Boric Acid Esters. I. A General Survey of Aromatic Ligands and the Kinetics and Mechanism of the Formation and Hydrolysis of Boric Acid Esters of Salicylamide, N-Phenylsalicylamide, and Disalicylimide

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Abstract: A spectrophotometric method was developed to detect the presence of boric esters of substituted phenols in aqueous borate buffers. A large series of phenols and related compounds was so examined to evaluate the effects of the number, basicity, and steric bulk of the ligand groups and their geometry upon the stability of resulting boric esters. Quantitative rate constants were measured (30°, solvent H_2O, ionic strength constant) for the formation of stable boric esters of salicylamide, N-phenylsalicylamide, and disalicylimide under conditions of constant pH and large excess of borate buffer over substrate. The resulting pH–rate profiles yielded the following rate equations: for the amides $-\text{d[amide]}/dt = k_{f_1}[\text{S}][\text{BH}] + k_{f_2}[\text{S}^-][\text{BH}]$ and for imide $-\text{d[imide]}/dt = k_{f_1}[\text{S}][\text{BH}] + k_{f_2}[\text{S}^-][\text{BH}] + k_{f_3}[\text{S}^{2-}][\text{BH}]$, where symbols are represented in Schemes I and II, respectively. The esterification of disalicylimide proceeded to completion forming an ester remarkably stable toward alkaline hydrolysis (at least 10^5 times slower rate of hydrolysis in 0.1 *M* KOH than triphenyl borate). The reaction with the amides was reversible, however, so the approach to equilibrium could be monitored in each direction. pH-dependent equilibrium constants were computed for ester formation, enabling one to obtain individual equilibrium constants and acid ionization constants for the boric esters. Although no esters were actually isolated, pH–rate profiles for their hydrolysis could be obtained: $-\text{d[ester]}/dt = k_{r_1}[\text{E}] + k_{r_2}[\text{E}^-] + k_{r_3}[\text{E}^-]a_{\text{OH}}$ (see Scheme I for symbols). A mechanism consistent with these kinetics is proposed and discussed. Pertinent features of this mechanism include a phenoxy-attached monoester intermediate in steady state, a concerted proton transfer in water or substrate attack upon boron, and hydroxyl ion attack upon tetracoordinated borate ester E^- (see Scheme IV). The rate constant for the latter step is comparable to that for alkaline hydrolysis of phenyl benzoate, illustrating the facility with which boric and borate esters undergo solvolytic reactions. The hydrolytic data provide evidence for the first example of a protic dissociation from a tetracoordinated borate anion: $\text{B–OH} \rightleftarrows \text{B–O}^- + \text{H}^+$. The relevant literature is critically discussed with reference to stoichiometry of boric esters, borate buffer catalysis of carboxylate ester hydrolysis, and a possible example of bifunctional catalysis of proton transfer, facilitated by acetic acid, in solvolysis of trialkyl borates.

For nearly a century it has been known that boric acid forms quite acidic complexes in aqueous solution with carbohydrates and certain polyhydroxylic compounds, useful initially in titrating this weak acid and more recently in determining carbohydrate structure.[3] Certain of the structural requirements of the reaction are known and mechanistic details have been investigated,[4] yet quantitative kinetic data regarding complex formation and hydrolysis are virtually nonexistent in the literature, with two exceptions as discussed herein. These complexes presumably equilibrate very rapidly in solution as Eyring has found for the polyborates.[5]

While studying the alkaline hydrolysis of salicylamide,[6] we noted a slow rate of appearance of the characteristic ultraviolet peak of dissociated salicylamide when solutions of salicylamide in borate buffers were made alkaline, a reaction normally "instantaneous." This was accompanied by the simultaneous disappearance of a peak closely resembling that of the phenol form. Since salicylamide is hydrolytically stable under these conditions and neither phosphate, carbonate, succinate, triethanolamine, nor N-ethylmorpholine buffers had this effect, it was concluded that hydrolysis of a boric ester of the phenol was being observed. Moreover, the reaction was readily reversible for the rate of esterification of boric acid by this phenol could also be conveniently followed.

Numerous studies have demonstrated the existence of, and sometimes the stoichiometry and stability constants of, boric acid complexes of phenols, enols, polyhydroxylic alcohols, etc., by means of conductivity,[3,7] potentiometry,[8–10] titrimetry,[11] polarimetry,[12]

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optical rotatory dispersion,[13] cryoscopy,[14] thermogravimetry,[15] spectrophotometry,[16–20] ion exchange,[8] calorimetry,[21] and others. Although many borate complexes have been isolated from aqueous solutions and so studied, neither the actual mixture of species in solution nor their stoichiometries must necessarily correspond to that isolated. Generally borates of glycols, polyhydroxylic alcohols, or amines are much more stable in solution than trialkyl or triaryl borates. In fact, only a few examples of monoborates of sterically bulky alcohols or phenols but no diborates have been prepared.[4b]

Steinberg and Hunter[11] were the first to measure the rate of a boric acid esterification. Their substrate, tris(isopropyl alcohol)amine, reacted with boric acid inordinately slowly presumably due to steric crowding around the boron atom of the product. Though no pH buffering was employed and data evaluation was complicated by the diastereomeric mixture of starting amines, these data pointed to an intramolecular B–N dative bond. Moreover, equilibrium between the ester and its hydrolysis products could be attained in either direction although the calculated equilibrium constant depended upon the direction due to system complexities.

The only other unequivocal case of a measured rate of boric esterification was reported by Neece and Fridovich,[19] who unfortunately did not extend their study beyond one pH and one borate concentration. Capon and Ghosh[22] were unable to detect spectrophotometrically any complexes of boric acid with substituted phenyl salicylates but invoked boric ester formation to explain their hydrolytic results in borate buffers. These and other studies will be critically discussed in a later section.

Scattergood and co-workers[23] and later Steinberg and Hunter[24] prepared and measured semiquantitative rate constants for the "alkaline" hydrolysis of a large series of trialkyl and triaryl borates.[25] Their correlations of rate with steric bulk of the ester moiety, solvent polarity, and temperature have afforded some mechanistic generalizations. Crowell and co-workers[26] established that the ethanolysis of tris(*sec*-butyl) borate was susceptible to general acid and general base catalysis in addition to ethoxide ion and specific acid catalysis.

In this paper we report qualitative observations on the complexibility of a large series of aromatic ligands with aqueous boric acid with special focus on boric ester structure, geometry, and stability. The results of a quantitative study of the rates of formation and hydrolysis and the equilibria for the boric esters of salicylamide, N-phenylsalicylamide, and disalicylimide are also presented. To our knowledge this represents the first instance of such a study directed toward the elucidation of the mechanism of this reaction.

Experimental Section

Materials.[27] **Salicylamide** was prepared by the method of Hahn[28] from salicylic acid and molten urea and was recrystallized six times from water, mp 139.5–141°.

N-Phenylsalicylamide was prepared by the gradual addition of a stoichiometric quantity of aniline in diethyl ether to a solution of salicyloyl chloride in petroleum ether (bp 30°–60°). Salicyoyl chloride was prepared by the reaction of thionyl chloride upon salicylic acid in petroleum ether.[29] A catalytic amount of pyridine is added to promote the reaction. Excess thionyl chloride was removed by evaporating the reaction mixture to one-half the original volume at 40°. Fresh petroleum ether was added and the evaporation repeated three times. To this *freshly* prepared solution of salicyloyl chloride was added the aniline very slowly and with stirring. The product was filtered, washed with dilute HCl, washed with water, and finally recrystallized twice from 25% aqueous ethanol, mp 136–7° (lit.[30] mp 135°).

Disalicylimide was prepared by the unusual route of treatment of salicylic acid with excess thionyl chloride. The mixture was evaporated and chilled aqueous ammonia added to the thick syrup. The resulting yellow product was washed and added to boiling aqueous ethanol, the insoluble yellow material being filtered while hot. Several recrystallizations of the insoluble material gave a pale yellow product, mp 203.5–204.5° (lit.[31] mp 203°), with infrared bands at 1660 and 1700 (C=O) and 3300 cm^{-1}.

N-Benzoylbenzamide (dibenzimide) was prepared by the method of Titherley,[32] mp 150–151° (lit.[32] mp 148°). The majority of the other phenols, imidazoles, benzimidazoles, etc., used in this study were either commercially available or had been prepared for previous studies from this laboratory and were not purified before use. The two amidines were specially prepared for an additional study.[33] Compounds **9**, **10**, **12**, and **13** of Table II were prepared by the standard methods and purified before use; **9**, mp 85–86° (lit.[30] mp 89°); **10**, mp 163–165° (lit.[34] mp 164–165°); **12**, mp 229–230.5° (lit.[30] mp 225°); **13**, mp 139.5–141.5° (lit.[30] mp 139, 143°).

Boric acid (Baker Analyzed) was dried at 110° before using. Potassium chloride and potassium hydroxide were analytical reagent grade chemicals. Stock solutions of boric acid and potassium borate, both 0.50 *M* in concentration and 0.50 *M* in ionic strength, were prepared from the requisite amounts of $B(OH)_3$, KCl, and KOH using twice distilled water and were stored in polythene bottles. Potassium borate was kept under nitrogen to prevent CO_2 absorption. All solutions containing KCl were filtered prior to spectrophotometric use. Imidazole (Eastman) was twice recrystallized from acetone–petroleum ether and stored in a desiccator before use. Triethanolamine hydrochloride was recrystallized before use, mp 180–182°. Other buffers utilized were prepared from reagent grade potassium acetate, acetic acid, potassium phosphates, or potassium carbonates.

Apparatus. A Zeiss PMQ II spectrophotometer was used for the kinetic studies with salicylamide. The kinetics with N-phenyl-

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(25) In their technique ester and alkali were mixed in a 2:1 ratio with solvent; the time necessary for the alkali to be used up, as indicated by phenolphthalein, was measured and reported as the half-life. It is obvious that even relative rates would be accurate only if all their boric esters had identical susceptibilities to H_2O and OH^- attack, an unlikely situation.
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salicylamide were performed utilizing a Gilford multiple sample absorbance recorder with either a Zeiss M4Q III or a Beckman DU monochromator since small OD changes were observed. The temperature in the spectrophotometer cell compartments was kept at 30.0 ± 0.1° (NBS-calibrated thermometer) and maintained with large-capacity circulating water baths. Acid dissociation constants of the substrates were determined utilizing the spectrophotometric titration cell designed by French and Bruice[35] together with the Zeiss spectrophotometer. Initial kinetic runs and all spectral scans were made with a Perkin-Elmer Model 350 recording spectrophotometer. Closely matched glass-stoppered cuvettes of 3.5-ml capacity and 1-cm path length were used throughout this work. A Radiometer Model PHA 630 PA scale expander coupled to a Radiometer Model 22 pH meter was used for pH measurements utilizing a combined glass–calomel electrode (Radiometer G.K. 2021C). The sample and electrode were always allowed to equilibrate at 30 ± 0.1° before measurement of pH. The equipment used for the potentiometric titration of boric acid has been previously described.[36] A 30-ml capacity titration cell has been used in this work. The use of an Olivetti–Underwood Programma 101 desk computer facilitated calculation of equilibrium constants and some of the rate constants and fitting of data to empirical equations.

Kinetics. All measurements were carried out at 30 ± 0.1° in water at an ionic strength of 0.30 *M* (with KCl) for salicylamide and N-phenylsalicylamide and at 0.50 *M* for disalicylimide. The rate of disappearance and appearance of salicylamide and N-phenylsalicylamide was monitored at 333 nm, the disappearance of disalicylimide at 360 nm. The concentration of borate buffer exceeded that of amide (or imide) by at least 100-fold, thus maintaining pseudo-first-order conditions.

For boric ester formation with salicylamide the pH was maintained constant by the boric acid–borate reactant itself, prepared by mixing various proportions of stock boric acid and potassium borate solutions and appropriate dilution. For N-phenylsalicylamide, however, ester formation in the pH range 6.99–7.64 utilized added imidazole buffer. Boric ester formation with disalicylimide was performed in the pH range 4.89–5.86 with added acetate buffer, in the range 6.10–6.75 with phosphate buffer, and at pH 5.89 with an equimolar mixture of phosphate and acetate buffers. Since these external buffers catalyzed somewhat the observed reaction, three concentrations of buffer were used at each pH, the reported rate constant being that obtained by extrapolation of the rate constants to zero external buffer. The solutions, in 3.5-ml capacity cuvettes, were temperature equilibrated in the spectrophotometer cell compartment for at least 10 min. A cuvette correction was obtained for each cuvette containing buffer (no substrate added) by measuring its optical density (OD) *vs.* the water blank. In order that a zero-time OD reading could be calculated, one drop of substrate in a suitable solvent[37] was added to the cuvette simultaneously with either starting a stopwatch or, for the more rapid reactions, an audible signal from an electronic interval timer. The concentration of substrate so obtained was *ca.* 1×10^{-4} *M*. The cuvette was instantly stoppered, inverted a few times for complete mixing, and placed in the cuvette compartment. With the Zeiss instrument the first reading could be taken after 8 or 10 sec from mixing. At least 12 subsequent OD readings were taken at various times to at least three half-lives and usually to infinite time. A continuous recording of OD *vs.* time was obtained with the Gilford recorder, its full-scale OD span being accurately preset to an appropriate value. At the conclusion of the run the infinite time OD was read manually utilizing the Gilford digital OD read-out. The pH of the sample was determined at the completion of all runs using the electrode standardized with Fisher Certified pH 6.98 and 4.01 buffers, and a pH 9.14 borax buffer prepared according to the method of Bates.[39] A few random rates, when plotted as $\log a/(a - x)$ *vs.* time, showed strict linearity to at least three half-lives. The disalicylimide ester formation rate constants (k_{obsd}) were computed by a general computer program, RATCON,[40] utilizing either the IBM 1620 or IBM 360. The program, completely general for all first- and second-order reactions, fitted the OD–time data to the appropriate theoretical concentration *vs.* time equation by adjusting the k_{obsd}, OD_i (the initial OD reading), and OD_∞ to their "best" values. An OD_∞ reading may be computed in cases where it is indeterminate or unstable or if the reaction was not followed entirely to completion. A "best" fit was assumed when a minimum error-square-sum was attained, the standard deviation of the experimental data generally falling below 0.001 OD unit. The amide ester formation rate constants were computed with the Programma computer utilizing the method of weighted least squares[41] for either reactions followed to infinite time or those normally treated by Guggenheim's method.[42] The integrated first-order rate expression (eq 1) may be arranged and solved for

$$OD_0 = (OD_t - OD_\infty)e^{k_{obsd}t} + OD_\infty \quad (1)$$

OD_∞ (eq 2). When the reaction was not followed entirely to completion, OD_∞ could alternatively be computed *via* eq 2. Values of the OD at *zero time*, OD_0, were then computed at each of two time values using eq 1 and averaged.

$$OD_\infty = \frac{OD_t e^{k_{obsd}t} - OD_1}{e^{k_{obsd}t} - 1} \quad (2)$$

The following technique was used to determine the rates of hydrolysis of the salicylamide and N-phenylsalicylamide boric esters. Borate buffers (25 ml) were prepared at 0.04 *M*, pH 8.35, and at 0.08 *M*, pH 8.30. Near these pH's the equilibrium lies farthest

$$\text{amide} + \text{borate} \overset{K_{pH}}{\rightleftharpoons} \text{ester} \quad (3)$$

toward ester. Buffer (3 ml) was pipeted into cuvettes and temperature equilibrated, and the cuvette correction was taken as previously described. Amide solution (1 drop) was placed in each cuvette and the OD determined at infinite time (10 min). The pH of each solution was increased suddenly to pH values in the range 9.86–13.06 by addition of aqueous 4.2 or 15 *M* KOH *via* a micrometer syringe buret. The volume of added alkali was always less than 1% of the total volume. The rate of appearance of amide was followed to at least three half-lives, if not to infinite time, and the final pH determined. The potassium ion error for the pH electrode was always less than 0.06 pH unit. Buffer capacity in this pH range was supplied by first borate itself and then KOH at the highest pH values. In the intermediate range, pH 10.5–11.5, the k_{obsd}'s are relatively insensitive to pH, thus obviating the need for an external buffer. The rate constants were computed as before with the Programma. Likewise, OD_0 and the OD_∞ value when necessary were computed for each run using eq 1 and 2. It was ascertained that neither the amides nor disalicylimide hydrolyzed detectably during the slowest runs at the highest or lowest pH's obtained in this study.

pK_a' Determinations. The pK_a' values for salicylamide, N-phenylsalicylamide, and disalicylimide were determined in duplicate at 30° and the ionic strength was used for the kinetic studies in the spectrophotometric titration cell of French and Bruice[35] using their experimental technique. Optical density and pH were thus measured simultaneously and these experimental data fitted to a theoretical curve. The criterion of a minimum error-square-sum was applied in choosing the pK_a' and values of OD_A and OD_B, the OD of the acid and base species, respectively. The results of these determinations are shown in Table I.

Table I. Acid Dissociation Constants of Title Compounds

Compound	λ, nm	pK_a'	Z^a
Salicylamide	333	8.04 ± 0.05[b]	31.8, 29.4
N-Phenylsalicylamide	333	7.285 ± 0.005[b]	9.15, 9.15
Disalicylimide	360	5.68 ± 0.01[b] (pK_{a_1}')	11.7, 18.4
		10.09 ± 0.02 (pK_{a_2}')	1.65, 1.67
Dibenzimide	280	9.55 ± 0.04	2.96, 2.86

[a] $Z = \epsilon_S^-/\epsilon_S = OD_B/OD_A$, determined in duplicate, where ϵ_i refers to molar extinction coefficients. [b] Range of pK_a' in which theoretical fit is equally good.

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(37) The following solvents were used: salicylamide–water; N-phenylsalicylamide–ethanol; disalicylimide–kinetically pure dioxane[38] kept under nitrogen.
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(39) R. G. Bates, "Symposium on pH Measurement," American Society of Testing Materials, 1957.
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The pK_a' values of boric acid at ionic strengths of 0.30 and 0.50 M and at several concentrations (0.01–0.12 M) were determined potentiometrically employing carbonate-free KOH,[43] 1.028 M, as titrant. Each boric acid solution (30 ml) was titrated in the titration cell with at least 15 additions of base, pH being read after each addition. The pK_a' values were computed by a program written for the Programma which corrected for dilution by titrant, for excess hydroxyl ions, and most importantly for over- or under-titration. For each titration at lower boric acid concentration the pK_a' values showed no trends and possessed a standard deviation no greater than 0.015 pH unit. However, at 0.08 and 0.12 M concentration the pK_a' at lower pH's was computed considerably lower than at higher pH's due to the more acidic polymers which are known to form in boric acid solutions.[44] These abnormally low pK_a' values were rejected from the averaging.

The averaged pK_a' value at ionic strength 0.30 M for 0.02, 0.04, 0.08, and 0.12 M boric acid was 9.02 ± 0.015, with no trends. The averaged value at ionic strength 0.50 M for 0.01 and 0.03 M boric acid was also 9.02 ± 0.02. Therefore a value of pK_a' (pK_B) of 9.02 was used in this study.

Equilibrium Constant Determination. Preliminary results showed that the over-all equilibrium constant, K_{pH}, for equilibrium 3 was dependent not only upon pH but also on the total borate concentration (B_T). The presence of additional equilibria involving boric acid polymers would be consistent with this situation and would preclude a simple determination of K_{pH} by the usual Benesi–Hildebrand method.[35,45] This problem has been treated quantitatively recently.[46] Alternatively the K_{pH} at any pH and B_T could be easily obtained from the OD–time data of each ester formation rate. The method is here outlined for the case of salicylamide. It is suitably accurate for equilibria as eq 3 where the spectra of ester alone may be impossible to obtain, but where at some wavelength the OD of amide is much different from that of ester. Assuming that the amide possesses only one pK_a' in the pH region of interest and that $B_T \gg S_T$ (the total concentration of free borate and amide species, respectively), the expression for the over-all

$$K_{pH} = \frac{E_T^{eq}}{S_T^{eq} B_T} \tag{4}$$

equilibrium constant (4) can be replaced with eq 5. (See the Appendix for the derivation of this equation.)

$$K_{pH} = \frac{1}{B_T}\left[\frac{OD_0 - OD_\infty}{OD_\infty - \frac{OD_0}{R}\left(\frac{K_S + a_H}{K_S + (a_H/Z)}\right)}\right] \tag{5}$$

In eq 5, OD_0 refers to the calculated OD at zero time (from eq 1), OD_∞ to the OD at infinite time (both corrected for cuvette mismatch), K_S to the acid dissociation constant of amide, and a_H to the activity of hydrogen ion as measured by the glass electrode. The factor Z is the ratio $\epsilon_{S^-}/\epsilon_S$ obtained from the pK_S determination (see Table I). The factor R, which is the ratio $\epsilon_{S^-}/\epsilon_{ester}$ at the analytical wavelength (333 nm), was determined by careful measurement of the ultraviolet spectra of salicylamide from 280 to 400 nm (with the Zeiss spectrophotometer) in 0.30 M borate buffer, pH 8.52 (solution F), and in triethanolamine buffer, pH 8.37 (solution G). The measurements were made at 30° at μ = 0.30. The spectrum of solution F exhibited a λ_{max} at 304 nm and small shoulder near 335 nm whereas solution G showed the characteristic λ_{max} of ionized amide near 330 nm. The salicylamide concentration in both buffers was identical; 2 ml of a stock solution, 5×10^{-4} M, has been pipeted into each of two 10-ml volumetric flasks and diluted to the mark with buffer, KCl solution, and water. From an inspection of the plotted spectra, the ester and undissociated amide do not absorb above 340 nm; hence in this region the curves have the same shape. Ratios of OD_{333} to the OD at each of several wavelengths (OD_λ) above 340 nm for curve G were calculated. These ratios were multiplied by the corresponding OD from curve F at the particular wavelength furnishing calculated values of OD_{333} for curve F. The difference between the observed value of OD_{333} from F and the average of the calculated values (OD_{calcd}) is simply OD_{diff}, the ester absorption at the analytical wavelength. Since the two pH's were not identical, the OD of solution G at 333 nm at the higher pH of 8.52 was easily calculated (OD_G) from the usual equation (eq 6). Hence one may calculate OD_{ester}, the OD of

$$pH = pK_a + \log\left(\frac{OD_G - OD_A}{OD_B - OD_G}\right) \tag{6}$$

solution F if all amide were esterified, as

$$OD_{ester} = OD_{diff}\left(\frac{OD_G}{OD_G - OD_{calcd}}\right) \tag{7}$$

Finally OD_{S^-}, the optical density were all amide in solution G ionized, may be calculated from eq 6. The ratio R is therefore given by eq 8. In these studies both R and Z are greater than 9

$$R = \epsilon_{S^-}/\epsilon_{ester} = OD_{S^-}/OD_{ester} \tag{8}$$

so that rather large errors in their determination are reflected as negligible errors in the computed K_{pH}.

Method of Detection of Boric Acid Ester Formation. The ultraviolet spectrum of phenolate anions is generally displaced to longer wavelengths relative to the phenol. Consequently esterification of the anion by boric acid should diminish the phenolate band and produce an ester whose λ_{max} is not greatly different from that of the corresponding phenol. If ester formation is slow, the rate of disappearance of the phenolate peak or appearance of ester peak could be measured.

Spectral scans were taken of a small amount of substrate in several buffers in order to determine the absorption maxima of phenol and phenolate species and, where necessary, a rough pK_a' value (see Table II). Substrate was now added to a borate buffer; within 15 sec any change in the OD of phenolate peak could be noted. Usually this procedure was repeated at several pH's and B_T concentrations, scanning at infinite time. In some cases KOH was added to a borate buffer containing subtrate, thereby forcing the pH to higher values; any changes from the expected spectrum were again noted.

In summation, the criteria for detectable boric ester formation were (a) significant spectral changes in the characteristic phenolate or phenol peaks in borate buffer relative to inert (carbonate, phosphate, acetate, etc.) buffers *at the same pH;* (b) changes in spectra, when alkali was added to substrate in borate buffers, inexplicable in terms of acid–base ionization; (c) time changes in the spectral alterations of (a) and (b); and (d) decrease in phenolate absorption with increasing B_T concentration as predicted by eq 3.

Results

For economy of space the following symbols will be consistently employed in this study: B_T = total concentration of boric acid species, BH = $B(OH)_3$, B^- = $B(OH)_4^-$, S_T = total substrate concentration (amide or imide), S (S^-, S^{2-}) denote a particular ionic species of substrate (see Schemes I or II), E_T = total concentration of boric ester of substrate; E (E^-, E^{2-}) denote a particular ionic species of boric ester (see Schemes I or II); K_B = acid ionization constant of boric acid (not thermodynamic); K_S = acid dissociation constant of substrate; K_E = acid ionization constant of boric ester; K_W = autoprotolysis constant of water at 30°; a_H = hydrogen ion activity as measured by the glass electrode; a_{OH} = hydroxyl ion activity calculated as K_W/a_H; k_f = apparent second-order rate constant for the reaction of substrate with borate; k_r = apparent first-order rate constant for the hydrolysis of boric ester to substrate and borate.

The results of the qualitative tests for boric ester formation with a wide variety of phenols and related compounds are presented in Table II. An important distinction was made in this tabulation between those

(43) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1964, p 24.

(44) (a) N. Ingri, G. Lagerström, M. Frydman, and L. G. Sillén, *Acta Chem. Scand.*, **11**, 1034 (1957); (b) N. Ingri, *ibid.*, **16**, 439 (1962); **17**, 573, 581 (1963). For other pertinent lead references regarding the aqueous chemistry of boric acid, consult ref 13.

(45) H. A. Benesi and J. H. Hildebrand, *J. Am. Chem. Soc*, **71**, 2703 (1949).

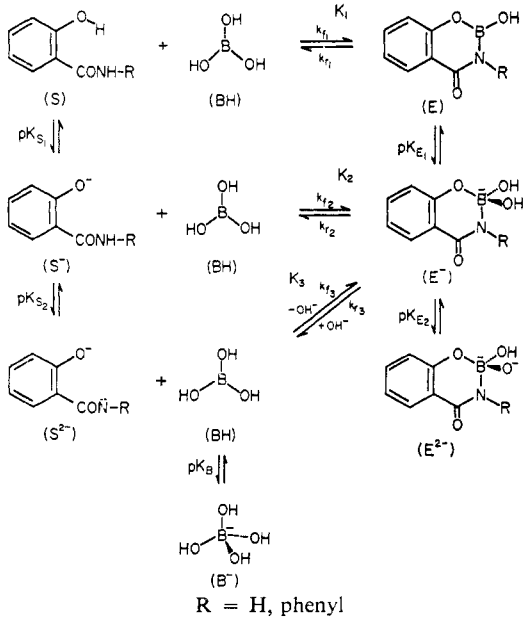
(46) D. W. Tanner and T. C. Bruice, *J. Phys. Chem.*, **70**, 3816 (1966).

Table II. Results of Tests for Boric Ester Formation with Phenols and Other Compounds[a]

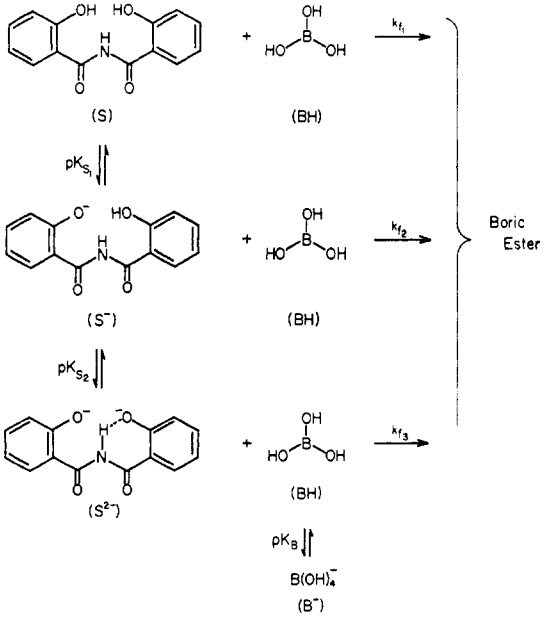
No.	Compound	pK_a	λ_{O^-}	λ_{OH}	Ester formation
Monodentate ligands					
1	*o*-Nitrophenol	7.23[b]	415	345	No
2	2,4-Dichlorophenol	~8	305	282	No
3	*p*-Chlorophenol	9.38[b]	297	278	No
4	*m*-Nitrophenol	8.35	385	325	No
5	*p*-Methoxyphenol	10.20[b]	304	286	No
6	3-Hydroxypryidine	~5	310	280	No
7	2-Phenylbenzimidazole	...	...	...	*d*
Bidentate ligands					
8	Salicylamide	8.04	330	296	Yes
9	N-Methylsalicylamide	~8	323	296	Yes
10	N,N-Dimethylsalicylamide	~8	298	276	No
11	N-Phenylsalicylamide	7.29	330	296 (sh)	Yes
12	5-Nitrosalicylamide	5.4	395		Yes[c]
13	N-Acetylsalicylamide	~6.5	355	310	No
14	2-Methoxybenzamide	...	...	...	No
15	4-Aminoimidazole-5-carboxamide	~10.5	275	267	*d*
16	Salicylamidine (sulfate salt)	6.59	345	296	Yes
17	N-Phenylsalicylamidine	6.28	345	295 (sh)	Yes
18	Methyl salicylate	~10	325	300	No
19	5-Nitrosalicylic acid	9.8	412	310	No
20	2-(4′-Imidazolyl)phenol	10.6	316	300	Yes
21	2,2′-Bisimidazole	...	...	...	No
22	2-(2′-Benzimidazolyl)phenol	>10	345		Yes
23	4-Hydroxybenzimidazole	9.5[b]	267	260	No
24	8-Hydroxyquinoline	~9.5	355, 335	305	No
25	Catechol	9.48[b]	~280	273	Yes
26	Resorcinol	9.15[b]	~280	272	*d*
27	1,8-Dihydroxynaphthalene-3,6-disulfonic acid	5.36[b]	365, 345	347, 330	Yes
28	*o*-Mercaptobenzoic acid	~8.4	265	295, 245 (sh)	No
29	Dihydroxyfumaric acid		296		Yes[e]
30	Salicylaldehyde	7.95[b]	375	322	Yes
31	3-Hydroxypyridine-4-aldehyde	4.05	385	284	Yes[f]
32	Pyridoxamine	<5	325	292	Yes
33	1-Hydroxyanthraquinone dioxime[g]	~8	325	292	Yes
Tridentate ligands					
34	Disalicylimide	5.68	360	315	Yes

[a] Ambient temperature. All numerical values not referenced were determined in this laboratory. [b] From a table of pK_a values furnished by W. P. Jencks. [c] Equilibrium lies far to the side of amide and borate. [d] No spectral changes observed in borate; however, little change expected on ester formation. [e] In borate a new absorption peak appears whose intensity at any pH increases with B_T concentration. [f] Rate constants for ester formation using stopped-flow apparatus were 1.24 sec^{-1} at pH 7.51 and 1.45 sec^{-1} at pH 8.65 (B_T = 0.25 *M*). K_{pH} values were roughly 8 and 3 M^{-1}, respectively. [g] Preparation of this compound (T. C. Bruice, unpublished results) paralleled that of 1-chloroanthraquinone dioxime (J. N. Rydon, *J. Chem. Soc.*, 1900 (1957)).

Scheme I



Scheme II



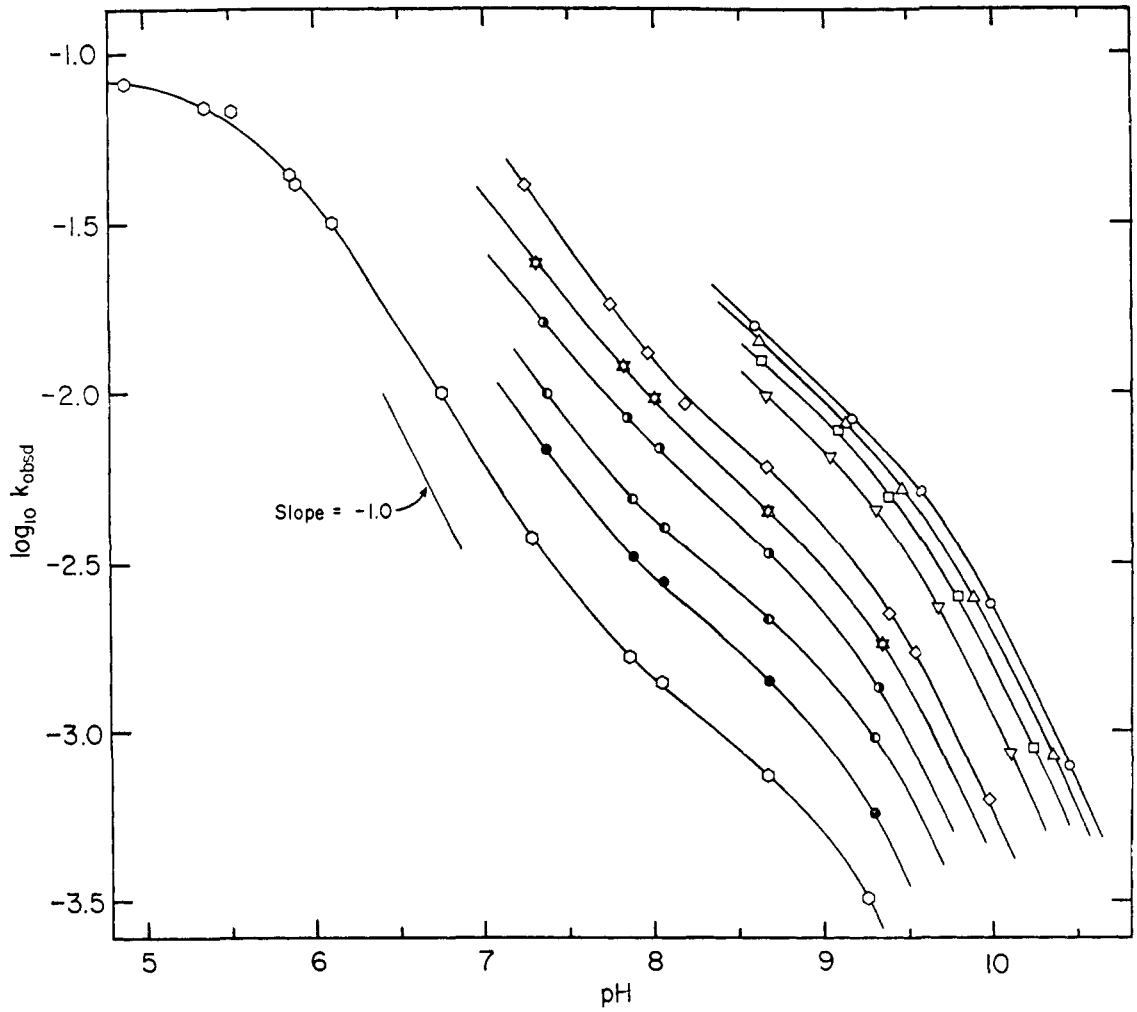


Figure 1. Plots of logarithm of observed pseudo-first-order rate constants *vs.* pH for the reaction of disalicylimide with various concentrations of boric acid (30°, μ = 0.50 with KCl): ○, 0.01 *M*; ●, 0.02 *M*; ◐, 0.03 *M*; ◑, 0.05 *M*; ☆, 0.07 *M*; ◇, 0.1 *M*; ▽, 0.2 *M*; □, 0.3 *M*; △, 0.4 *M*; ⊙, 0.5 *M*. Below pH 7, additional acetate, phosphate, or acetate–phosphate buffer was added to maintain constant pH, in which case k_{obsd} was obtained as the extrapolated value at zero added buffer concentration. Unit of rate constats is sec^{-1}.

compounds where negative results imply no ester formation (Table II) and those where such results indicate merely that an ester, if formed, absorbs in the ultraviolet region like its parent compound (footnote *d*, Table II).

Disalicylimide, salicylamide, and N-phenylsalicylamide were chosen for a more detailed, quantitative kinetic study of boric ester formation and hydrolysis. These results will be presented separately for each substrate because of the dissimilarity of their observed kinetics.

Disalicylimide. As boric ester formation proceeded with disalicylimide at constant pH, the characteristic peak of the anionic form of imide (360 nm) disappeared completely while a peak near 320 nm, similar to the absorption maximum of the neutral species, appeared. It follows, as expected, that the ester must closely resemble the neutral species electronically. Over the entire range of B_T concentration studied (0.01–0.50 *M*) the spectrum of the reaction mixture at equilibrium was always the same; hence no unesterified imide could be detected. This evidence indicates that the boric ester of disalicylimide possesses remarkable hydrolytic stability relative to triphenyl borate,[24] for example. Another measure of the stability of this ester relative to that of the free imide was its resistance to alkaline hydrolysis (ester, half-life 8 hr at pH 12.8; imide, half-life 1 hr at pH 12.4). Plots of the pseudo-first-order rate constants (k_{obsd}) *vs.* pH for the reaction of the imide with borate buffers are presented in Figure 1. The k_{obsd} values below pH 7 have a considerably larger standard deviation of *ca.* 15%; they were obtained by extrapolation of experimental rate constants measured in various concentrations of added buffer (in addition to boric acid) to zero added buffer concentration. At every 0.2 interval from pH 4.8 to 10.2 the k_{obsd} values at all B_T concentrations were procured from smoothed lines through the experimental points and were plotted *vs.* B_T. Representative plots of k_{obsd} *vs.* B_T at several pH's are shown in Figure 2. These plots are linear at very low B_T, the extrapolated line intersecting the origin at all pH values. At low pH values and at $B_T > 0.03$ *M* the slope of the line decreases until at $B_T > 0.30$ *M* there is little further increase in the rate constants. At the higher pH's, however, these plots (see Figure 2) show only small deviations from linearity even at high B_T concentrations. The nonlinearity in these plots may be attributed to polyborate formation.[44] The slopes, calculated from the initial linear portion of each of these plots,

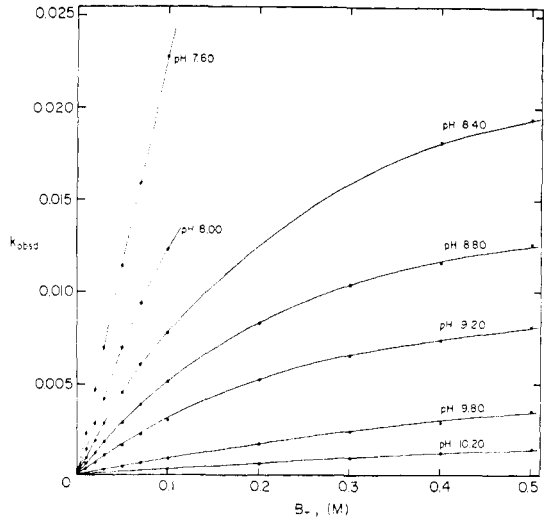


Figure 2. Dependence of pseudo-first-order rate constants for the reaction of disalicylimide with boric acid upon the concentration of boric acid buffer at several pH values (30°; μ = 0.50 with KCl). Unit of rate constants is sec^{-1}.

are then the apparent second-order rate constants (k_f) for ester formation.

$$-\frac{dS_T}{dt} = v_f = k_f B_T S_T \quad (9)$$

Therefore

$$k_{obsd} = k_f B_T \quad (10)$$

These k_f values are plotted *vs.* pH as the points in Figure 3. The rate expression for the simplest model of boric ester formation consistent with the experimental points involves reaction of each ionic species of substrate with boric acid (BH), presumably a good electrophile, *viz.*

$$v_f = k_{f_1}[S][BH] + k_{f_2}[S^-][BH] + k_{f_3}[S^{2-}][BH] \quad (11)$$

where S, S^-, and S^{2-} represent the three ionic species of imide below pH 12 shown in Scheme II. The structure of S^{2-} was portrayed as in Scheme II since the pK_a' of the imide nitrogen of dibenzimide was found to be 9.55, only 0.5 pH unit lower than pK_{S_2}.

We define B_T = [BH] + [B^-] at low B_T, solve B_T in terms of [BH], and substitute the expression for [BH] into eq 11. Next defining S_T = [S] + [S^-] + [S^{2-}] and utilizing the acid dissociation constants in Scheme II, one may solve for the concentration of each ionic species in terms of S_T, a_H, and these dissociation constants. Substituting these expressions also into eq 11 and subtracting the resulting equation from eq 9 yields eq 12. The solid line of Figure 3

$$k_f = [k_{f_1}a_H^2 + k_{f_2}K_{S_1}a_H + k_{f_3}K_{S_1}K_{S_2}] \times \left(\frac{a_H}{K_B + a_H}\right)\left(\frac{1}{a_H^2 + K_{S_1}a_H + K_{S_1}K_{S_2}}\right) \quad (12)$$

was computed from eq 12 utilizing the individual rate constants listed in Table III, the dissociation constants listed in Table I, and pK_B = 9.02. The root-mean-square (RMS) error of the points from the best calculated line is 4.2% (excluding points below pH 5.0) and is comparable to the experimental and graphical errors. In this and every "best" fit an attempt was also made to minimize as closely as possible the algebraic sum of relative errors. Errors in these determined rate constants are probably no more than 10–15% although a much more sophisticated error analysis as that of Nelder and Mead[47] would be required to determine their exact values. Though calculated on the basis of BH as the reactive species, each term of eq 11 has one or more equivalent and kinetically indistinguishable expressions. Calculated values of individual rate constants for some of these alternate expressions have been provided in Table III.

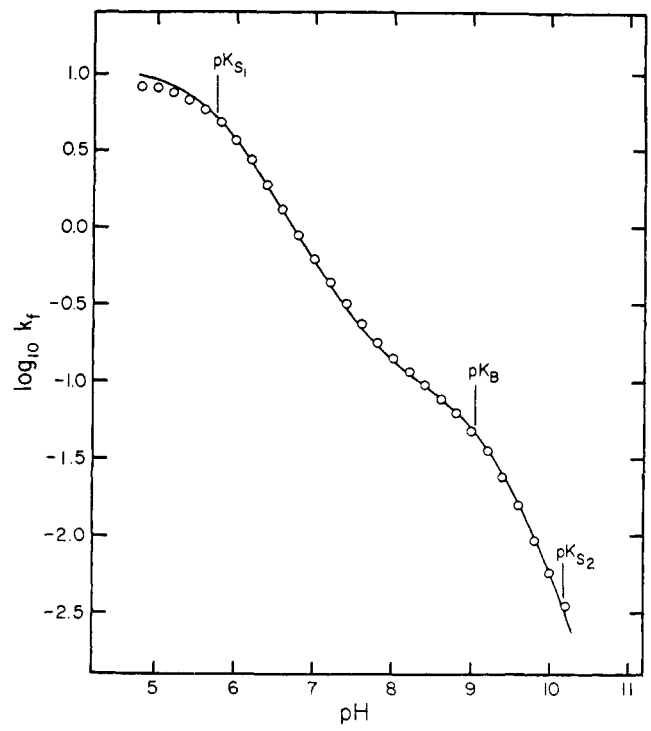


Figure 3. Plot of logarithm of second-order rate constants *vs.* pH for the reaction of disalicylimide with boric acid buffers (30°, μ = 0.50 with KCl). Effects of polyborates in solution upon k_f have been eliminated. The line was computed from eq 12 utilizing individual rate and acid dissociation constants tabulated in Tables I and III. Unit of rate constants is M^{-1} sec^{-1}.

Salicylamide boric ester formation was studied in the pH range 7.79–9.98 at 0.04, 0.08, and 0.12 *M* B_T. Both k_{obsd} and K_{pH} (from eq 5) were computed from the data collected for each kinetic run. The K_{pH} *vs.* pH profiles are portrayed in Figure 4. The errors of these computed K_{pH} values are probably within 4–6% with the probability of systematic errors being rather small due to the nature of the experimental data. Therefore, the dependence of K_{pH} upon B_T appears to be real and may result from (a) the known presence of polyborates in solution,[44] (b) from formation of two or more isomeric 1:1 boric esters, or (c) from two or more esters of differing stoichiometry at equilibrium. The latter situations have been treated analytically previously[48] and from these results one predicts a much smaller dependence of K_{pH} upon B_T than observed. Therefore, the first rationale is postulated for our system. Analysis of the observed dependence of K_{pH} upon B_T and pH in our convenient

(47) J. A. Nelder and R. Mead, *Computer J.*, 8, 308 (1965).
(48) G. D. Johnson and R. E. Bowen, *J. Am. Chem. Soc.*, 87, 1655 (1965).

Table III. Over-All Rate Constants for Boric Ester Formation[a]

	Rate equation: $-dS_T/dt = k_{f_1}[S][BH] + k_{f_2}[S^-][BH] + k_{f_3}[S^{2-}][BH]$ Salicylamide	N-Phenylsalicylamide	Disalicylimide
k_{f_1} $k[S][BH]$	0.325	<0.004[b]	11
$k[S^-][BH_2^+]$[c]	$3.3 \times 10^7 \times K_{B^+}$[d]	$<4 \times 10^4 \times K_{B^+}$[b,d]	$5.3 \times 10^6 \times K_{B^+}$[d]
k_{f_2} $k[S^-][BH]$	0.038	0.071	0.099
$k[S][B^-]$[c]	0.38	3.85	217
k_{f_3} $k[S^{2-}][BH]$	...	...	0.018
$k[S^-][B^-]$[c]	1.1×10^{-5}[e]	3.4×10^{-5}[e]	0.0015
K_1	3.35	0.1	>300[f]

[a] All units of rate constants are M^{-1} sec^{-1} or sec^{-1}. [b] No term found; listed is the largest value that would have gone undetected kinetically. [c] Kinetically indistinguishable term. [d] The acid dissociation constant for the hypothetical $B(OH)_3H^+$ species in acidic medium (see eq 35). [e] No term detectable; computed from k_{r_3} values in Table IV and relevant acid dissociation constants, etc. [f] Not evaluated experimentally; listed is minimum possible value consistent with the spectrophotometric observations (see text).

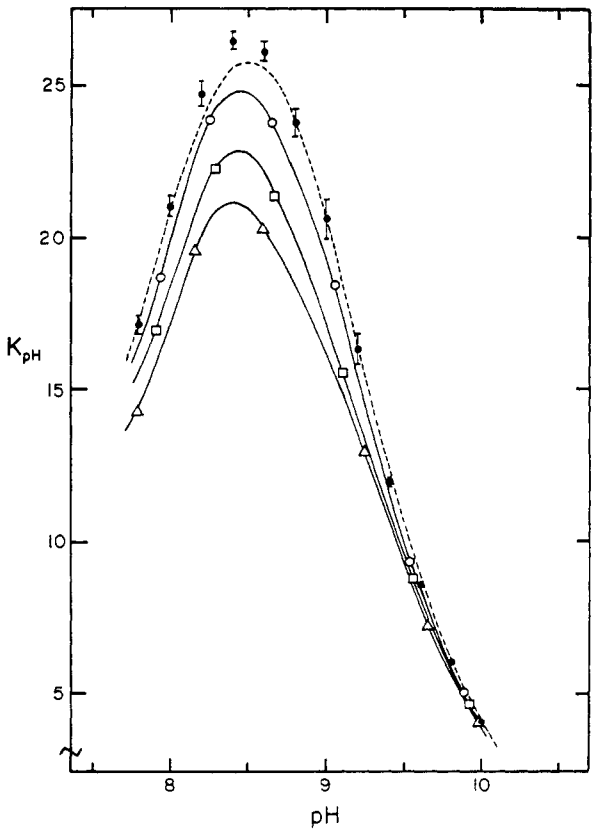


Figure 4. Plots of pH-dependent over-all equilibrium constant *vs.* pH for the salicylamide–boric acid–boric ester equilibrium (30°, μ = 0.3 with KCl). The experimental points were computed from eq 5 at various borate buffer concentrations: ○, 0.04 *M*; □, 0.08 *M*; △, 0.12 *M*. The upper points (●) are values of K^0_{pH}, the equilibrium constant obtained by extrapolation of K_{pH} to $B_T = 0$; these points and their error limits were derived from least-squares analysis. The dashed line (- - -) represents the calculated plot of K^0_{pH} which best fit the extrapolated points. Unit of K_{pH} is M^{-1}.

system should provide a reasonably accurate evaluation of formation constants and pK_a' values of the various polyborate species.[49] At 0.2 pH intervals K_{pH} values at the three B_T concentrations were read from the smoothed lines of Figure 4. These values, extrapolated to $B_T = 0$, furnished K^0_{pH}, defined as the over-all equilibrium constant at vanishingly small B_T concentrations. Assuming that the ester possesses a single pK_a' (pK_{E_1}) in the pH region of interest, we may assume $E_T = [E] + [E^-]$. (Kinetic data for ester hydrolysis in Table IV confirm this assumption.)

(49) R. B. Martin, A. Parcell, and R. I. Hedrick, *J. Am. Chem. Soc.*, 86, 2406 (1964).

Table IV. Over-All Rate Constants for Boric Ester Hydrolysis[a]

Rate equation: $-dE_T/dt = k_{r_1}[E] + k_{r_2}[E^-] + k_{r_3}[E^-]a_{OH}$	Salicylamide	N-Phenylsalicylamide
k_{r_1} $k[E]$	0.097[b]	<0.04[c]
$k[E^-]a_H$[d]	8.2×10^5	$<1.3 \times 10^4$[c]
k_{r_2} $k[E^-]$	8.2×10^{-5}	1.23×10^{-2}
$k[E]a_{OH}$[d]	9.8×10^2	3.9×10^6
k_{r_3} $k[E^-]a_{OH}$	0.0157	0.365
pK_{E_1}	6.92 ± 0.05	5.5 ± 0.2
pK_{E_2}	12.7 ± 0.15	11.58 ± 0.1

[a] All units of rate constants are M^{-1} sec^{-1} or sec^{-1}. [b] Calculated from forward rate expression and equilibrium constants. [c] No term found; listed is the largest value that would have gone undetected. [d] Kinetically indistinguishable term.

Since $B_T = [BH] + [B^-]$ at very low B_T concentration and $S_T = [S] + [S^-]$, eq 4 then becomes

$$K^0_{pH} = \frac{[E]\left(\frac{K_{E_1} + a_H}{a_H}\right)}{[BH]\left(\frac{K_B + a_H}{a_H}\right)[S]\left(\frac{K_S + a_H}{a_H}\right)} = K_1 \frac{a_H(K_{E_1} + a_H)}{(K_B + a_H)(K_S + a_H)} \quad (13)$$

where

$$K_1 = \frac{[E]}{[S][BH]} \quad (14)$$

K_1 is the equilibrium constant for equilibrium 15. By systematically varying K_1 and K_{E_1} in the right

$$S + BH \underset{k_{r_1}}{\overset{K_1}{\underset{k_{f_1}}{\rightleftharpoons}}} E \quad (15)$$

expression of eq 13 it was possible to compute values of K^0_{pH} over the entire pH range which differed from those in Figure 4 by only 2.4% RMS error, well below experimental error. The value of K_{E_1} was chosen so that the correct shape of the low pH leg of the "bell"-shaped curve was attained; the parameter K_1 is merely

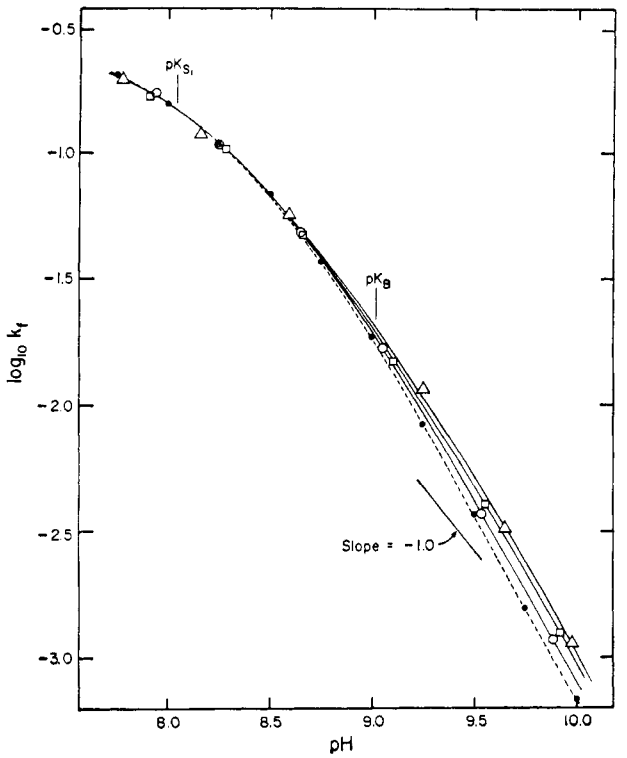


Figure 5. Plots of logarithm of second-order rate constants *vs.* pH for the reaction of salicylamide with borate buffers at several borate concentrations (30°, μ = 0.30 with KCl): ○, 0.04 *M*; □, 0.08 *M*; △, 0.12 *M*. The lower points (●) represent values of k^0_f, the rate constant corrected for effects of polyborates and obtained by extrapolation of k_f values to B_T = 0. The dashed (---------) line, computed from eq 18, afforded the best fit to these points. Unit of rate constants is M^{-1} sec^{-1}.

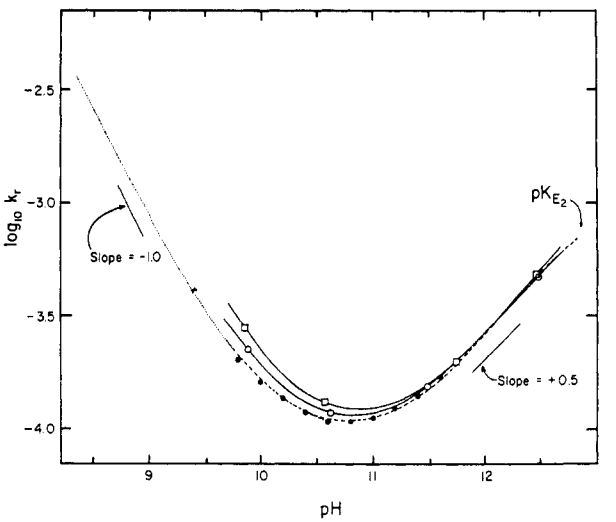


Figure 6. Plots of logarithm of first-order rate constants *vs.* pH for the hydrolysis of the boric ester of salicylamide in borate buffers (30°, μ = 0.30 with KCl): ○, 0.04 *M*; □, 0.08 *M*. The lower points (●) represent values of k^0_r obtained by extrapolation of k_r to B_T = 0. The dashed line (---------) which best fit these points was computed from eq 21 with values for the rate and acid ionization constants listed in Table IV. The dotted line (.....) was computed from an equation similar to eq 21 but with values for the rate constants derived from the pertinent ester formation rate and equilibrium constants in Table III. The dashed and dotted lines diverge above pH 10.6 because eq 21 included a term which becomes significant at higher pH and which could not be calculated from the formation data.

a scale factor adjusted for minimum RMS error. These best values are presented in Tables III and IV.

For the simple reversible esterification scheme, shown in eq 3, it is easily shown[50] that the observed rate constant for ester formation, when boric acid is the reactant in excess, is given by eq 16, where k_f is the

$$k_{obsd} = k_f[K_{pH}B_T + 1]/K_{pH} \quad (16)$$

over-all second-order rate constant for ester formation. Values of k_f, computed from eq 16 utilizing k_{obsd}, and K_{pH}, computed from the formation rate data, are displayed in Figure 5. A small dependence of k_f upon B_T may be noted at higher pH's, a result not unexpected since, by definition, $K_{pH} = k_f/k_r$, where k_r is the apparent rate constant for ester hydrolysis and K_{pH} is significantly dependent upon B_T. Therefore, the k_f values were extrapolated to B_T = 0 at every 0.2 pH interval furnishing k^0_f, considered as the apparent second-order rate constant corrected for effects of polyborates. Figure 5 illustrates that at higher pH the slope of the log k^0_f *vs.* pH profile approaches −2 while at lower pH's the slope continuously diminishes to a value less than −0.5 at pH 7.8. This suggested the possible rate equation (17). The

$$-\frac{dS_T}{dt} = k_{f1}[S][BH] + k_{f2}[S^-][BH] \quad (17)$$

corresponding expression for k^0_f, derived in a manner analogous to eq 12, becomes

$$k^0_f = \left[k_{f_1}\left(\frac{a_H}{K_S + a_H}\right) + k_{f_2}\left(\frac{K_S}{K_S + a_H}\right)\right]\left(\frac{a_H}{K_B + a_H}\right) \quad (18)$$

Equation 18 fits the extrapolated points of Figure 5 satisfactorily (RMS error, 1.6%) utilizing rate constants listed in Table III. It should be emphasized that no terms such as $k_{f_3}[S^-][B^-]$ or $k_{f_0}[S][BH]a_H$ were demanded by the data and so are considered undetectable.

Salicylamide ester hydrolysis was studied at 0.04 and 0.08 *M* B_T in the pH range 9.86–12.48, calculating k_{obsd} and K_{pH} as before. Similarly from equilibrium 3 the relationship given by eq 19 is readily derived for

$$k_{obsd} = k_r[K_{pH}B_T + 1] \quad (19)$$

the observed first-order rate constant for boric ester hydrolysis. The k_{obsd} − K_{pH} data were reduced *via* eq 19 to k_r values which are plotted as log k_r *vs.* pH in Figure 6. Only two concentrations of B_T were employed since the values of k_r were only slightly dependent upon B_T even at low pH. Values of k^0_r (extrapolation of k_r to B_T = 0) increase at the higher pH's with a slope near +0.5 (see Figure 6). The latter observation indicates first that the rate equation contains a term involving hydroxyl ion catalyzed ester hydrolysis and, second, that one must postulate for the ester a second acid dissociation constant, K_{E_2}, in the high pH region. One may therefore assume the rate equation (20) for the over-all hydrolysis of the

$$-\frac{dE_T}{dt} = k^0_r E_T = k_{r_1}[E] + k_{r_2}[E^-] + k_{r_3}[E^-]a_{OH} \quad (20)$$

(50) D. S. Auld, Ph.D. Dissertation, Cornell University, Ithaca, N. Y., 1967, p 67.

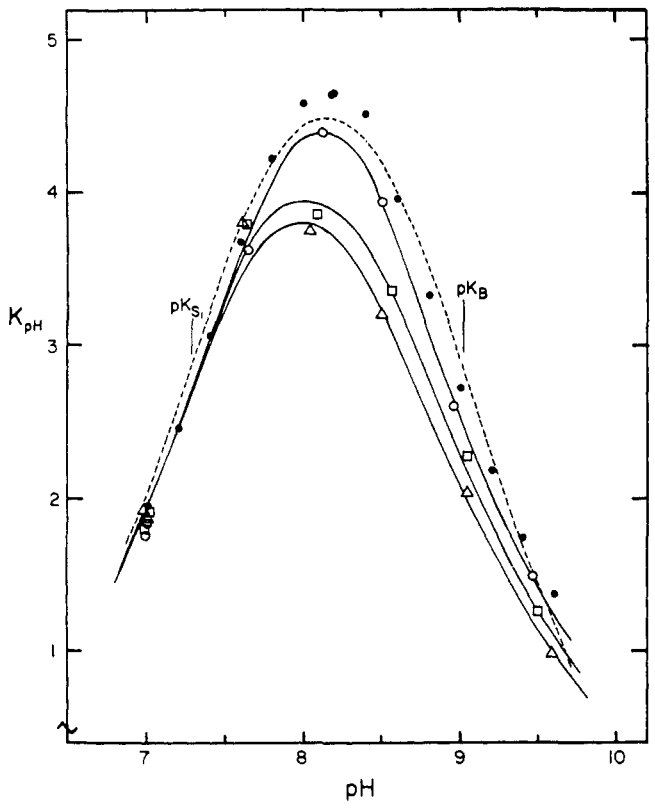


Figure 7. Plots of pH-dependent over-all equilibrium constant *vs.* pH for the N-phenylsalicylamide–boric acid–boric ester equilibrium (30°, μ = 0.3 with KCl). The experimental points were computed from eq 5 at various borate buffer concentrations: ○, 0.04 *M*; □, 0.08 *M*; △, 0.12 *M*. The upper points (●) are values of K^0_{pH}, the equilibrium constant obtained by extrapolation of K_{pH} to B_T = 0. The dashed line (---------) represents the calculated plot of K^0_{pH} which best fit the extrapolated points. Unit of K_{pH} is M^{-1}.

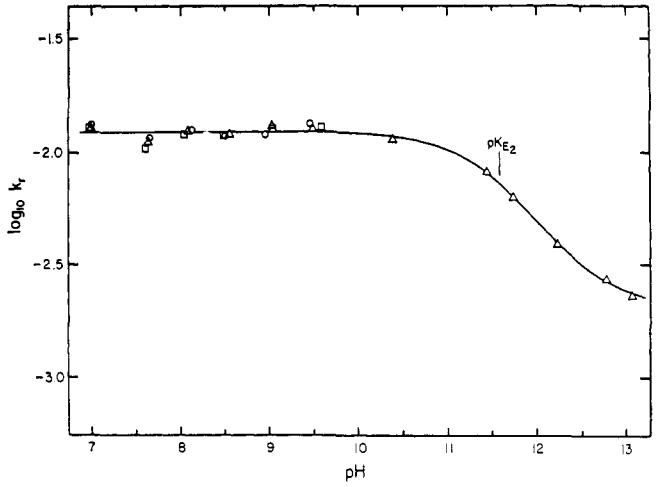


Figure 8. Plots of logarithm of first-order rate constants *vs.* pH for the hydrolysis of the boric ester of N-phenylsalicylamide in borate buffers (30°, μ = 0.3 with KCl): ○, 0.04 *M*; △, 0.08 *M*; □, 0.12 *M*. The line which best fit these points was computed from eq 23 with rate and acid ionization constants listed in Table IV.

ester. Defining $E_T = [E] + [E^-] + [E^{2-}]$ and utilizing expressions for acid ionization constants for the ionic species of ester, one may easily solve for the concentrations of E and E^- in terms of E_T, a_H, and these ionization constants. Substitution of the resulting expressions into eq 20 leads to eq 21. Figure 6 clearly

$$k^0_r = [k_{r_1}a_H^2 + k_{r_2}K_{E_1}a_H + k_{r_3}K_{E_1}K_w] \times \left(\frac{1}{a_H^2 + K_{E_1}a_H + K_{E_1}K_{E_2}}\right) \quad (21)$$

illustrates that the line constructed from eq 21 with the individual rate and ionization constants of Table IV provides an excellent fit (RMS error, 2%) to the data. The value of k_{r_1} was calculated from the identity $k_{r_1} = k_{f_1}/K_1$ using values in Table III. The autoprotolysis constant of water, K_w, equals 1.47×10^{-14} under these conditions.[51] Furthermore, values of k^0_r computed from a rate expression similar to eq 21 but with individual rate constants derived from ester *formation* rate constants and equilibrium constants coincide very closely below pH 10.6 with the line obtained from hydrolysis rates (see Figure 6). Spectral scans at various times during the esterification reaction showed very tight isosbestic points. These observations support the validity of the simple equilibrium scheme depicted by eq 3 and exclude the occurrence of side reactions or stable intermediates (such as monoesters).

Substitution of k_r from the expression $k_r = k_f/K_{pH}$ into eq 19 furnishes the right-hand side of eq 16, which related the k_{obsd} for ester *formation* to rate and equilibrium constants. In general, therefore, *in treatments of association equilibria such as eq 3 where one reactant is in large excess, the observed pseudo-first-order rate constant (k_{obsd}) for formation of product must be identical with the k_{obsd} for dissociation of product to reactants at the identical conditions of pH, B_T, temperature, etc.*

N-Phenylsalicylamide. Ester formation with this amide was studied at 0.04, 0.08, and 0.12 *M* B_T over the pH range 6.97–9.59, computing k_{obsd} and K_{pH} from the rate data. Plots of K_{pH} *vs.* pH, drawn in Figure 7, were similar in every respect to those of salicylamide including the B_T dependence. Therefore, the data treatment was identical with that for salicylamide (*vide supra*), the resulting best values of K_1 and K_{E_1} (RMS error, 5.3%) appearing in Tables III and IV.

Since the k_{obsd} values for ester formation exhibited a wide plateau in the pH range studied, values of k_r were computed *via* eq 19, where k_{obsd} may refer to either ester formation or hydrolysis as shown above. Figure 8 shows that these values are virtually independent of B_T and pH.

Ester hydrolysis rates were considerably more rapid than those of salicylamide. They were measured at only 0.08 *M* B_T since the anticipated dependence of of k_{obsd} upon B_T (eq 19) was less than the error in the k_{obsd} measurements. Consequently, k_r was calculated *via* eq 19 from each observed rate constant (k_{obsd}) and K_{pH} extrapolated from the curves of Figure 7. (Since $K_{pH}B_T \ll 1$ at hgh pH, k_r is nearly equal to k_{obsd} anyway.) Rather surprisingly, a sigmoid k_r *vs.* pH profile was obtained as depicted in Figure 8. These data require for the ester not only a second acid dissociation (K_{E_2}) in the alkaline region but also a term for hydroxyl ion catalyzed hydrolysis. Since pK_{E_1}

(51) H. S. Harned and R. A. Robinson, *Trans. Faraday Soc.*, **36**, 973 (1940).

< 6, the relevant rate equation and expression for k_r which best fit all the data of Figure 8 become simply

$$v_r = k_r E_T = k_{r_2}[E^-] + k_{r_3}[E^-]a_{OH} \quad (22)$$

$$k_r = \left[k_{r_2} + k_{r_3}\left(\frac{K_W}{a_H}\right)\right]\left(\frac{a_H}{K_{E_2} + a_H}\right) \quad (23)$$

The values of the rate constants and pK_{E_2} used to obtain the best fit are provided in Table IV.

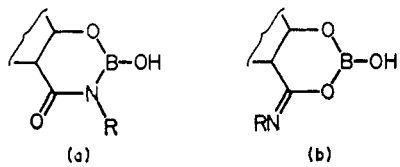
From pH 7 to 10, values of k^0_f were computed at 0.25 pH intervals ($k^0_f = k_r K^0_{pH}$). These values exhibited a symmetrical "bell"-shaped profile and followed accurately (RMS error, 4%) eq 24 with no low pH deviations. If 10% of the apparent rate constants

$$k^0_f = 0.071\left(\frac{a_H}{K_B + a_H}\right)\left(\frac{K_S}{K_S + a_H}\right) \quad (24)$$

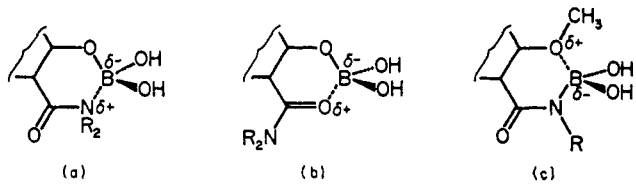
k^0_f or k^0_r at pH 7.00 were due to undetected terms involving the reaction of S and BH or of E, respectively, the maximum possible values of these rate constants for N-phenylsalicylamide would be as follows: $k_{f_1} = 0.004\ M^{-1}\ sec^{-1}$ and $k_{r_1} = 0.04\ sec^{-1}$.

Discussion

Qualitative Tests for Boric Ester Formation. Our methods were unable to detect any boric ester with monodentate ligands, such as compounds **1**–**7** in Table II, regardless of the pK_a of the ligands. This is in agreement with evidence that in the solvolysis of trialkyl borates the intermediate di- and monoborates solvolyze completely and very rapidly.[26a] Although the NO_2 group is feebly basic[52] and has been shown to bond intramolecularly to boron in catechol esters of *o*-nitrophenylboronic acid,[53] nevertheless *o*-nitrophenol does not form a stable ester with boric acid. The second group of compounds in Table II could possibly serve as bidentate ligands toward boron. With some of these compounds the loss of phenolate anion absorption is indeed observed in borate buffers. Since bidentate ligands possessing a phenolic group and a neighboring amide or N-methylamide function (compounds **8**, **9**, and **11**) form detectable esters while no ester formation occurs if the amide is tertiary, each ligand presumably participates by forming two fully covalent bonds with the boron atom (Ia or b) rather than by coordinating as IIa or b.



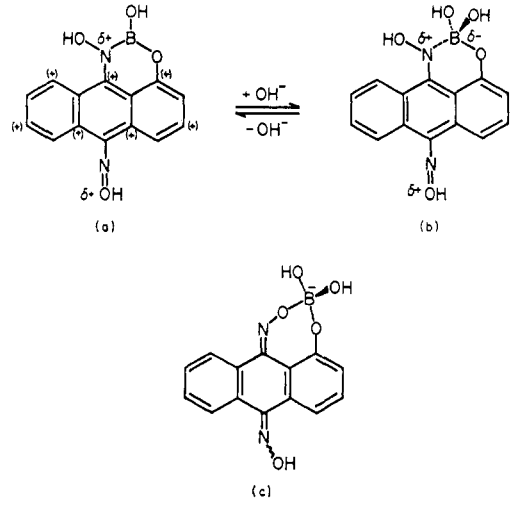
compound I



compound II
R = H, alkyl, aryl

It might be contended that the second N-methyl group of compound **10** exerts an unexpectedly large steric effect preventing bidentate chelation. Observationally, the over-all value of K_{pH} diminished roughly threefold on introduction of one N-methyl group into salicylamide. However, the second N-methyl group further lowered K_{pH} by an additional factor of *at least* 300,[54] a factor much larger than anticipated.[55] Moreover, pseudo-first-order rate constants for boric ester formation with salicylamide and N-methylsalicylamide were very similar which indicates again only a small steric effect, if any, for the N-methyl group and supports Ia or b. This is further substantiated by comparison with the corresponding methyl ester **18** and with **14** where the phenol group is methylated (see IIb,c).

1-Hydroxyanthraquinone dioxime proved to be a surprising exception to the previous generalizations. This substrate (**33**, stereochemistry unknown) was in mobile equilibrium with its boric ester, whose formation constant was estimated to be roughly five times greater than that of salicylamide at pH 8.6. Salicylaldoxime also forms in solution a boric ester,[16,56,57] of somewhat greater stability than **33**. If the oximino group in either compound is *syn* with respect to the phenolic hydroxyl group, a seven-membered heterocyclic ring would result as in IIIc. However, owing to



compound III

the rarity of metal ion complexes containing seven-membered rings,[58] the seven-membered ring in IIIc should likewise be strained and relatively destabilized. If, on the other hand, the oximino group has the *anti*

(52) M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

(53) R. Hemming and D. G. Johnston, *J. Chem. Soc., Sect. B*, 314 (1966).

(54) If ester formation actually occurs when **10** is added to borate buffers of pH ~8.5, the largest OD change which could have been overlooked is 0.003 at an initial OD of 0.500. The maximum calculated K_{pH} is therefore 0.01 M^{-1}.

(55) By contrast, the formation constant of the $(CH_3)_3B$–$NH(CH_3)_2$ adduct in the gas phase decreases only 20-fold on substitution of a third methyl group for the N–H hydrogen atom. See H. C. Brown, H. Bartholomay, Jr., and M. D. Taylor, *J. Am. Chem. Soc.*, **66**, 435 (1944), and subsequent papers by Professor Brown.

(56) Some of the results of Ripan and co-workers[16] with this compound were verified in this laboratory. Note that their formation constant was derived incorrectly from a graphical plot as 3×10^{-3} at pH 9.2. It should be the reciprocal of this value, or 250 M^{-1}. Any value as small as they reported should be immediately suspect,[54,57] because only a negligible fraction (<0.5%) of substrate would be in the form of product.

(57) W. B. Person, *J. Am. Chem. Soc.*, **87**, 167 (1965).

(58) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1962, p 546.

configuration, then relatively strain-free dative bonding should occur as in IIIa, creating a partial positive charge on N. Several factors might contribute, however, to enhanced stabilization of IIIa relative to an analogous ester of **10**: (a) a smaller loss of rotational entropy on esterification since the ligands are sterically fixed, (b) delocalization of the positive charge on nitrogen as shown in IIIa,b, and (c) somewhat greater basicity of an oxime nitrogen as compared to the amide nitrogen ($pK'_a = -1$ to -3). The configuration of the salicylaldoxime sample employed by Ripan, *et al.*, was not reported. An unequivocal choice between possible ester structures hence cannot be made at this time.

From our data no clear pattern emerged for the preferred geometry of boric esters. It was found, for example, that **20**, **22**, and **25** (Table II) give rise to stable boric esters whereas **21**, **23**, and **24** are not esterified by boric acid. Catechol exists in borate buffers predominantly as its boric ester[9] even though the O–O distance in catechol[4a] is probably significantly greater than that preferred by both trigonal and tetrahedral borate esters, *i.e.*, 2.40 ± 0.05 A.[59] Compounds **22** and **23** are both hydroxybenzimidazoles capable of incorporating boron into six- and five-membered rings, respectively. Since metal ion cyclic chelates with five-membered rings are generally stabler than those with six-membered rings,[58] it is somewhat puzzling that 4-hydroxybenzimidazole is unesterified. It is possible that the chelating atoms in this compound are constrained by the imidazole ring to lie too far apart for complexation to occur. Similar geometry in **21** (2,2′-bisimidazole) also could preclude chelation. Although 8-hydroxyquinoline might be expected to complex with boric acid since it is an excellent complexing agent for metal ions, no complexation with boric acid was observed.

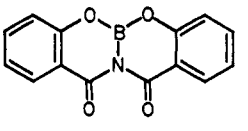
That the extent of ester formation depends upon the basicity of the phenolate anion, as expected, is seen by comparison of **8** and **12**. Comparison of some ester-forming bidentate ligands whose phenol pK_a values are similar reveals that the extent of their ester formation is, however, not related in a discernible fashion to the basicity of the second ligand atom attached to boron. Thus, the boric ester of chromotropic acid (**27**, Table II) is much more stable than the salicylamide ester even though its pK_{a_1} is 5.36 whereas the pK_{a_2} of salicylamide probably exceeds 14. This could result from a lack of rotational entropy of the two fixed hydroxyl groups or to a greater B–O bond energy owing to an element effect or enhanced overlap of the oxygen lone pair (relative to the nitrogen lone pair) with the vacant p orbital of trigonal boron. In this regard, it is significant that no boric ester could be detected with 0.3 *M* malonamide, while considerable ester formation occurred with 2,3-dimethyl-1,3-propanediol.[60] For both substrates the geometry of the resulting boric esters would be similar. That N-acetylsalicylamide furnishes no ester while the ester of **11** is detectable, even though phenol pK_a's for these substrates are similar, indicates that the N-acetyl group is effective primarily in decreasing the basicity of the N atom rather than in exerting an unfavorable steric effect.

Although the existence of boric acid complexes of salicylate[14,17,61] in solution has been deduced spectrally and from solubility data, our methods could not detect any ester with 5-nitrosalicylate. Of course, the 5-nitro group lowers markedly the basicity of the phenolate anion and sodium disalicyloyl borate decomposes entirely in absolute ethanol.[17] Therefore, the results for 5-nitrosalicylate are those expected. Salicylic acid was not tested for boric ester formation because its second pK_a of 12.95[62] is so high that undetectable concentrations of phenolate anion would exist in the weakly alkaline pH range; our simple spectrophotometric tests could therefore give no information.

Appreciable amounts of ester are clearly absent with **28**, *o*-mercaptobenzoic acid. Its thiol pK_a is quite normal (*cf.* **28**, $pK_a = 8.88$;[63] benzenethiol, $pK_a = 7.78$[64]), which is consistent with the presence of only a weak hydrogen bond between thiol and carboxylate groups (bond energy = 0.9 kcal/mole)[65] and allows one to predict that thiolsalicylamide boric ester might be much less stable than the salicylamide ester.

Aldehydes **30** and **31** are in mobile equilibrium with corresponding boric esters whose ultraviolet spectra are nearly identical with the undissociated phenolic form of the aldehyde. Since **31** is known to exist in partially hydrated form[66,67] and since 3-hydroxypyridine (**6**) furnishes no ester, boric acid is presumably attached to the 3-OH group and one of the hydroxyls of the $CH(OH)_2$ group. From measured esterification rates we calculate that the second-order rate constant, k_f (k_f[aldehyde]B_T), exceeds by at least an order of magnitude that for salicylamide at pH 8 (see footnote *f*, Table II).

In summation, those bi- and tridentate ligands of suitable structure, geometry, and basicity which can exchange a hydrogen ion upon formation of each B–X bond generally equilibrate with their boric acid esters in solution. Monoesters of phenols are stable only if at least one neighboring group with $pK_a > 0$ is capable of coordinating with the boron atom within a six-membered ring. Disalicylimide was quantitatively esterified by boric acid even though all its ligands are less basic than those of salicylamide and despite the bulk of the second salicyloyl group. This is strong evidence that the ester possesses the cyclized structure, *viz.*



+ Anionic form (?)

This ester is far more stable than the bidentate esters, being surprisingly resistant to alkaline hydrolysis,

(59) (a) J. Dale, *J. Chem. Soc.*, 922 (1961); (b) A. J. Hubert, B. Hargitay, and J. Dale, *ibid.*, 931 (1961).

(60) Utilizing a method to be reported in a future communication.

(61) H. Schäfer, *Z. Anorg. Allgem. Chem.*, **250**, 82 (1942).

(62) J. Hermans, Jr., S. J. Leach, and H. A. Scheraga, *J. Am. Chem. Soc.*, **85**, 1390 (1963).

(63) R. J. Irving, L. Nelander, and I. Wadsoe, *Acta Chem. Scand.*, **18**, 769 (1964).

(64) J. P. Denehy and C. J. Noel, *J. Am. Chem. Soc.*, **82**, 2511 (1960).

(65) I. M. Ginzberg and L. A. Loginova, *Dokl. Akad. Nauk SSSR*, **156**, 1382 (1964).

(66) K. Nakamoto and A. E. Martell, *J. Am. Chem. Soc.*, **81**, 5863 (1959).

(67) D. S. Auld and T. C. Bruice, *ibid.*, **89**, 2090 (1967).

more so than free imide even though the presence of a B–N bond should both make the carbonyl groups more susceptible to attack and prevent N–H ionization which retards imide hydrolysis.[68,69] The observed order of ester stability, tridentate > bidentate > monodentate, would be expected on the basis that the reduced loss of entropy in the intramolecularly formed esters as compared to triphenyl borate, for example, should be the important factor in lowering the free energy of the ester *relative* to the substrate. The incorporation of all ligands in the same molecule should therefore result in increasingly positive values of $\Delta S°$ in the formation of boric esters as shown for metal ion complexes of polydentate ligands.[70] These results indicate that the "inordinate" hydrolytic stability of tris(isopropyl alcohol)amine borate[11] relative to tris(isopropyl) borate may be ascribed primarily to this entropy effect rather than wholly to an intramolecular B–N dative bond as postulated by the authors.[11]

From these qualitative results we might conclude that the use of borate buffering with systems possessing two or more neighboring groups such as hydroxyl, amino, amide, peptide, amidine, guanidine, imidazole, may well lead to bi- or tridentate esterification with boric acid. This could have important consequences in physicochemical measurements of proteins, polypeptides, and other macromolecules, utilizing boric acid as buffer. For example, the rate of hydrolysis of *p*-nitrophenyl acetate catalyzed by α-chymotrypsin is diminished in borate buffers.[71] The authors' evidence suggests that a molecule of $B(OH)_3$ is noncompetitively attached to the imidazole moiety of a histidine unit of the enzyme.

Kinetic Results of Boric Ester Formation and Hydrolysis. Although 2:1 and even 3:1 complexes such as pyridinium di- and tricatetchol borate have been isolated from aqueous solution,[9,72] only 1:1 stoichiometry has been demonstrated to date for various phenol and enol boric esters in very dilute solution.[10,16,19] A 2:1 complex has been potentiometrically demonstrated in much more concentrated solutions of pyridoxine (vitamin B_6) and boric acid.[20] Reexamination of the data of Knox and Pitt[18] leads to a revised 1:1 stoichiometry also (see Comments). We shall likewise assume hereafter 1:1 stoichiometry for the boric esters studied since $S_T \sim 1 \times 10^{-4}$ *M* and B_T ranges from 0.01 to 0.50 *M*.

In Table III are summarized the equilibrium constants and kinetic results of ester formation with disalicylimide, salicylamide, and N-phenylsalicylamide. Any effects of polyborates have been eliminated. All rate terms were calculated initially with $B(OH)_3$ as the reactive species since nucleophilic attack on $B(OH)_4^-$ by very weak nucleophiles such as amide or undissociated phenol would *a priori* seem to be more difficult than attack on trigonal boron. In support of this contention no kinetic terms for ester formation such as $k[S^{2-}][B^-]$ for the imide or $k[S^-][B^-]$ for the amides could be detected (see Schemes I and II for representations of symbols).

Table IV presents the results pertaining to the ester hydrolyses. Hydrolysis of these boric esters involves specific base catalyzed as well as "spontaneous" hydrolysis of E^-; for salicylamide but not its N-phenyl derivative the "spontaneous" hydrolysis of E was also detected.

It was hoped that a comparison of the determined rate constants for the two amides (Tables III and IV) might exclude some of the many conceivable mechanisms for this esterification and implicate others. However, *initially assuming no steady-state intermediates*, several inexplicable anomalies arise from these comparisons, which seem to prevent mechanistic inferences.

(1) In Table III the order of reactivity for the various ionic species of disalicylimide (toward BH), $S \gg S^- > S^{2-}$, was unexpected. This order indicates that the lowest energy pathway involves un-ionized substrates, certainly much poorer nucleophiles toward trigonal boron.

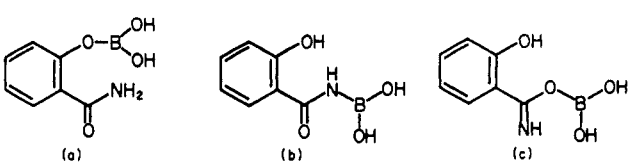
(2) The same order of terms was observed for salicylamide, but anamolously the reverse order was obtained for N-phenylsalicylamide.

(3) The values of k_{f_2} for reaction of S^- with BH are nearly the same for all substrates regardless of large differences in the pK_a of the phenolic hydroxylic group and presumably of amide nitrogen, as well as differing steric bulks of the N substituents. Hence unassisted nucleophilic attack of S^- upon BH appears inconsistent with these data.

(4) For disalicylimide it is curious that k_{f_1}/k_{f_2} is so large. Even if the reaction of the undissociated phenol with BH is more facile than that of phenolate anion with BH, k_{f_1} and k_{f_2} should still be similar since the monoionized species possesses at least one undissociated phenol group.

(5) Finally, comparing terms involving "spontaneous" hydrolysis, ionized N-phenylsalicylamide ester E^- is more reactive than salicylamide but, when protonated (E), is less reactive. The discrepancy within comparison 5 is even more apparent in view of the fact that the N-phenylsalicylamide ester, E, is considerably less stable than salicylamide ester.

Although no intermediates were observed kinetically, it is reasonable to assume a steady-state concentration of monoester since in the over-all reaction at least two bonds are made and two broken.[73] Since the boric esters of 2,2-dimethyl-1,3-propanediol and N-phenylsalicylamide (E) have similar formation constants while malonamide forms no ester,[60] the salicylamide monoester IVa is probably more stable than IVb or c. Attachment of boron at amide oxygen is of

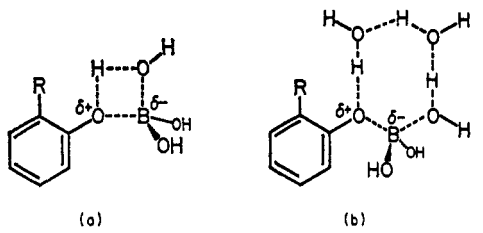


compound IV

course impossible with disalicylimide. From the fact that k_{f_1} is generally much larger than k_{f_2}, except for

(68) J. T. Edward and K. A. Terry, *J. Chem. Soc.*, 3527 (1957).
(69) M. T. Behme and E. H. Cordes, *J. Org. Chem.*, **29**, 1255 (1964).
(70) See ref 58, pp 546–547.
(71) I. V. Berezin, G. Ya. Kolomiitseva, A. V. Levashov, and K. Martinek, *Dokl. Akad. Nauk SSSR*, **171**, 1213 (1966).
(72) D. F. Kuemmel and M. G. Mellon, *J. Am. Chem. Soc.*, **78**, 4572 (1956).
(73) The hydrolysis of succinamide involves intermediate monoamide; see M. Vigneron, P. Crooy, F. Kézdy, and A. Bruylants, *Bull. Soc. Chim. Belges*, **69**, 616 (1960).

N-phenylsalicylamide, one might infer a facile mechanism for the k_{f_1} step involving either a four-centered[35] or a water-mediated proton transfer in the transition state (as suggested by Lane[74] for acidic hydrolysis of ethyl acetate), *viz.*, V. On the other hand, formation

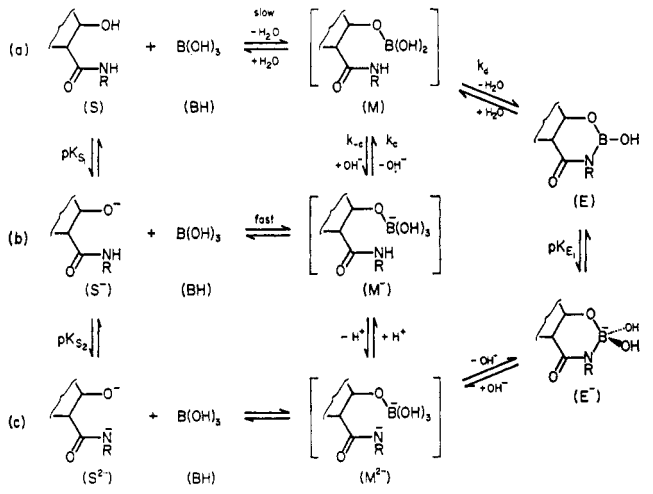


compound V

R = $COHN_2$, $CONHC_6H_5$, COHN-salicyloyl

of a monoester from phenolate anion and BH should intuitively be more facile than formation of the monoester from undissociated phenol and BH involving either mechanisms shown in Va or b. However, if cyclization of the former monoester should be sufficiently unfavorable energetically relative to cyclization of the latter monoester, then a point might be reached where $k_{f_1} > k_{f_2}$. The mechanistic scheme depicted in Scheme III incorporates this possibility. In this mechanism both steps in (a) of Scheme III are faster

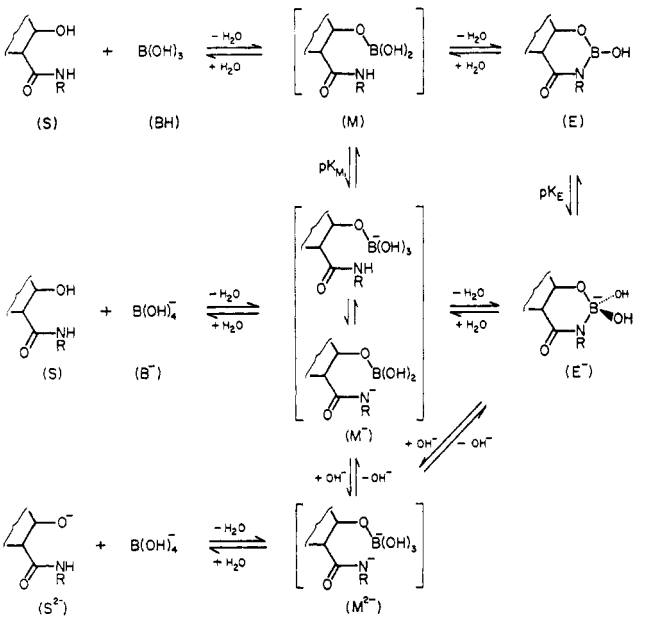
Scheme III



than the k_c step but of course much slower than preequilibrium formation of monoester M^- in (b). There is reason to believe that the value of k_c might be relatively small. Eyring, *et al.*,[5] have estimated the rate constant for attack of hydroxyl ion upon BH as 10^{10} M^{-1} sec^{-1}. Estimating the pK_a of monoester M of Scheme III as *ca.* 6–8 and assuming $k_{-c} = 10^{10}$ M^{-1} sec^{-1}, one calculates a value for k_c of 10^2–10^4 sec^{-1}, but if the k_c step is associated with a higher free energy than that for formation of M from S and BH, then for the retrograde, H_2O must be a much better nucleophile toward M than OH^-. This is of course absurd because k_{-c} is estimated to be near 10^{10} M^{-1} sec^{-1} or approximately diffusion controlled. Therefore we must adopt the kinetically equivalent mechanism shown in Scheme IV for the k_{f_2} step involving the reaction of protonated phenol with borate anions and, by extension, cyclization of M^- by attack of amide upon the substituted borate anion. Over-all rate constants,

(74) C. A. Lane, *J. Am. Chem. Soc.*, 86, 2521 (1964).

Scheme IV



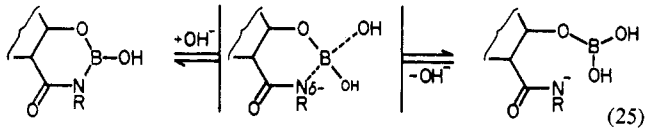
calculated for this alternative mechanism and listed in Table III, increase from salicylamide to disalicylimide. The acidity of the phenolic hydroxyl group of these substrates also increases in that order. The observed order of rate constants would be expected if one imagines a transition state involving considerable proton transfer but little bond formation between the phenolic hydroxyl oxygen and boron. Such a transition state would be pictorially very similar to those illustrated by V for the reaction of S with BH except that in this case the boron atom would possess an additional hydroxyl group. This argument depends upon the assumption that the initial bimolecular step is rate determining. This is possible since cyclization of M^- presumably could occur through essentially the same mechanism as in the first step or conceivably *via* the kinetically equivalent attack of amide anion on $O\text{-}B(OH)_2$ as in Scheme IV; either alternative would be expected by entropy considerations to be more rapid than the initial step. For disalicylimide it is seen that S^- reacts nearly 10^5 times slower with B^- than does S even though both species possess an undissociated phenol group. This may be a consequence of electrostatic repulsion between the two anionic reactants or intramolecular catalytic effects or perhaps different molecular conformations of the two species. However, the computed values of k_{f_3} for the two amides in Table III are 50–100 times less than the determined value for disalicylimide. This indicates that monoionized disalicylimide is still much more reactive than anticipated, presumably since it can react with B^- *via* its remaining undissociated phenol group.

We can develop no rationale from our data to explain the anamolously low reactivity of N-phenylsalicylamide relative to salicylamide in the k_{f_1} step.

The over-all rate of hydroxyl ion catalyzed hydrolysis of the ionized ester (E^-) of N-phenylsalicylamide exceeds by a factor of 23 that of the salicylamide ester (see values of k_{r_3}, Table IV). This is probably a reflection of the proportionately lower stability constant of the boric ester (E) of the N-phenyl derivative (*cf.* K_1 values, Table III). Either step of reaction c in

Scheme IV could be the slow one since the predicted over-all rate ratio (N-phenylsalicylamide/salicylamide), assuming either step as the slow one, is in accord with the observed ratio.

Some of the many conceivable mechanisms for ester formation and hydrolysis can fortunately be discarded. A choice between four kinetically indistinguishable mechanisms for "spontaneous" hydrolysis of E^- appears possible. As an alternative to the reverse reaction of (b) in Scheme IV, let us consider first an attack of hydroxyl ion on the trigonal boron of E concerted with the departure of one of the ligands to yield monoester (eq 25). It has recently been demonstrated



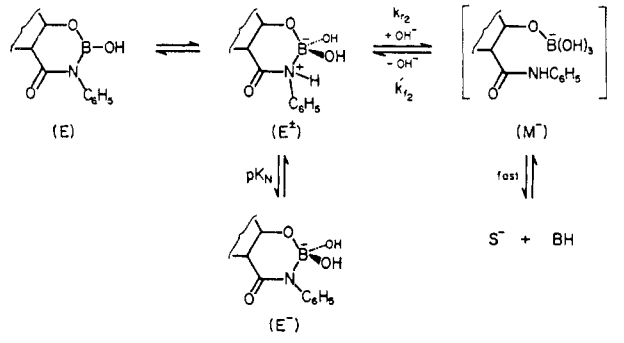
(E) Transition state Monoester (25)

R = H, phenyl

that a metastable tetrahedral intermediate occurs along the reaction path in water-catalyzed hydrolysis of activated carboxylate esters;[75,76] in addition, scant evidence exists that a concerted displacement-like mechanism is a significant pathway for hydrolysis of carboxylate esters. Since the analogous "tetrahedral intermediate" in boric esters is simply the perfectly stable tetracoordinated borate anion, E^-, mechanism 25 should be even less likely here than for carboxylate esters.

Secondly, the calculated rate constant k'_{r_2} for hydroxyl ion attack on the zwitterionic ester ($E^{\pm}$) in Scheme V exceeds 10^{12} M^{-1} sec^{-1} when pK_N is less than 0,

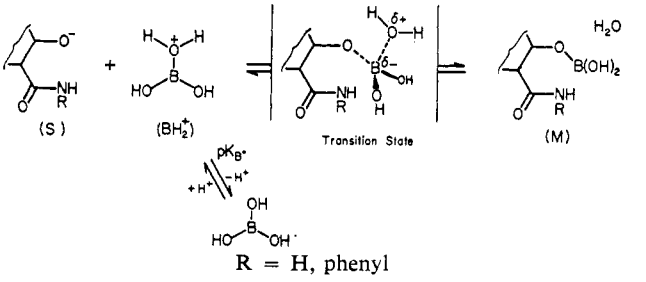
Scheme V



which is almost surely the case. Since $K_N = [E^-]a_H/[E^{\pm}]$ in Scheme V, the expression $k_{r_2}[E^-]$ may be transformed into the kinetically equivalent expression $k_{r_2}K_N[E^{\pm}]a_{OH}/K_W$, from which k'_{r_2} can be evaluated as $k_{r_2}K_N/K_W$. If $pK_N < 0$, then by microscopic reversibility principles one may also rule out step k'_{f_2}, *i.e.*, intramolecular amide displacement of hydroxyl ion from monoester M^-. Finally, unimolecular breakdown of E^- to monoester *via* B–N bond scission involves expulsion of an amide anion, a poor leaving group. Alternative expulsion of phenolate anion from E^-, an otherwise favorable process, generates the less stable monoester, attached at the amide group (*e.g.*, see IVb). For these reasons the proposed Scheme IVb appears energetically most favorable of these four possibilities.

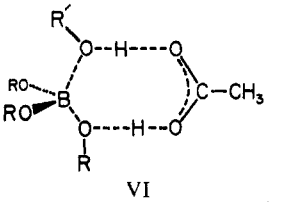
Table III shows that rate constants calculated for Scheme VI are large and for salicylamide exceed dif-

Scheme VI



R = H, phenyl

fusion-controlled limits if the hypothetical acidic pK_a of boric acid (pK_{B^+}) is less than *ca.* −4. To our knowledge, no literature accounts of an acidic pK_{B^+} such as that shown in Scheme VI have appeared.[77] According to microscopic reversibility principles, the retrograde of Scheme VI would also be excluded if $pK_B < -4$. If hydrolysis of monoester M then involves a concerted proton transfer as in compound V to eliminate protonated phenol, then water displacement of alkoxide anion from trialkyl borates should surely require a similar proton transfer since alkoxide is a much poorer leaving group than phenoxide. The question of concerted or subsequent proton transfer in the hydrolysis of trialkyl (and triaryl) borates has not been experimentally resolved. Furthermore, experimental difficulties have heretofore prevented even a careful kinetic analysis of hydrolysis data to determine separate rate constants for hydroxyl ion attack and water attack (if any) upon these substrates. The low slope of the Brønsted plot for general base catalyzed ethanolysis of tris(*sec*-butyl) borate (0.43) has led Denson and Crowell[26b] to suggest that the general base may remove a proton after addition of ethanol to the trigonal boron rather than base addition followed by unimolecular elimination of alkoxide. As an important sidelight, these workers discovered but could not rationalize the fact that acetic acid was *ca.* 500 times as effective a general acid catalyst in their ethanolysis reaction as predicted by a rough Brønsted plot, whereas acetate ion is even less efficient a general base than anticipated from the Brønsted plot of general base rate constants. An interpretation[78,79] involving bifunctional catalysis of cyclic proton transfer, performed by acetic acid, is consistent with this remarkable finding.



VI

R = *sec*-butyl; R′ = ethyl

(75) L. R. Fedor and T. C. Bruice, *J. Am. Chem. Soc.*, **87**, 4138 (1965).

(76) M. L. Bender and H. d'A. Heck, *ibid.*, **89**, 1211 (1967).

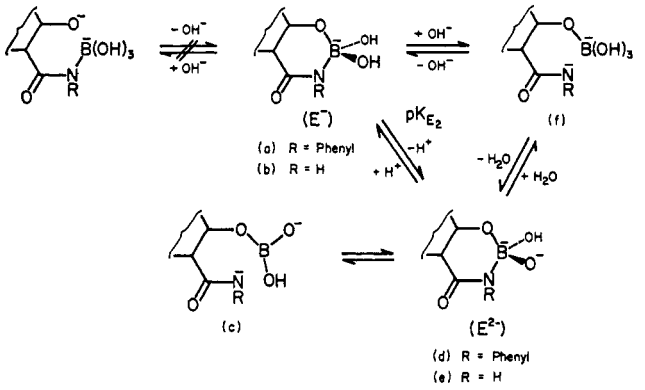
(77) R. J. Gillespie and E. A. Robinson, *Can. J. Chem.*, **40**, 1009 (1962).

(78) For a compilation of references of other work in this area, see B. A. Cunningham and G. L. Schmir, *J. Am. Chem. Soc.*, **88**, 551 (1966); **89**, 917 (1967).

(79) S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, **20**, 1892 (1966).

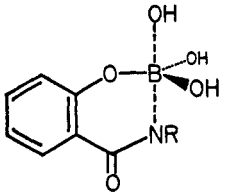
Finally, designation of the k_{r_3} term (see Table IV) as hydroxyl ion attack on E^- according to reaction c of Scheme III will now be supported. The kinetically determined, second acid dissociation constant K_{E_2} of VIIa (Scheme VII) must refer to dissociation of one

Scheme VII



compounds VII

of the B–OH protons producing VIId, since ester E^- must be cyclized for stability. Alternate dissociation of the N–H proton in VIIb might occur instead. This apparently is the first case known where the *second* pK_a of a boric acid derivative has been determined in aqueous solution and constitutes direct evidence that the boron atom in E^- is tetrahedral. Boric acid behaves solely as a monobasic acid in solution.[44a] Borate anion itself is tetrahedrally symmetrical up to the most alkaline pH's studied,[80] which probably rules out unimolecular breakdown to VIIc.[81] Water attack upon VIId and e to generate monoester VIIf should likewise prove unfavorable by analogy with amide hydrolysis and because water must attack a dianionic group and expel an amide anion. Normal SN2 displacement on VIIa by hydroxyl ion can only occur by attack on tetrahedral boron from the top, leading to expulsion of anilide anion, rather than from the bottom, resulting in phenoxide displacement. Molecular models clearly illustrate that the N-phenyl group prevents all access from the bottom. If hydroxyl ion attack on E^- is the correct representation, then presumably an SN2-like transition state such as VIII is involved. The



VIII

R = H, phenyl

pertinent second-order rate constant, where R = phenyl, is very similar to that for alkaline hydrolysis of phenyl benzoate even though the site being attacked here is both tetrahedral and possesses a formal negative charge. This emphasizes the much greater facility of boric and borate esters to hydrolytic interconversions compared to carboxylate esters.

Of course, some mechanistic details of our *intra*molecular esterification reaction could possibly differ from those of the *inter*molecular counterpart of this reaction,[82] *e.g.*, triphenyl borate.

It is doubtful that Hammett substituent correlations or measurement of D_2O solvent kinetic isotope effects would provide much additional mechanistic information in our reaction (Scheme IV) in which several intermediates and many acid dissociations doubtless occur.

Comments on Previous Work. In order to explain the unusually high catalytic constants for borate buffer catalyzed hydrolysis of phenyl salicylate relative to catechol monobenzoate or phenyl *o*-methoxybenzoate, Capon and Ghosh[22] have proposed a novel mechanism involving complex formation between un-ionized ester and borate anions (or the kinetically equivalent ionized ester and boric acid) followed by or concerted with carboxyl ester cleavage by water and hydroxyl ions. This theory was advanced since the catalytic rate for phenyl salicylate was stated to follow eq 26,

$$v_{\text{borate}} = k_{\text{borate}} S_T B_T = k_a[S][B^-] + k_b[S][B^-][OH^-] \quad (26)$$

in which S and B^- have their present designation. However, their derived values of k_a and k_b furnish a calculated profile of k_{borate} *vs.* pH from eq 26 which is between 10- and 100-fold greater than that observed. Furthermore, the calculated profile possesses an entirely different shape.[83] Our reevaluation of their "kinetic analysis" revealed that their derived expression for k_{borate} was independent of the fraction of B^- or BH, clearly inconsistent with eq 26. Moreover, the line of their Figure 5 was drawn utilizing points taken only from the middle flat portion of the experimental "bell";[83] in fact, the complete curve, utilizing all points, showed marked curvature. In the absence of an accurate pK_B at their temperature, we find instead that their k_{borate} values roughly follow eq 27a and b which

$$v_{\text{borate}} = 0.30[S^-][BH] + 0.045[S][BH] \quad (27a)$$

$$v_{\text{borate}} = 5000[S][BH]a_{OH} + 0.045[S][BH] \quad (27b)$$

are similar in form to rate equations found in the present study. These authors reported but did not analyze additional experimental k_{borate} *vs.* pH data for a series of phenyl salicylates substituted in the phenol portion (series 1) and for a series substituted in the 5 position of the acyl moiety, *i.e.*, *para* to the hydroxyl group (series 2). Utilizing apparent pK_S values (not furnished by the authors but calculated from sigmoid plots of their hydrolysis rate constants *vs.* pH), each set of experimental data demonstrated a reasonable fit to eq 28, where k_{borate} is the over-all second-order rate

$$k_{\text{borate}} = k_{AB}\left(\frac{K_S}{K_S + a_H}\right)\left(\frac{a_H}{K_B + a_H}\right) + k_{AA}\left(\frac{a_H}{K_S + a_H}\right)\left(\frac{a_H}{K_B + a_H}\right) \quad (28)$$

(80) J. O. Edwards, G. C. Morrison, V. F. Ross, and J. W. Schultz, *J. Am. Chem. Soc.*, 77, 266 (1955).

(81) Various boronic acids (R–B(OH)$_2$) also behave as Lewis acids accepting an OH^- ion, whereas proton dissociation from the B–OH group occurs when the boron is a member of an aromatic ring: M. J. S. Dewar and R. Jones, *ibid.*, 89, 2408 (1967).

(82) As in the case of carboxyl participation in ester hydrolysis see, for example, A. R. Fersht and A. J. Kirby, *ibid.*, 89, 4853 (1967).

(83) The calculated curve is sigmoid, the titration of an acid of $pK_a \sim 8.8$, whereas the experimental points form a rough "bell" centered at pH 8.4.

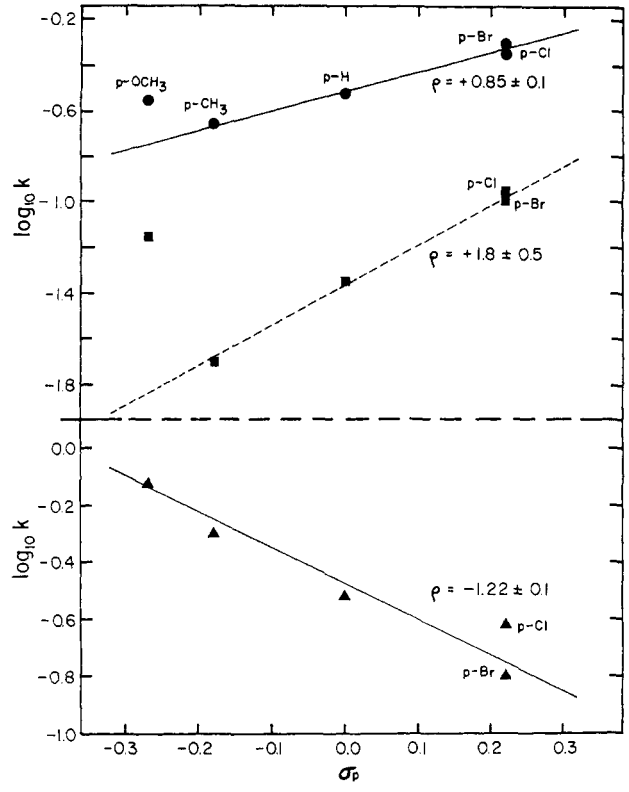
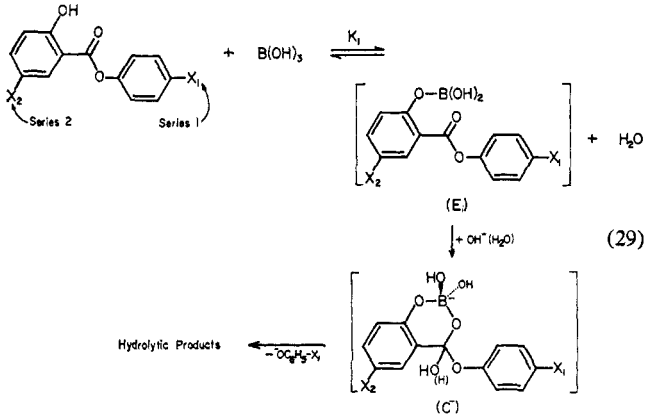


Figure 9. Hammett substituent correlations of second-order rate constants for borate buffer catalyzed hydrolysis of a series of substituted phenyl salicylates. Upper half: ———, k_{AB} from eq 28 for substituents in phenol moiety; ---------, k_{AA} from eq 28 for same substituents. Lower half: k_{AB} from eq 28 for substituents in 5 position of the acyl part. Capon and Ghosh[22] noted that the *p*-OCH_3 point exhibited a positive deviation on the corresponding plot for uncatalyzed hydrolysis also.

constant for rate equation 27a. Significantly, k_{AB} was from four to ten times larger than k_{AA} in every case.

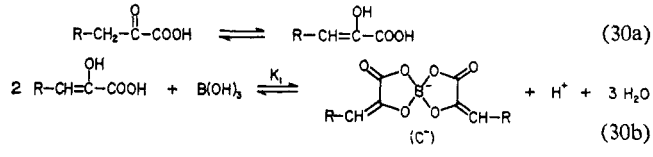
Although a unique mechanism may not be written, nevertheless it is logical to suppose that borate catalysis occurs *via* formation of monoester E in eq 29 followed



(29)

by attack of either hydroxyl ion or water upon the carbonyl carbon. The formation of bidentate complex,[22] C^-, concerted with this attack, could stabilize the tetrahedral intermediate and the transition state leading to its formation. Hammett plots with rate constants k_{AA} and k_{AB} using σ_p constants appear fairly linear[84] and are presented in Figure 9. For series 1, it was found that $\rho = +0.85$ for the k_{AB} term and $+1.8$ for the k_{AA} term of eq 28. The pK_S values of this series are nearly invariant as anticipated (8.4–8.8); therefore, these ρ values may be compared to those found for alkaline hydrolysis of phenyl acetates ($\rho = +0.8$)[85] and phenyl benzoates ($\rho = +1.28$).[86] A value of $\rho = -1.22$ for the k_{AB} term of series 2, however, is opposite in sign to that expected for alkaline hydrolysis of acyl-substituted phenyl benzoates ($\rho = +2.00$).[86] A reasonable interpretation is that the equilibrium constant for monoester formation diminishes with electron withdrawal while nucleophilic attack is favored, the former effect being the most sensitive one. For the mechanism of eq 29 the calculated rate term $k_{AB}[S^-][BH]$ would correspond to $k'_{AB}[E]a_{OH}$, where k'_{AB} is given by $k_{AB}(K_S/K_1K_W)$ and K_1 is the formation constant for boric ester E. Because no boric ester was observed spectrally,[22] K_1 must be less than 0.01 M^{-1}.[54] Calculated rate constant k'_{AB} must then exceed *ca.* 10^6 M^{-1} sec^{-1} for phenyl salicylate. This value is 10,000 times greater than the *calculated* rate constant for hydroxyl ion attack on un-ionized phenyl salicylate itself; therefore, if bidentate ester is formed, it must break down to products most rapidly. Boron functions in this system analogous to metal ions in the hydrolysis of metal ion complexes of dicarboxylic acid monoesters,[87,88] lowering the free energy barrier to nucleophilic attack by forming C^-. This is known to be the slow step in the basic hydrolysis of phenyl benzoate.[89]

Knox and Pitt[18] have reported that *p*-hydroxyphenylpyruvic acid (*ca.* 10^{-4} *M*) equilibrates with its boric ester "immediately" upon solution of the crystalline enol form into borate buffers. Formation constants for this rapid esterification (eq 30b) were computed at



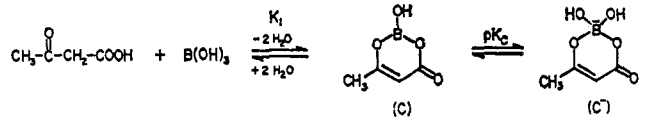
several B_T concentrations for three possible enol-borate complexes of 1:2, 1:1, and 2:1 stoichiometry (R = C_6H_4OH). Only the set of constants computed assuming a 2:1 complex remained relatively invariant over the range $B_T = 0.085$–0.85 *M* at pH 6.55, hence supporting the illustrated complex, C^-. Clearly, any polyborate species in solution could not participate in this equilibrium; therefore, we have computed the fraction of free $B(OH)_3$ and corrected their formation constants for 1:1 and 2:1 complexes utilizing the formation constants of Ingri, *et al.*,[44] for the tri-, tetra-, and pentaborates. Above $B_T = 0.3$ *M*, values for 1:1 stoichiometry now remain constant within experimental error whereas those for 2:1 increase considerably. This evidence, while certainly not excluding the possibility of more than one complex, favors simple 1:1 stoichiometry and does not support the proposed structure C^- in eq 30b as the sole complex.

The enol borate of acetoacetate has provided a sensitive spectral assay for acetoacetic decarboxylase,[19]

(84) Owing to considerable error in k_{AA} and k_{AB}, such good straight lines are a bit fortuitous. Plotted against σ_m constants, however, series 2 substituents gave rather random points.

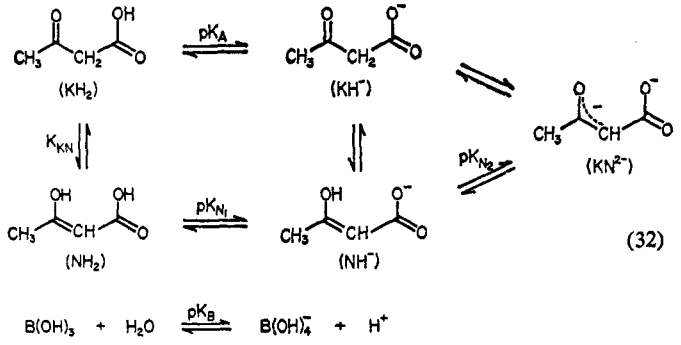
(85) T. C. Bruice and M. F. Mayahi, *J. Am. Chem. Soc.*, **82**, 3067 (1960).
(86) Private communication from Dr. Jack Kirsch.
(87) J. I. Hoppé and J. E. Prue, *J. Chem. Soc.*, 1775 (1957).
(88) R. W. Hay and N. J. Walker, *Nature*, **204**, 1189 (1964).
(89) C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1079 (1956).

because at low enzyme concentration the decarboxylation reaction was presumably very slow compared to the dissociation of enol borate. However, Neece and Fridovich[19] were able to monitor separately the complex-forming reaction at pH 5.8 by mixing identical buffers containing boric acid and acetoacetate. Since the reaction appeared to produce a highly absorbing complex of negligible concentration relative to acetoacetate, tautomerization could not be the process being observed. The observed rate constant (*ca.* 0.02 sec^{-1}) must in this case refer to the rate of hydrolysis of the complex and not to its formation, by analogy with the mathematical treatment presented above. The authors concluded from additional equilibrium experiments that C in eq 31 was the predominant ultraviolet radiation absorbing species in the pH range 3.0–10.1 and that the ionized complex C^- must be unstable. Their



(31)

proposed mechanism included as intermediates the carboxyl-attached monoester of both enol and keto tautomers. It will now be shown that this mechanism predicts a far different relationship than observed between the optical density of C and pH (OD was maximal near pH 5). Pertinent acid–base equilibria are shown schematically in eq 32. (Only monomeric boric acid is



(32)

$$B(OH)_3 + H_2O \overset{pK_B}{\rightleftharpoons} B(OH)_4^- + H^+$$

present at $B_T = 0.05\ M$). With the aid of the pertinent equilibrium constants in eq 31 and 32, the concentration of C may be derived as

$$[C] = \underbrace{K_1[\text{acetoacetate}_T]B_T}_{\text{constant}} \times \frac{\left(\frac{a_H}{K_B + a_H}\right)}{\left[\left(\frac{K_a + a_H}{a_H}\right) + K_{KN}\left(\frac{a_H^2 + K_{N_1}a_H + K_{N_1}K_{N_2}}{a_{H2}}\right)\right]} \quad (33)$$

Utilizing known values of pK_A[90] and pK_B and estimated $pK_{N_1} \sim 3$, calculated values of [C] approximate a sigmoid curve typical of the titration of a base of $pK_a = pK_A$ regardless of the chosen value of K_{KN} as long as $pK_{N_2} > 7$. We conclude that perhaps C^- may be stable and a significant ultraviolet radiation absorber. As shown in the present paper, several possible pathways are possible for boric esterification, so until much more detailed work is performed on this system, the mechanism of this esterification must remain in doubt.

(90) J. T. Edsall and J. Wyman, "Biophysical Chemistry," Vol. I, Academic Press Inc., New York, N. Y., 1958, p 466.

Acknowledgment. This work was supported by grants from the National Science Foundation and the National Institutes of Health.

Appendix

Derivation of the Expression for Equilibrium Constant, K_{pH}. If $B_T \gg S_T$, then K_{pH} may be expressed as

$$K_{pH} = \frac{E_T^{eq}}{S_T^{eq}B_T} = \frac{1}{B_T}\left[\frac{S_T^0 - S_T^{eq}}{S_T^{eq}}\right] \quad (1a)$$

where S_T° is the total concentration of substrate at zero time. If S has only one ionization constant (K_S) in the pH region of interest, we may write expressions for OD_0, the OD were no borate present, and for OD_∞, the OD when ester and substrate are in equilibrium, *viz.*

$$OD_0 = \epsilon_S[S]_0 + \epsilon_{S^-}[S^-]_0 \quad (2a)$$

$$OD_\infty = \epsilon_S[S]_{eq} + \epsilon_{S^-}[S^-]_{eq} + \epsilon_{ester}E_T \quad (3a)$$

Defining $R = \epsilon_{S^-}/\epsilon_{ester}$ and $Z = \epsilon_{S^-}/\epsilon_S$ and substituting the expressions for [S] and [S⁻] in terms of S_T and K_S into eq 2a and 3a afford eq 4a and 5a.

$$OD_0 = S_T^0\left[\frac{\epsilon_{S^-}}{Z}\left(\frac{a_H}{K_S + a_H}\right) + \epsilon_{S^-}\left(\frac{K_S}{K_S + a_H}\right)\right] \quad (4a)$$

$$OD_\infty = S_T^{eq}\left[\frac{\epsilon_{S^-}}{Z}\left(\frac{a_H}{K_S + a_H}\right) + \epsilon_{S^-}\left(\frac{K_S}{K_S + a_H}\right)\right] + \frac{\epsilon_{S^-}}{R}[S_T^0 - S_T^{eq}] \quad (5a)$$

Substitution of the expression for S_T° from eq 4a into eq 5a and solution of the resulting equation for S_T^{eq} furnish

$$S_T^{eq} = \left[OD_\infty - OD_0\left(\frac{K_S + a_H}{K_S + (a_H/Z)}\right)\right] \Big/ \epsilon_{S^-}\left[\left(\frac{K_S + (a_H/Z)}{K_S + a_H}\right) - \frac{1}{R}\right] \quad (6a)$$

Substitution of the expressions for S_T° and S_T^{eq} from eq 4a and 6a into eq 1a leads finally to eq 7a after suitable algebraic manipulation.

$$K_{pH} = \frac{1}{B_T}\left[\frac{OD_0 - OD_\infty}{OD_\infty - \frac{OD_0}{R}\left(\frac{K_S + a_H}{K_S + (a_H/Z)}\right)}\right] \quad (7a)$$