sodium, the liberation of hydrogen was not additive. For example, an equimolecular mixture of glycine and tyrosine liberated 67% of the amount of hydrogen that they would liberate if taken separately; a mixture of glycine, alanine and tyrosine in the proportions in which they are present in silk liberated 72%; an equimolecular mixture of glycylglycine and diketopiperazine liberated about 2%, and a mixture of 2 moles of glycylglycine and 1 mole of diketopiperazine liberated 5% of the calculated amount. This unexpected decrease in the quantity of hydrogen liberated may be due to a more complete reduction of diketopiperazine by sodium and an acid than by sodium alone. We have no explanation to offer for the anomalous behavior of the mixtures of amino acids. If partial condensation of amino acids took place with formation of dipeptides and water or some diketopiperazine and water, they would act in this way.

Summary

1. A study of the reaction of sodium in liquid ammonia with certain amino acids, dipeptides, diketopiperazine, and type compounds has been made.

2. Glycine and alanine react as monobasic acids. The phenol group of tyrosine is slightly acidic. Some tyrosine seems to be reduced in the treatment. Leucine liberates more hydrogen than does a monoaminomonocarboxylic acid. Cystine is reduced by sodium, in part, by sodium acting directly upon the disulfide bond.

3. The peptide linkage in dipeptides is not acidic in liquid ammonia.

4. Diketopiperazine is reduced by sodium in liquid ammonia.

5. Mixtures of amino acids and of amino acids and diketopiperazine do not liberate hydrogen, additively, as is to be expected.

CHICAGO, ILLINOIS RECEIVED DECEMBER 16, 1933

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Dissociation Constants of the Chlorophenyl and Phenetyl Boric Acids[1]

BY G. E. K. BRANCH, DAVID L. YABROFF AND BERNARD BETTMAN

The idea that a group possesses a single characteristic, called variously its negativity, polarity and electron-sharing ability, or group electric dipole, whereby it influences the dissociation of an acid, is quite old. This theory could not have persisted for so long a time without having a large element of truth, but it gives an incomplete picture of the effects of groups on acidic strength. That other influences exist is shown by the fact that even the sign of the effect upon substituting one group for another is often dependent on the rest of the molecule. For example, the dissociation constant of chloroacetic acid is greater than that of acetoacetic acid, but acetic acid is stronger than hypochlorous acid. Also cyanacetic acid is stronger than chloroacetic acid but hydrogen cyanide is much weaker than hydrogen chloride. The effects of groups on dissociation constants should therefore be studied in all possible types of acids. We propose to obtain and compare the dissociation constants of a variety of substituted boric acids. That these constants have not been investigated by other workers is sufficient excuse for the work. The dissociation constants of these substances, however, are especially interesting, since they depend on the possibilities of molecular resonances that arise through the lack of a completed octet in the valence shell of the trivalent boron atom.

Since many substituted boric acids are but sparingly soluble in water, we have used a 25% solution of ethyl alcohol (by volume) in water as the solvent. The results are therefore not directly comparable with those obtained in water but only among themselves. Some of the more soluble acids have also been measured in water solution. The dissociation constants are all smaller in the alcohol solution than in water. The ratio of the constants, in water and in alcohol solution, is about five for boric acid and about seven for phenylboric and *o*-tolylboric acids.

The ionization of boric acid and probably of its derivatives can be complex,[2] involving poly-

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[1] It is suggested by the Referee of this paper that the name aryl boric acid, as applied to $ArB(OH)_2$, should be changed to aryl boronic acid in analogy to the sulfonic acids. We agree with this suggestion since the "aryl boric" acids are actually misnamed. We have retained the old nomenclature, however, since many of these compounds have been known for a long time and are catalogued under that name. It might be advisable that the Referee's suggestion be adopted by contributors to THIS JOURNAL.

[2] Kolthoff, *Rec. trav. chim.*, **45**, 501 (1926).

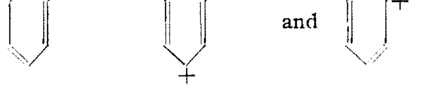
merization and the formation of polyvalent ions. We are, however, desirous of measuring only the simplest reaction. We have therefore used dilute solutions and have measured the dissociation at several concentrations. When the constants for the reaction $RB(OH)_2 = RBO_2H^- + H^+$ are approximately the same at varying concentrations, it can be assumed that polymerization is negligible. This test also shows that the values obtained are approximately valid for infinite dilution. All the boric acids described in the present article fulfil this requirement.

In this paper we have restricted ourselves to a study of the effects of negative groups possessing unshared electron pairs, on the dissociation of phenylboric acid. We have chosen the two groups $-Cl$ and $-OC_2H_5$. For purposes of comparison we have also measured the three chlorophenols in 25% ethyl alcohol solution as well as boric acid. The chlorophenols have been measured by various investigators[3] in different solvents, but very consistent results have not been obtained. Our results for the meta and para isomers are fairly consistent, being of about the same accuracy as the boric acids that we have measured. The results for the ortho isomer are less satisfactory, being about half as accurate as the other values. This difficulty with *o*-chlorophenol has already been noted by Kuhn and Wassermann,[3] who obtained constants which varied by as much as 70%. Phenylboric acid has been remeasured in aqueous solution, giving a more accurate value than that obtained before.[4] The results are given in the table. The values for the nitro and hydroxy phenols have been taken from Landolt and Börnstein.[5]

Acid	Solvent	$Ka \times 10^{10}$ at 25°
Boric	Water	6.53
Phenylboric $C_6H_5B(OH)_2$	Water	13.7
Boric	25% EtOH	1.34
Phenylboric	25% EtOH	1.97
o-Chlorophenylboric	25% EtOH	14.0
m-Chlorophenylboric $Cl—C_6H_4—B(OH)_2$	25% EtOH	14.5
p-Chlorophenylboric	25% EtOH	6.23
o-Phenetylboric	25% EtOH	0.910
m-Phenetylboric $C_2H_5O—C_6H_4—B(OH)_2$	25% EtOH	3.05
p-Phenetylboric	25% EtOH	0.608
o-Chlorophenol	25% EtOH	7.97
m-Chlorophenol	25% EtOH	3.30
p-Chlorophenol	25% EtOH	1.46
o-Nitrophenol	Water	680
m-Nitrophenol	Water	53
p-Nitrophenol	Water	650–700
o-Hydroxyphenol	Water	3.3
m-Hydroxyphenol	Water	3.6
p-Hydroxyphenol	Water	1.1

In aromatic acids there are at least two influences that a substituent group may exert. The first is the so-called I-effect or negativity, which arises from the electric dipole of the group. When only this factor is effective, the substitution of one group for another changes the dissociation constants of aromatic and saturated fatty acids in the same direction. The magnitude of the effect is greater the nearer the substituted groups are to the dissociating hydrogen atom. Groups may then be ordered fairly consistently according to their negativities, *e. g.*, NO_2, Cl, COR, OH, C_6H_5, H, CH_3, and with groups more negative than the hydrogen atom, the order of strength of isomeric aromatic acids is ortho, meta, para. The second type of influence arises from what may be called molecular resonance. The actual structure of the molecule may not be that usually assigned to it, but a combination of structures. These resonances are particularly liable to arise in aromatic compounds. When resonance is present, the exchange of one group for another, say OR for H, may produce an effect in one acid which is opposite to that produced in another, and the natural ortho, meta, para order of strengths of aromatic acids may be changed.

The effects on the strengths of aromatic acids produced by resonance can be very complex, but here we shall only consider the simpler ones. There are two types of groups whose conjugations with the aromatic nucleus produce diametrically opposite effects on acidic strengths. The first of these has an oxygen atom doubly bonded to the atom attached to the ring. This type may be exemplified by the groups NO_2 and COR. Resonance arises between the structures



The last two structures contribute a positive potential to the ortho and para atoms and thus en-

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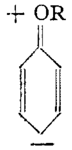
[3] Kuhn and Wassermann, *Helv. Chim. Acta*, **11**, 3 (1928); Mizutani, *Z. physik. Chem.*, **118**, 318, 327 (1925); Bader, *ibid.*, **6**, 295 (1890).

[4] Yabroff, Branch and Almquist, This Journal, **55**, 2935 (1933).

[5] Landolt and Börnstein, Vol. 2, ed. 5, 1923, pp. 1139, 1142, 1144, 1147.

hance the strengths of the ortho and para nitro acids. The meta positions are not so markedly affected, as the charging up of the meta atoms, if possible at all, would be due to the much smaller contributions of the very unstable meta quinoidal configurations. The second type of resonating group has a pair of unshared electrons on the atom attached to the benzene ring. This type is exemplified by halogen, hydroxyl, alkoxyl and amino groups. The quinoidal structures that combine with the benzenoid are



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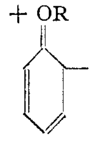
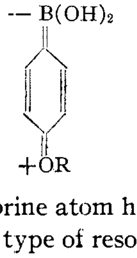


A negative charge is produced in the ortho and para positions, and the resonance diminishes the strength of the ortho and para acids. Again the meta acids are much less affected.

The effects of these resonances may be greatly enhanced if an added acidic group in the ortho or para position is capable of supplying electrons in the case of the nitro type of resonance, or of receiving electrons in the case of the alkoxyl type of resonance. Thus in *p*-nitrophenol the quinoidal form  contributes considerably to the structure of the molecule, and the acidic strength is greatly enhanced by this resonance. *p*-Nitrophenol is about ten times as strong an acid as its meta isomer.

In a phenylboric acid derivative the boron atom is capable of receiving electrons, and the alkoxyl type of resonance is enhanced. The quinoidal forms involved in the resonance are



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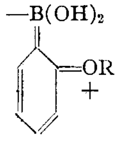

Since a chlorine atom has unshared electron pairs, the alkoxyl type of resonance is possible in chloroaromatic acids. The tendency of the chlorine atom to form more than one bond is very small and the negativity of the atom is great, hence the importance of resonance relative to negativity is small in chloro compounds.

We might summarize as follows: the relative importance of the alkoxyl type of resonance to the negativity factor is greater with alkoxyl than with chloro compounds, and is greater in phenylboric acid derivatives than in phenols. This is borne out by the data shown in the table. The chlorophenols are all much stronger than phenol and they have the normal ortho, meta, para order of strengths. The chlorophenylboric acids are all stronger than phenylboric acid, but the ortho, meta, para order of strengths is changed, the ortho acid being no stronger than the meta isomer. In the dihydroxybenzenes the ortho isomer is only about ten per cent. weaker than the meta, but in the phenetyl boric acids the ortho acid is only about one-third the strength of the meta isomer. *m*-Phenetylboric acid is about fifty per cent. stronger than phenylboric acid due to the negativity of the ethoxyl group. The weakening effect of resonance (which occurs only to a very slight extent in the meta isomer) in the ortho and para positions, overcomes the effect of negativity and we find that both the ortho and para phenetylboric acids are weaker than the unsubstituted acid.

The study of the dissociation constants of other substituted boric acids and of certain phenols, anilines and benzoic acids is being continued in this Laboratory.

Experimental Section

Simplified Boron Analysis.—In a previous paper[6] the observation was made that phenylboric acid could be somewhat accurately titrated with sodium hydroxide solution in the presence of glycerine with phenolphthalein as the indicator. We have now investigated the titration of other organic boric acids and find that a slightly modified method is capable of an accuracy of about 2–4% if the dissociation constant of the boric acid is about 10^{-10}. With weaker acids the titration is not complete at the phenolphthalein end-point. An acid of the strength of about 10^{-12} may be titrated only about 90%. Adding more mannitol in these cases does not appreciably affect the results. This analysis has the advantage of being simple and rapid as well as reasonably accurate in those cases where it can be used.

Enough of the organic boric acid to give a titer of 20 to 30 cc. of 0.1 *N* alkali is weighed out and suspended in 50 cc. of 50% ethyl alcohol. About 50 cc. of water is added and the mixture is warmed to effect solution. The solution is cooled to room temperature, and 10 to 15 g. of mannitol and about 0.5 cc. of phenolphthalein solution are added. The solution is titrated with 0.1 *N* sodium

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[6] Branch and Yabroff, THIS JOURNAL, **54**, 2569 (1932).

hydroxide solution to a definite pink end-point. Mannitol gives much better and more accurate end-points than glycerine. If the solution is titrated while warm, the end-point will be obtained when 2 to 3% too little alkali has been added.

Melting Points.—It has already been noted by Seaman and Johnson[7] that the melting point of an organic boric acid depends on the rate of heating of the bath as well as the temperature from which the substance is heated. This occurs because most of these substances decompose or form anhydrides even on gentle heating. We have therefore obtained our melting points by instant immersion of a capillary tube into a bath. A fresh sample is used for each immersion until the melting temperature is found. In several of the present compounds we have obtained melting points which are quite different from those previously reported. In these cases the compound has been recrystallized at least once more and the melting point redetermined. In every case the melting point was unchanged after further purification.

***o*-Chlorophenylboric Acid.**—This compound was prepared by the improved ester method of Bean and Johnson[8] by the interaction of *n*-butyl borate and *o*-chlorophenylmagnesium bromide at −75°. *o*-Chlorobromobenzene was prepared by the Sandmeyer reaction with *o*-chloroaniline according to the method of Van der Linden.[9] It was found that the $B(OH)_2$ group is very readily removed from the phenyl nucleus in the presence of alkali in this particular boric acid, so the steam distillation under reduced pressure (to remove butyl alcohol from the crude reaction mixture[8]) was carried out in neutral solution. Because of this decomposition it was necessary to add the alkali just before measurements were taken with the electrode. The measurements were completed about fifteen minutes after the addition.

o-Chlorophenylboric acid crystallizes in the form of needles from water. Upon instant immersion the acid melts completely at 97–98° (corr.). Repeated recrystallizations from water, ligroin and kerosene failed to raise the melting point. If the substance is heated below its melting point the anhydride slowly forms and the sample does not melt until 167–169°. Some of the acid was dehydrated in a vacuum desiccator containing concentrated sulfuric acid. The anhydride thus obtained (loss of water correct for the ArBO compound) melted at 171–172° (corr.). The anhydride is quite hygroscopic. Koenig and Scharrnbeck[10] report the melting point of the acid as 149°.

Anal. Calcd.: Cl, 22.7; B, 6.92. Found: (Carius, free acid) Cl, 22.4; (direct titration) B, 6.83, 6.79.

***m*- and *p*-Chlorophenylboric Acids.**—These were both prepared by the interaction of the corresponding chlorophenylmagnesium bromides with boron trifluoride. The meta compound has not been prepared previously. It crystallizes in sheets and plates from water, m. p. 189–190° (corr.). The para compound crystallizes from water in the form of needles or plates, depending on the concentrations used and on the rate of cooling of the solutions. It melts at 306–307° (corr.). Krause[11] gives 275° as the melting point of this compound.

Anal. Calcd.: Cl, 22.7; B, 6.92. Found: (Carius) Cl, meta 22.4, 22.5; para 22.3, 22.4; (direct titration) B, meta 7.01, 7.02; para, 6.91, 6.91.

The *m*-chlorobromobenzene was prepared from *m*-chloroaniline in the same manner[9] as the ortho compound; *p*-chlorobromobenzene was available commercially.

***m*-Phenetylboric Acid.**—*m*-Bromoaniline was diazotized and hydrolyzed,[12] giving rise to a 70% yield of crude *m*-bromophenol. A 95% yield of the bromophenetole was obtained by treating the phenol with diethyl sulfate in alkaline solution according to the usual method.[13] The *m*-bromophenetole obtained readily formed a Grignard reagent, and this was treated with *n*-butyl borate, giving a 50% yield of *m*-phenetylboric acid. This compound crystallizes in short needles from water. It melts at 130° (corr.) with vigorous effervescence on instant immersion and then resolidifies. The new solid (the anhydride) melts at 152–153° (corr.). This compound has not been prepared previously.

Anal. Calcd.: B, 6.52. Found: (direct titration) B, 6.51, 6.50.

***o*- and *p*-Phenetylboric Acids.**—These were prepared from the corresponding phenetylmagnesium bromides and *n*-butyl borate. The two bromophenetoles were available commercially. The ortho acid crystallizes in long needles from 20% alcohol, m. p. 102–103° (corr.). Michaelis and Becker[14] report a melting point of 171°. The para isomer crystallizes from water in the form of needles. It melts rapidly at 150° (corr.) with the liberation of moisture on instant immersion and then resolidifies. The new solid (the anhydride) melts at 171° (corr.). The melting point of the acid has been reported[14] as 159°.

Anal. Calcd.: B, 6.52. Found: (direct titration) B, ortho 6.25, 6.23; para 6.34, 6.30.

Miscellaneous Materials.—Phenylboric acid was repeatedly recrystallized from water. Consistent results with the electrode, however, were not obtained until the compound had been recrystallized from hot benzene. Boric acid was purified by recrystallization from water. *n*-Butyl borate was prepared by the method of Bean and Johnson.[8] All of the arylboric acids described were air dried and stored in an empty desiccator.

Apparatus.—The dissociation constants were obtained as before[4] by measuring the *P*H of a series of partially neutralized solutions with a hydrogen electrode. A more sensitive measuring apparatus was used. The electromotive forces were obtained by balancing with a Leeds and Northrup potentiometer using a Leeds and Northrup lamp-scale type galvanometer No. 2420-C. A modified Clark shaking vessel[15] was used. The reproducibility of electromotive force measurements on different samples of the same solution was of the order of 0.1 to 0.2 millivolt. A saturated calomel cell was used and checked against

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[7] Seaman and Johnson, THIS JOURNAL, **53**, 711 (1931).

[8] Bean and Johnson, *ibid.*, **54**, 4415 (1932).

[9] Van der Linden, *Rec. trav. chim.*, **30**, 305 (1911).

[10] Koenig and Scharrnbeck, *J. prakt. Chem.*, [2] **128**, 153 (1930).

[11] Krause, German Patent 371,467; *Chem. Abs.*, **18**, 992 (1924).

[12] Holleman and Rinkes, *Rec. trav. chim.*, **30**, 52 (1911).

[13] Fisher, "Laboratory Manual of Organic Chemistry," 2d ed., John Wiley and Sons, New York, 1924, pp. 180–181.

[14] Michaelis and Becker, *Ber.*, **27**, 244 (1894).

[15] Clark, "The Determination of Hydrogen Ions," 3d ed., Williams and Wilkins Co., Baltimore, 1928, p. 293.

potassium acid phthalate and the standard acetate buffer. As a further check the dissociation constant of boric acid was determined in aqueous solution and found to be 6.53×10^{-10}, in good agreement with the accepted value of 6.6×10^{-10}.[16] The measurements were carried out in an air thermostat at 25°. The solutions were previously brought to that temperature in a water thermostat.

There was some difficulty in obtaining electrodes suitable for use in the alkaline alcohol solutions. Six electrodes were usually treated at one time. After being cleaned, they were electrolyzed in 10% sulfuric acid and then were platinized directly, using a current density of 0.05 ampere per square centimeter for five minutes in a 3% platinum chloride solution. The electrodes were stored in 2% sulfuric acid and were allowed to "age" for about a week before being used. Alternate cathodic and anodic deposition seemed to have no advantages over the method used. Of these six electrodes, five to six were suitable for measurements in aqueous solution. Only two to three, however, could be used in the alcoholic solutions, the others showing a drift in voltage so that the potentiometer could not be balanced. The life of the good electrodes (in alcoholic solution) was about a week of constant use. After that they became sluggish and were discarded.

Calculation of Results.—The constants were calculated by means of the equation

$$Ka = \frac{[\mathrm{H}^+]\,[\mathrm{Na}^+ + \mathrm{H}^+ - Kw/\mathrm{H}^+]}{M - [\mathrm{Na}^+ + \mathrm{H}^+ - Kw/\mathrm{H}^+]}$$

the parenthetical expression of which is obtained by the equating of the positive and negative ions. *M* here represents the total concentration of the boric acid in the form of both acid and salt. In water solutions the *P*H obtained is almost exactly equal to the negative logarithm of the hydrogen-ion concentration. The use of a 25% alcohol solution instead of water may appreciably alter this relationship. We have made the assumption, however, that it does not. What we have called the dissociation constant is the hydrogen-ion activity when the molal ratio of the undissociated acid to its salt is unity. This is equivalent to arbitrarily attributing the whole effect of the alcohol solution, on the electromotive force of the hydrogen electrode, to its influence on the dissociation constant of the acid.

Any error introduced in this way is common to all our measurements and does not affect the comparison between the strengths of the acids we have measured. The value for *Kw* was assumed to be 10^{-14} in aqueous solution and 5×10^{-15} in the alcoholic solutions. The value which one uses for *Kw* (10^{-14} or 5×10^{-15}) in the calculation of the dissociation constants has but little effect except in the case of very weak acids ($Ka \sim 10^{-11}$) at low concentrations.

The experimental data are summarized in the table below. Each substance was measured at three to four different molalities, and at each molality three solutions were measured having an acid-salt ratio of $^2/_3$, 1, and $^3/_2$, respectively. The percentage deviation from the mean *Ka* has been calculated for each value and the average percentage deviation for each substance is given in the last column of the table. These dissociation constants should be of an accuracy of about 5–10%, except in the case of *o*-chlorophenol. The accuracy there is about 10–20%.

SUMMARY OF DISSOCIATION CONSTANTS AT 25°

Acid	Solvent	Molality range	Number of measurements	Range of *Ka*	Mean *Ka* $\times 10^{10}$	Av. dev. from mean *Ka*, %
Boric	Water	0.06–0.01	12	6.26–6.85	6.53	2.3
Phenylboric	Water	.03– .005	12	13.0–14.2	13.7	2.6
Boric	25% EtOH	.06– .02	9	1.29–1.43	1.34	2.7
Phenylboric	25% EtOH	.03– .01	9	1.91–2.01	1.97	1.3
o-Chlorophenylboric	25% EtOH	.03– .01	8	13.5–14.6	14.0	2.2
m-Chlorophenylboric	25% EtOH	.06– .02	9	14.2–14.9	14.5	1.5
p-Chlorophenylboric	25% EtOH	.06– .02	9	6.12–6.33	6.23	0.8
o-Phenetylboric	25% EtOH	.03– .01	8	0.881–0.952	0.910	2.7
m-Phenetylboric	25% EtOH	.06– .02	9	3.02–3.09	3.05	0.6
p-Phenetylboric	25% EtOH	.06– .02	9	0.588–0.638	0.608	2.5
o-Chlorophenol	25% EtOH	.06– .02	9	7.31–8.53	7.97	5.0
m-Chlorophenol	25% EtOH	.06– .02	9	3.15–3.49	3.30	2.6
p-Chlorophenol	25% EtOH	.06– .02	9	1.41–1.54	1.46	2.9

Summary

The dissociation constants of phenylboric acid, boric acid, the chlorophenylboric acids, the phenetylboric acids, and the chlorophenols have been measured in twenty-five per cent. ethyl alcohol solutions. A more accurate value has been obtained for phenylboric acid in water. These results have been compared and discussed on the basis of the negativities and resonances of the groups involved.

BERKELEY, CALIF. RECEIVED DECEMBER 18, 1933

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[16] Landolt and Börnstein, Vol. 2, 5th ed., 1931, p. 1120.