

Acknowledgments. The authors gratefully acknowledge the financial support of the National Research Council to C. R. E. and D. L. W. We thank Dr. Cecil Frye and the Dow Corning Corporation for providing

us with a sample of *m*-nitrophenyltriethanolnitrosilane. The stimulating discussions with our colleagues Drs. A. R. Burke, B. Y. Ho, and C. D. LeCroix are also acknowledged.

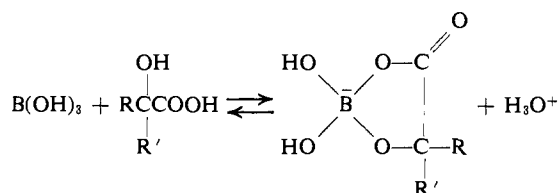
Complexation of Phenylboronic Acid with Lactic Acid. Stability Constant and Reaction Kinetics

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Abstract: Phenylboronic acid, $\text{PhB}(\text{OH})_2$, forms a 1:1 complex with lactic acid in which the hydroxyl proton of the ligand is displaced by boron. The stability constant for the reaction was determined by pH titration methods and found to be 3.7×10^{-3} ($\pm 10\%$). The kinetics were studied by the temperature-jump relaxation technique. The rate constant for the reaction of fully protonated lactic acid with $\text{PhB}(\text{OH})_2$ is $140 \text{ M}^{-1} \text{ sec}^{-1}$ ($\pm 10\%$); the rate constant for the reaction of the acid anion is $1500 \text{ M}^{-1} \text{ sec}^{-1}$ ($\pm 10\%$). This is discussed in terms of a mechanism in which the interaction of the electron-rich carboxylate anion with the phenyl ring on $\text{PhB}(\text{OH})_2$ is reflected in the relatively greater rate constant for the reaction of the acid anion.

Boric acid forms complexes with α -hydroxy carboxylic acids in which the hydroxyl proton of the ligand is displaced by boron.¹ On this process boron undergoes a change in coordination number from three to four, the ligands being bidentate and forming five-membered chelate rings. The overall reaction is then



The existence of the proposed five-membered chelate rings in solution has recently been demonstrated by vibrational spectroscopy for both α -hydroxy carboxylic acid complexes² and polyol complexes.³

There are a few studies in the literature on fast boric acid reactions. Eyring⁴ has shown that polyborate formation is quite rapid. In his interpretation of the kinetics, it was assumed that the reaction of $\text{B}(\text{OH})_3$ with OH^- to produce the tetrahedral $\text{B}(\text{OH})_4^-$ is diffusion controlled. The assumption has been questioned recently.⁵ In either case, this process is faster by several orders of magnitude than the overall complexation of boric acid with tartaric acid⁶ and is clearly not responsible for the differences in rate observed among various ligands.

The results of the study of the tartaric acid complexation suggest that at least two factors are important in accounting for differences in reaction rate among ligands. One is the acidity of the ligand and the other

is the notion that any interaction of ligand with boric acid which stabilizes a four-coordinate species would be reflected in an increased rate.

The present study, the reaction of phenylboronic acid, $\text{PhB}(\text{OH})_2$, with lactic acid, was undertaken to examine further the effect of ligand donor atom protonation on the reaction rates. Secondly, a first study of the effect on reaction of substitution on boron can be carried out.

Experimental Section

Phenylboronic acid (Alfa) and lactic acid (minimum 85%, Mallinkrodt Analytical Reagent) were used without further purification. Stock solutions of lactic acid were prepared by dilution. They were refluxed for at least 12 hr to effect complete hydrolysis of the anhydride present in the 85% solution.⁷ Stock solutions were standardized by pH titrations using a Corning Model 12 research pH meter. pH was accurate to ± 0.01 pH unit. Titrations were carried out in a nitrogen atmosphere in a double-walled beaker which was maintained at 25° by a circulating water bath. All solutions were made up to an ionic strength of 0.1 *M* by addition of KNO_3 .

Stability constants were also determined by pH titration methods. The activity coefficient of H^+ ion was calculated using the Davies equation.⁸

$$\log \gamma_{\pm} = -0.5|z_+z_-| \left\{ \frac{\sqrt{\mu}}{1 + \sqrt{\mu}} - 0.3\mu \right\}$$

All kinetic experiments were carried out on a temperature-jump instrument which utilizes the method of Joule heating. The temperature jump is produced by the discharge through the solution of a 0.1 μf high voltage capacitor charged to 30 kV. The ionic strength of the solution is maintained at a minimum of 0.1 *M*. Under these conditions the resistance of the cell is about 100 Ω . The rise time is of the order of a few microseconds. About 1 ml of solution is heated, the temperature rise being 10°. Reactions are monitored spectrophotometrically and recorded on a storage oscilloscope. Relaxation times are measured from photographs of the reaction traces.

The experimental reaction traces were plotted semilogarithmically. In all cases simple exponentials were observed. The relaxation

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- (2) R. Larsson and G. Nunziata, *Acta Chem. Scand.*, **24**, 2156 (1970).
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Table I. Titration of PhB(OH)₂ with H₂L^a

H ₂ L added (ml)	pH	[PhB(OH) ₂] ₀ , M	[H ₂ L] ₀ , M	[HL ⁻] ₀ , M	[ΔH ⁺], M	[PhB(OH)L ⁻], M	K
10	1.817	0.0969	0.1248	0.0020	0.0026	0.0030	3.94 × 10 ⁻³
20	1.787	0.0895	0.2288	0.0037	0.0037	0.0046	3.90 × 10 ⁻³
30	1.772	0.0835	0.3167	0.0052	0.0043	0.0057	3.92 × 10 ⁻³
40	1.766	0.0767	0.3922	0.0064	0.0045	0.0063	3.90 × 10 ⁻³

^a Both solutions are initially at pH 1.900 and μ = 0.1 M KNO₃. Initial volume of the PhB(OH)₂ solution is 100 ml.

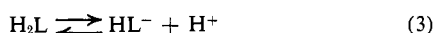
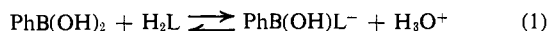
times were taken as the average of at least three traces. The error is at most ±10%.

Blank solutions of phenylboronic acid with indicator and lactic acid with indicator were prepared. No effect was observed in any time range at any pH with either reactant. The time range examined was from 10 μsec to 1 sec (the long time is limited by the onset of convective cooling of the cell). The pH range examined was from 1.5 to 9.4. Under these conditions the solutions possess widely varying ratios of acid anion to neutral acid. Depending on the pH of the solution either Orange IV (Allied Chemical) or Bromophenol Blue (Fisher) was used to monitor the reactions. For the high pH blanks, phenolphthalein was used as the indicator.

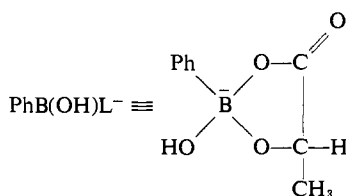
Stability Constants

Solutions of both PhB(OH)₂ and lactic acid were prepared and made up to 0.1 M ionic strength with KNO₃. They were titrated with standard 0.1 N NaOH. In both cases the measured pK was in close agreement with the literature value: pK_a (PhB(OH)₂) = 8.72 (lit.⁹ 8.70 at 25.5°, μ = 0.107 M NaNO₃); pK_a (lactic acid) = 3.69 (lit.¹⁰ 3.74 at 20°, μ = 0.2 M KCl).

Mixtures of PhB(OH)₂ and lactic acid of varying concentration ratios were then titrated with base. The following reactions are possible



where



H₂L is fully protonated lactic acid and HL⁻ is the lactate anion. Assuming that these are the only reactions which take place, it can easily be shown that the concentration of complex is given by the following equation

$$[\text{PhB(OH)L}^-] = \frac{\{[\text{Na}^+] + [\text{H}^+] - \frac{[\text{B}]_0}{A} - \frac{[\text{L}]_0}{B} - [\text{OH}^-]\}}{\left\{1 - \frac{1}{A} - \frac{1}{B}\right\}}$$

where [B]₀ = PhB(OH)₂ + PhB(OH)₃⁻ + PhB(OH)L⁻, [L]₀ = H₂L + HL⁻ + PhB(OH)L⁻, A = 1 + H⁺/K_{PhB(OH)₂}, and B = 1 + H⁺/K_{H₂L}. The results are

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(10) R. K. Cannan and A. Kibrick, *J. Amer. Chem. Soc.*, **60**, 2314 (1938).

that only one complex is formed and its formation is described by eq 1. The stability constant for this reaction is 3.7 × 10⁻³ (±10%).

In this method a systematic error of ±0.01 pH unit results in an error of at least 10% in the calculated stability constant. This type of error can be avoided by titrating a solution of PhB(OH)₂ made up to a given pH and ionic strength with a solution of H₂L adjusted to the same initial pH and ionic strength. Assuming that eq 1-3 describe the system, it can be shown that

$$[\text{PhB(OH)L}^-] = [\Delta\text{H}^+] + [\text{HL}^-]_0 - \frac{\{[\text{H}_2\text{L}]_0 - [\Delta\text{H}^+]\} K_{\text{H}_2\text{L}}}{[\text{H}^+]_f}$$

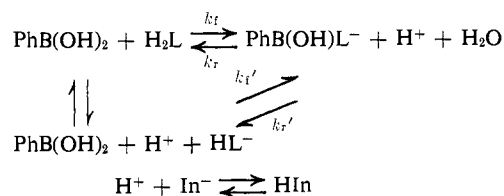
where [ΔH⁺] = change in hydrogen ion concentration on titration, [H⁺]_f = final hydrogen ion concentration, [HL⁻]₀ = concentration of HL⁻ at the initial pH before reaction, and [H₂L]₀ = concentration of H₂L at the initial pH before reaction. From this the stability constant can be calculated. One set of data is given in Table I. A similar method was used by Edwards in a study of the PhB(OH)₂-polyol complexes.¹¹

The principal disadvantage of this method is that the ionic strength changes during the titration. The average ionic strength for the titration in Table I is 0.12 M. However, this method does support the previous conclusions. In particular, it is important to note that the hydroxyl proton of the ligand is displaced even in acidic media below pH 2.

Kinetic Results and Treatment of Data

The following is the complete reaction scheme (Scheme I).

Scheme I



This reaction scheme possesses two relaxation times (neglecting the indicator) only one of which is characteristic of the complexation of PhB(OH)₂. This relaxation time can be calculated under the assumption that the indicator and lactic acid equilibria are very fast protolytic reactions.⁶ These reactions are always in equilibrium and they adjust in response to the much slower processes involving PhB(OH)₂.

(11) J. P. Lorand and J. O. Edwards, *J. Org. Chem.*, **24**, 769 (1959).

The relaxation time is given by

$$\frac{1}{\tau} = k_t \left\{ \gamma [\overline{\text{PhB}(\text{OH})_2}] + [\overline{\text{H}_2\text{L}}] + \frac{1}{K} (\epsilon [\overline{\text{PhB}(\text{OH})\text{L}^-}] + [\overline{\text{H}^+}]) \right\} + k_t' \left\{ \beta [\overline{\text{PhB}(\text{OH})_2}] + [\overline{\text{HL}^-}] + \frac{K_{\text{H}_2\text{L}}}{K} \right\}$$

where

$$\alpha = \frac{K_{\text{HIn}} + [\overline{\text{H}^+}] + [\overline{\text{In}^-}]}{K_{\text{HIn}} + [\overline{\text{H}^+}]}$$

$$\beta = \frac{K_{\text{H}_2\text{L}} + [\overline{\text{HL}^-}]/\alpha}{K_{\text{H}_2\text{L}} + [\overline{\text{HL}^-}]/\alpha + [\overline{\text{H}^+}]}$$

$$\gamma = \frac{[\overline{\text{H}^+}]}{K_{\text{H}_2\text{L}} + [\overline{\text{HL}^-}]/\alpha + [\overline{\text{H}^+}]}$$

$$\epsilon = \gamma/\alpha$$

The concentrations are all equilibrium concentrations of the various species.

At low pH (~ 2), the first term is dominant, allowing k_t to be accurately determined. At higher pH (~ 4), the second term is dominant, allowing k_t' to be accurately determined. The best fit over the entire pH range is obtained with $k_t = 140 \text{ M}^{-1} \text{ sec}^{-1}$ and $k_t' = 1500 \text{ M}^{-1} \text{ sec}^{-1}$. The results are presented in Table II

Table II. Relaxation Spectra of $\text{PhB}(\text{OH})_2\text{-H}_2\text{L}$ Solutions

$[\text{PhB}(\text{OH})_2]_0, M$	$[\text{L}]_0, M$	$[\text{HIn}]_0, M$	pH	τ_{exptl} (msec)	τ_{calcd} (msec)
0.0258	0.1550	4.41×10^{-5}	3.20	5.0	4.9
0.0258	0.1550	4.41×10^{-5}	3.49	4.5	4.7
0.0118	0.3875	1.57×10^{-4}	1.96	1.6	1.7
0.1030	0.5430	1.67×10^{-4}	2.59	2.0	2.1
0.1030	0.5430	1.67×10^{-4}	2.39	1.8	1.7
0.1030	0.5430	1.67×10^{-4}	2.19	1.4	1.3
0.0484	0.0775	4.00×10^{-5}	3.19	5.0	4.8
0.0973	1.1600	1.64×10^{-4}	2.57	1.8	1.7
0.0973	1.1600	1.64×10^{-4}	1.88	0.80	0.83
0.0430	0.3880	5.50×10^{-5}	1.90	1.2	1.3
0.0430	0.3880	5.50×10^{-5}	2.18	2.0	1.9
0.0430	0.3880	5.50×10^{-5}	1.59	0.75	0.83
0.0241	0.1550	2.25×10^{-5}	3.70	4.0	4.4
0.0362	0.0155	5.50×10^{-5}	2.11	2.7	2.5
0.0973	1.1600	1.64×10^{-4}	2.39	1.5	1.5
0.0973	1.1600	1.64×10^{-4}	2.19	1.2	1.2
0.0779	0.0310	2.17×10^{-5}	3.48	4.7	4.5
0.0779	0.0310	2.17×10^{-5}	3.79	5.0	4.8
0.0779	0.0310	2.17×10^{-5}	4.17	5.0	5.0
0.0763	0.0608	2.13×10^{-5}	3.49	4.5	4.5
0.0763	0.0608	2.13×10^{-5}	4.21	5.0	4.9
0.0853	0.0310	5.50×10^{-5}	1.98	1.8	1.9

^a This is the total initial concentration of lactic acid in solution as H_2L and HL^- . ^b All solutions below pH 2.59 contain Orange IV as the indicator. All those above pH 3.19 contain Bromophenol Blue as the indicator. All reactions were followed at λ 580 nm.

with the experimental and calculated relaxation times reported to two significant figures. In all cases τ could be calculated to within 10%.

Discussion

In an earlier paper⁶ the mechanism of the reaction of tartaric acid with boric acid was discussed. The mecha-

nism proposed involved the attack of the ligand hydroxyl oxygen on boron and chelate ring closure involving water loss in the case of the fully protonated acid and loss of hydroxyl in the case of the acid anion. Intramolecular hydrogen bonding to a hydroxyl on boron to form a leaving water molecule was advanced as a possible explanation for the greater (by a factor of two) rate constant observed for the fully protonated ligand. Although it is very difficult to argue the relative importance of various factors in discussing a difference of only a factor of two in rate, the basic point is that any interaction which stabilizes the four-coordinate species will be reflected in an increased rate constant. In this case the four-coordinate species must exist long enough to permit loss of the ligand hydroxyl proton. Much less acidic diols do not complex with boric acid,¹² possibly because transfer of the hydroxyl proton on the ligand to the hydroxyl group on boron is too slow relative to the rate of reversion to the planar structure.

The rate constants from this study and the $\text{B}(\text{OH})_3\text{-tartaric acid}$ study are presented in Table III. Since

Table III. Rate Constants for the $\text{B}(\text{OH})_3\text{-Tartaric Acid}$ Reaction and for the $\text{PhB}(\text{OH})_2\text{-Lactic Acid}$ Reaction

Reaction	$k, \text{M}^{-1} \text{sec}^{-1}$
$\text{B}(\text{OH})_3 + \text{tartaric acid}^6$	475
$\text{B}(\text{OH})_3 + \text{tartrate anion}^6$	215
$\text{PhB}(\text{OH})_2 + \text{H}_2\text{L}$	140
$\text{PhB}(\text{OH})_2 + \text{HL}^-$	1500

tartaric acid has two equivalent sites for reaction, the rate constants should be divided by a factor of two for comparison.

Consider first the rate constants for the fully protonated ligands. The corrected rate constant for the $\text{B}(\text{OH})_3$ reaction with tartaric acid is $240 \text{ M}^{-1} \text{ sec}^{-1}$. If one site on boron is blocked, as in $\text{PhB}(\text{OH})_2$, this could be further decreased by a statistical factor of one-third. Making these statistical corrections, the two rate constants are $160 \text{ M}^{-1} \text{ sec}^{-1}$ for the $\text{B}(\text{OH})_3\text{-tartaric acid}$ reaction and $140 \text{ M}^{-1} \text{ sec}^{-1}$ for the $\text{PhB}(\text{OH})_2\text{-lactic acid}$ reaction. Given errors of at least $\pm 10\%$, these rate constants are the same within experimental error.

In the case of the acid anions, markedly different results are apparent. Applying the same statistical factors to the tartrate anion the result is $70 \text{ M}^{-1} \text{ sec}^{-1}$. The rate constant for lactate anion reacting with $\text{PhB}(\text{OH})_2$ is $1500 \text{ M}^{-1} \text{ sec}^{-1}$, greater by a factor of 20. Without even making a direct comparison of the two systems, it is clear that in one system the acid anion reacted more slowly than the protonated acid by a factor of about two and in the other reacted faster by a factor of about ten. Clearly a number of factors are important in determining reactivities, ligand acidity being one of them. However, the great similarity of the $\text{PhB}(\text{OH})_2\text{-lactic acid}$ and the statistically corrected $\text{B}(\text{OH})_3\text{-tartaric acid}$ rate constants suggests that this is not the factor responsible for the difference in the anion rate constants.

It is possible that the interaction of the delocalized π -system of the carboxylate anion with the π -system of

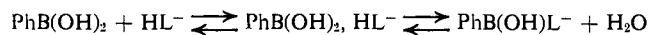
(12) T. P. Onak, H. L. Landesman, R. E. Williams, and I. Shapiro, *J. Phys. Chem.*, **63**, 1533 (1959).

the phenyl ring in PhB(OH)_2 is significant. This interaction is not possible in reactions with unsubstituted B(OH)_3 or in the reactions of fully protonated acids. In support of this, there is evidence that the vacant p orbital of boron can participate in π bonding to an adjacent carbon in a π -bond system.¹³ In this case, there could be an association¹⁴ between the carboxylate anion and the phenyl ring in PhB(OH)_2 which is bound to the electron-withdrawing boron substituent. This is certainly not a strong association;¹⁵ an interaction of approximately 2 kcal/mol is all that is required to account for an order of magnitude difference in rate constant at 25°.

A comparison can be made here with labile metal substitution reactions. The general mechanism for these processes involves water loss as the rate-determining step.¹⁶ The overall forward rate constant is then given by the product of the ion pairing constant^{17,18} and the rate constant for water exchange of the metal. Recently, it has been emphasized that the orientation of the ligand in the ion pair is important.¹⁹⁻²¹ That is, it must be properly oriented in order to compete successfully with water for a vacant coordination site on the metal ion. In addition, the ion pairing constant is in-

creased by non-Coulombic terms such as hydrogen bonding. This has been advanced as one possible interpretation of the relatively large rate constants observed in simple polyamine complexations.²²

The reaction of lactate anion with PhB(OH)_2 is a system in which both of these effects are possible. The mechanism can be written as



The first step represents the rapid, reversible association of PhB(OH)_2 and HL^- . The second represents the (rate determining) loss of ligand proton and the chelation process. The association of the carboxylate anion with the phenyl ring is reflected in an increase in the association constant represented by the first step in the mechanism. Further, considering the notion that reaction occurs *via* attack of the hydroxyl oxygen on boron,⁶ this association orients the carboxylate properly for chelation.

These two problems, the magnitude of association constants of rapid, reversible processes and the factors which influence the orientation of the reactants, are encountered in relatively simple substitution processes as well as more complex interactions such as inhibitors with enzymes.¹⁴ The result here indicates that, in kinetic systems of this kind, small interactions which cause an increase in association constant and/or provide the proper orientation for reaction may lead to a significant increase in rate of reaction compared with very similar systems in which such interactions are not possible.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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