no suitable reference system has been available to permit a quantitative estimate of the magnitude of the *ortho* effect. The pyridine bases appear to provide a reasonably satisfactory reference system of this kind.

LAFAYETTE, INDIANA

(35) R. W. Taft, Jr., THIS JOURNAL, **74**, 2729, 3120 (1952); **75**, 4231, 4538 (1953).

(36) L. P. Hammett, ref. 5, pp. 184–193.

(37) H. H. Jaffe, *Chem. Revs.*, **53**, 191 (1953).

[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Base-catalyzed Methanolysis of *l*-Menthyl *m*- and *p*-Alkylbenzoates

BY MELVIN S. NEWMAN AND ELIOT K. EASTERBROOK[1]

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The rates for the sodium methoxide catalyzed methanolysis of *p*-alkyl *l*-menthyl benzoates fall in the order, $CH_3 < C_2H_5 < i\text{-}C_3H_6 < t\text{-}C_4H_9$, which indicates that the hyperconjugative effect is predominant. In the *m*-series the same order is obtained. To account for this order in the *m*-series a steric effect is suggested. The rates for all of the compounds fall very close together and all rates are slower than that for *l*-menthyl benzoate.

Two mechanisms of electron release by alkyl groups are recognized—the inductive and hyperconjugative. We were interested in observing the effect of methyl, ethyl, *i*-propyl and *t*-butyl groups in the *meta* and *para* positions relative to a carboxylic acid derivative in a typical reaction of the carbonyl addition type. In this paper we report on the base-catalyzed methanolysis of *l*-menthyl benzoates in absolute methanol at 30 and 40°.

This reaction was chosen for a study of the polar effects of alkyl groups on a carbonyl addition reaction since the ρ-value of +2.62 computed from published data[2] indicated that the methanolysis of *l*-menthyl benzoates at 30° was more sensitive to polar effects than the alkaline hydrolysis at 30° of ethyl benzoates in 87.83% by weight ethanol for which a ρ-value of 2.498 had been calculated.[3]

The *m*-alkylbenzoic acids, except for *m*-toluic acid, were prepared from the corresponding alkylbenzenes. Nitration afforded a mixture of *o*- and *p*-nitroalkylbenzenes which, without isomer separation, were reduced to the corresponding amino compounds. By means of acetylation, bromination, deacetylation and deamination, these amines were converted into the corresponding *m*-bromoalkylbenzenes. The latter were converted to nitriles which were hydrolyzed to acids. The *m*-isopropylbenzoic acid thus obtained melted at 49–50°. Since at the time a m.p. of about 20° had been reported,[4] this compound was prepared by an alternate method from *m*-bromobenzoyl chloride. The

(1) This paper is based on the Ph.D. thesis of E. K. E., Ohio State University 1953. E. K. E. was holder of the Visking Chemical Corporation fellowship, 1952–1953.

(2) R. W. Taft, Jr., M. S. Newman and F. H. Verhoek, THIS JOURNAL, **72**, 4511 (1950).

(3) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 189.

(4) W. S. Calcott, J. W. Tinker and V. Weinmayer, THIS JOURNAL, **61**, 1010 (1939). Later a m.p. of 47–48° was reported—see ref. 14.