Mechanism of the Complexation of Phenylboronic Acid with Oxalic Acid. A Reaction Which Requires Ligand Donor Atom Protonation

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Abstract: Oxalic acid, H_2Ox, forms a 1:1 complex with phenylboronic acid. The stability constant was determined by pH titration methods. For the reaction $PhB(OH)_2 + H_2Ox \rightleftarrows PhB(OH)Ox^- + H_3O^+$, the stability constant is 3.2 ± 10%. The kinetics were studied by the temperature-jump method. The rate constant for the reaction of fully protonated H_2Ox is 2000 M^{-1} sec^{-1} ± 20%, for HOx^- the rate constant is 330 M^{-1} sec^{-1} ± 10%, and for Ox^{2-} it is ≤0.1 M^{-1} sec^{-1}. For the fully protonated ligand, these results are discussed in terms of a mechanism involving intramolecular hydrogen bonding from a ligand carboxyl to a hydroxyl on boron to form a leaving water molecule. In the case of the acid anion, an interaction of the carboxylate with the phenyl ring in $PhB(OH)_2$ is possible. Finally, the surprising relative (perhaps absolute) lack of reactivity of the dianion is attributed to a misorientation of ligand due to charge repulsion between one end of the dianion and a leaving OH^- on boron. This reactivity pattern suggests that ligand donor atom protonation is required to minimize this repulsion even though the proton is displaced on reaction.

Phenylboronic acid, $PhB(OH)_2$, forms 1:1 complexes with polyols[1] and α-hydroxycarboxylic acids[2] in which boron undergoes a change in coordination number from three to four and the bidentate ligands form five-membered chelate rings. These reactions are similar to reactions of unsubstituted boric acid which, unlike $PhB(OH)_2$, can also form complexes of 1:2 stoichiometry with these ligands.[3]

We have reported mechanistic studies on two boron substitution reactions, the complexation of tartaric acid with boric acid[4] and the complexation of phenylboronic acid with lactic acid.[2] The reaction rate constants were ligand dependent and much slower than the boron trigonal–tetrahedral interconversion.[5-7] These studies suggest that ligand acidity, interactions which stabilize a four-coordinate species, and, in the case of $PhB(OH)_2$, an attractive interaction of the phenyl ring with the carboxylate anion all influence the reaction rate.

The present study reports the reaction of $PhB(OH)_2$ with oxalic acid. The ligand is similar to the others in its ability to form five-membered chelate rings but it is considerably more acidic, providing a more definitive examination of the effect of ligand acidity on reaction rate. In addition, the reaction of the acid dianion is the first ligand examined whose reaction does not involve proton displacement. This will provide the first study of the possible role of donor atom protonation in these reactions.

Experimental Section

Phenylboronic acid (Alfa) and oxalic acid (Mallinckrodt Analytical Reagent) were used without further purification. The acid dissociation constants and stability constant for the complexation reaction were determined by pH titration methods 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. The activity coefficient of H^+ was calculated using the Davies equation.[8,2]

All kinetic experiments were carried out on the temperature-jump instrument described previously.[2] The experimental reaction traces were plotted semilogarithmically. In all cases simple exponentials were observed. Above pH 2.7 the effects were of large amplitude, and the error in relaxation time is at most ±10%. Below pH 2.7 the effects were of much smaller amplitude, and the uncertainty in relaxation time is ±20%.

Blank solutions were prepared with each reactant over the entire pH range examined. No effect was observed in any time range at any pH with either reactant. Depending on the pH of the solution either Orange IV (Allied Chemical), Bromophenol Blue (Fisher), or Chlorphenol Red (Fisher) was used to monitor the reaction.

Stability Constants

The pK_a of $PhB(OH)_2$ was reported previously[2] and found to be 8.72. pK_{a1} and pK_{a2} for oxalic acid at μ = 0.1 M KNO_3 and 25° were determined by titration with standard 0.1 N NaOH. The data were analyzed by the method of Noyes.[9] The results were in good agreement with the literature values: pK_{a1} = 1.04, pK_{a2} = 3.78 (lit.[10] 1.14 and 3.85 at 20°, μ = 0.2 M KCl).

The stability constant for the complexation was determined by two titration methods. The following reactions were considered in the analysis of the data:

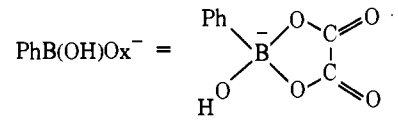
$$PhB(OH)_2 + H_2Ox \rightleftarrows PhB(OH)Ox^- + H_3O^+ \quad (1)$$

$$PhB(OH)_2 + H_2O \rightleftarrows PhB(OH)_3^- + H^+ \quad (2)$$

$$H_2Ox \rightleftarrows HOx^- + H^+ \quad (3)$$

$$HOx^- \rightleftarrows Ox^{2-} + H^+ \quad (4)$$

where



and Ox^{2-} is the oxalate dianion.

In one type of titration, solutions of one reactant made up to a particular pH and ionic strength were titrated with the other reactant at the same initial pH and ionic strength. At low initial pH (~2), large concentrations of reactants are required to produce a small (~0.03 pH units) change in pH, the solution becoming more acidic. The change in pH is not sufficient to allow an accurate determination of the stability constant. However, at higher initial pH values (above pK_{a2}) this type of titration occurs with an increase in pH. The concentrations of reactants can be kept sufficiently low that the ionic strength is effectively constant on titration. Stoichiometrically, this can be thought of as the result of the reaction of the oxalate dianion with displacement of OH^- from $PhB(OH)_2$. The concentration of complex at each point of the titration is given by:

$$[PhB(OH)Ox^-] = \left\{\frac{K_{a1}[(H_2Ox) - \Delta(H^+)] - H^+[(HOx^-) + \Delta(H^+)]}{2(H^+) + K_{a1}} - \frac{(H^+)(Ox^{2-}) - K_{a2}[(HOx^-) + \Delta(H^+)]}{2K_{a2} + H^+}\right\} \Big/ \left\{\frac{K_{a2}}{2K_{a2} + (H^+)} - \frac{(H^+)}{2(H^+) + K_{a1}}\right\}$$

where $\Delta(H^+)$ = change in hydrogen ion concentration on titration and H_2Ox = concentration of oxalic acid at the initial pH before reaction and similarly for HOx^- and Ox^{2-}. Since the titrations were all carried out well below the pK_a of $PhB(OH)_2$, no account of the $PhB(OH)_2$-$PhB(OH)_3^-$ equilibrium is included in the above equation. This equation reduces to that given previously for monobasic acids[2] where K_{a2} is equal to zero. From the equilibrium concentration of complex, the stability constant can then be calculated. For eq 1, the value is 3.2 ± 10%. Some results from three different titrations are given in Table I.

The second titration method was the usual one of titrating mixtures of $PhB(OH)_2$ and H_2Ox with base. These data were analyzed in the same manner as the $PhB(OH)_2$-lactic acid data,[2] the only difference being an additional term to account for eq 4. Because of the many different protolytic processes, a small difference in pH leads to a large difference in calculated stability constant. To avoid this problem, the above determined value of the stability constant was then used to calculate the titration curves of mixtures of $PhB(OH)_2$ and H_2Ox. In all cases the calculated and experimental titration curves were in agreement within experimental error. Therefore, only one complex is formed over the entire pH range and its formation is described by eq 1.

Kinetic Results and Treatment of Data

The complete reaction scheme is given in Scheme I.

Scheme I

$$PhB(OH)_2 + H_2Ox \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} PhB(OH)Ox^- + H^+ + H_2O$$

$$PhB(OH)_2 + HOx^- + H^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} PhB(OH)Ox^- + OH^- + 2H^+$$

$$PhB(OH)_2 + Ox^{2-} + 2H^+ \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} PhB(OH)Ox^- + OH^- + 2H^+$$

$$H^+ + In^- \rightleftharpoons HIn$$

This reaction scheme possesses only one relaxation time characteristic of $PhB(OH)_2$ assuming all of the protolytic processes to be very fast and always in equilibrium.[11] The reciprocal of the relaxation time is given by

$$\frac{1}{\tau} = k_1\left\{\alpha[\overline{PhB(OH)_2}] + [\overline{H_2Ox}] + \frac{1}{K}([\overline{H^+}] - \varphi[\overline{PhB(OH)Ox^-}])\right\} + k_2\left\{\beta[\overline{PhB(OH)_2}] + [\overline{HOx^-}] + \frac{K_{a1}}{K}\right\} + k_3\left\{\epsilon[\overline{PhB(OH)_2}] + [\overline{Ox^{2-}}] + \frac{K_{a1}K_{a2}}{KKw}\left([\overline{OH^-}] + \frac{\varphi[\overline{PhB(OH)Ox^-}][\overline{OH^-}]}{[\overline{H^+}]}\right)\right\}$$

All the concentrations are equilibrium concentrations of the species in solution. The coefficients α, β, ϵ, and φ are also functions of equilibrium concentrations and expressions for them are given in the Appendix.

Over the range from pH 3 to 5 the second term is dominant, allowing an accurate determination of k_2. At lower pH the first term begins to make a significant contribution. However, the effects are of lower amplitude and the uncertainty in k_1 is larger. Above pH 5 the coefficient of k_3 becomes quite large, yet there is no appreciable change in relaxation time for a particular solution as the pH is increased. This indicates a very low value for k_3.

The best fit over the entire pH range is given by k_1 = 2000 M^{-1} sec^{-1} ± 20%, k_2 = 330 M^{-1} sec^{-1} ± 10%, and $k_3 \leq 0.1$ M^{-1} sec^{-1}. The results are presented in Table II. In all cases τ could be calculated to close to 10% or better. The rate constants from this and the previous studies appear in Table III.

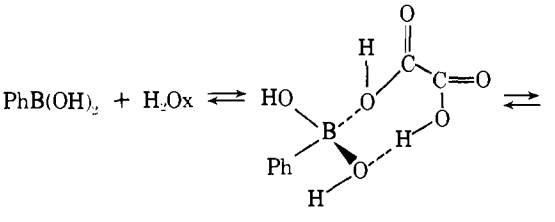
Discussion

These substitution reactions of boron involve nucleophilic attack on the vacant p orbital of boron with loss of a hydroxyl on boron and incorporation of the second ligand donor atom at that site. Boron undergoes a change in hybridization from sp^2 to sp^3. The results of the tartaric acid study[4] suggest that the possibility of intramolecular hydrogen bonding from the carboxyl group in the fully protonated ligand to the leaving hydroxyl on boron may be a factor which accounts for the larger rate constant of this ligand relative to that of the acid anion. The fact that much less acidic diols do not complex with trigonal $B(OH)_3$[12] while α-hydroxy acids do suggests that the ligand hydroxyl attacks the vacant boron p orbital (with loss of ligand proton) while the carboxylate end of the ligand replaces the leaving hydroxyl. The fact that these complexes are all very acidic suggests that the ligand hydroxyl proton is easily displaced by boron. In addition, if the reaction mechanism is written as[2]

$$PhB(OH)_2 + HL^- \rightleftharpoons PhB(OH)_2, HL^- \rightleftharpoons PhB(OH)L^- + H_2O$$

where the first step is a diffusion controlled association followed by the rate determining substitution process, any interaction which increases the association constant will be reflected in an increased rate. The association of the carboxylate anion with the phenyl ring bound to the electron withdrawing boron substituent may be responsible for the much greater rate constant of lactate anion with $PhB(OH)_2$ compared to the rate constant of tartrate anion with $B(OH)_3$. The results of this present study will be discussed in terms of these considerations.

Consider first the reactions of the fully protonated ligands. The α-hydroxy acids both react with the same rate constant within experimental error (Table III). Oxalic acid reacts more rapidly. The two α-hydroxy acids are of nearly the same acidity (taking into account the fact that tartaric acid is dibasic) while oxalic acid is more acidic by over two orders of magnitude. This suggests the possibility of intramolecular hydrogen bonding to the leaving hydroxyl (I).



I

$$PhB(OH)Ox^- + H^+ + H_2O$$

The importance of this interaction may be more to orient the carboxylate properly for attack on boron once the water molecule leaves than to assist the leaving of the hydroxyl. This type of interaction would depend on the acidity of the

Table I. Titrations of One Reactant with the Other[a]

Initial pH	Titrant added (ml)	pH	$[H_2Ox], M$	$[HOx^-], M$	$[OX^{2-}], M$	$[PhB(OH)_2], M$	K
4.900[b]	5	5.060	9.10×10^{-9}	9.65×10^{-5}	1.26×10^{-3}	1.46×10^{-2}	3.2
4.900[b]	30	5.020	4.06×10^{-8}	3.92×10^{-4}	5.23×10^{-3}	1.00×10^{-2}	3.0
3.900[b]	10	4.040	1.47×10^{-6}	1.08×10^{-3}	1.42×10^{-3}	1.34×10^{-2}	3.3
3.900[b]	20	4.030	2.53×10^{-6}	1.85×10^{-3}	2.43×10^{-3}	1.15×10^{-2}	3.0
3.900[c]	20	3.954	6.42×10^{-6}	4.70×10^{-3}	6.16×10^{-3}	9.49×10^{-3}	3.3

[a] Both solutions initially at the same pH and $\mu = 0.1$ M. Initial volumes of the solutions to be titrated are 51 ml. [b] $PhB(OH)_2$ solution titrated with H_2Ox. [c] H_2Ox solution titrated with $PhB(OH)_2$.

Table II. Relaxation Spectra of $PhB(OH)_2$–H_2Ox Solutions

$[PhB(OH)_2], M$	$[Ox], M$[a]	$[HIn], M$[b]	pH	τ_{exptl} (msec)	τ_{calcd} (msec)
0.0792	0.1194	1.92×10^{-4}	1.94	14	15
0.0792	0.1194	1.92×10^{-4}	2.48	24	22
0.0437	0.1021	2.18×10^{-5}	2.96	27	27
0.0437	0.1021	2.18×10^{-5}	3.66	33	33
0.0771	0.1432	2.25×10^{-5}	2.92	24	23
0.0771	0.1432	2.25×10^{-5}	3.48	26	26
0.0866	0.1194	4.00×10^{-5}	5.60	29	27
0.0519	0.1194	4.00×10^{-5}	5.13	38	38
0.0519	0.1194	4.00×10^{-5}	5.69	38	38
0.0841	0.0597	4.00×10^{-5}	5.08	28	28
0.0841	0.0597	4.00×10^{-5}	5.72	30	28
0.0803	0.0597	1.93×10^{-5}	3.43	28	31
0.0803	0.0597	1.93×10^{-5}	4.28	29	31
0.0832	0.1194	1.93×10^{-5}	3.37	24	27
0.0832	0.1194	1.93×10^{-5}	4.36	29	31
0.0909	0.1194	1.92×10^{-4}	2.00	18	17
0.0909	0.1194	1.92×10^{-4}	2.56	26	23

[a] This is the total initial concentration of oxalic acid in solution as H_2Ox, HOx^-, and Ox^{2-}. [b] All solutions at pH 2.56 and below contain Orange IV as the indicator. Between pH 2.92 and 4.36 Bromophenol Blue was used. Above pH 5.08 Chlorphenol Red was used. All reactions were followed at λ 580 nm.

Table III. Rate Constants for Boron Substitution Reactions

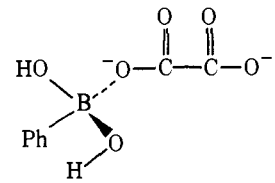
Reaction	k, M^{-1} sec^{-1}
$B(OH)_3$ + tartaric acid[4]	160[a]
$B(OH)_3$ + tartrate anion[4]	70[a]
$PhB(OH)_2$ + lactic acid[2]	140
$PhB(OH)_2$ + lactate anion[2]	1500
$PhB(OH)_2 + H_2Ox$	2000
$PhB(OH)_2 + HOx^-$	330
$PhB(OH)_2 + Ox^{2-}$	≤ 0.1

[a] These rate constants have been statistically corrected for direct comparison. See ref 2.

ligand. Finally, there is no requirement that the other carboxyl proton be displaced directly by boron. Rather attack could occur via the carbonyl oxygen with the proton being lost from the other side of the ligand molecule. In the reactions of α-hydroxy acids, attack on the boron p orbital must occur via the hydroxyl oxygen. Oxalic acid may thus be favored by a statistical factor of two since it has two possible donor atoms (although they are not equivalent).

In the case of the acid anions, lactate reacts with $PhB(OH)_2$ faster than does tartrate with $B(OH)_3$ by more than an order of magnitude, a result discussed[2] in terms of the interaction of the carboxylate anion with the phenyl ring. The oxalate rate constant with $PhB(OH)_2$ is somewhat less than the lactate-$PhB(OH)_2$ rate constant but still larger than the tartrate-$B(OH)_3$ rate constant. In considering the different ligands, a direct comparison of the lactate and oxalate anions presents the possibility that intramolecular hydrogen bonding is responsible for the difference in reactivity. Due to the greater acidity of the carboxyl proton in binoxalate compared with the hydroxyl proton in lactate, intramolecular hydrogen bonding would be expected to be more important in binoxalate. This hydrogen bond would decrease the association of the anion with the phenyl ring which already bears a slight positive charge due to electron delocalization into the vacant boron p orbital.[13] This diminished interaction is reflected in the lower rate constant. This constant is still greater than the tartrate–$B(OH)_3$ rate constant, a system where this interaction is not possible.

The most surprising result in this study is the relative (perhaps absolute) lack of reactivity of the oxalate dianion. In this case there will be charge repulsion between the leaving hydroxide on boron and the incoming carboxylate anion as shown in II. The carboxylate is oriented away from the



II

leaving hydroxide and is not oriented properly for coordination to boron. Hence, rather than successful chelation, on loss of hydroxide boron will revert to a planar structure with rapid hydrolysis to $PhB(OH)_2$. This is a direct consequence of the rapid trigonal-tetrahedral interconversion rates of boron.[5-7] Successful chelation then requires that the ligand be properly oriented such that ring closure occurs immediately on loss of OH^-. This recalls the lack of reactivity of fully protonated diols where loss of ligand proton (in a manner analogous to I) would be slow relative to reversion to the planar configuration and subsequent hydrolysis. The problem of ligand misorientation resulting in slow reaction rates has also been noted in metal ion systems where both charge repulsion[14] and hydrogen bonding to an inner sphere water molecule[15] were the interactions responsible for the effect.

This result also suggests that ligand donor atom protonation is required to minimize charge repulsion between the incoming ligand and the leaving OH^-. That is, in ligands which contain only one protonated donor atom, this proton may be transferred to the leaving hydroxyl to form a leaving water molecule. Even in the case of α-hydroxy acids, the hydroxyl proton could be transferred to the leaving hydroxyl rather than bulk solvent. For a fully protonated ligand there is no requirement that the proton be lost in this way and it could react as in I.

The results of this study are interesting to compare with recent results of metal ion complexations with similar ligands. Generally, in metal ion substitution processes the order of reactivity with respect to ligand protonation is the exact opposite of the present result. The overall forward rate constant in normal metal ion substitution reactions is given by the product of the metal-ligand ion pairing constant and the rate of water exchange of the metal.[16] The ion

pairing constant is obviously strongly dependent on ligand charge.

Early studies on some oxalate[17,18] and malonate[19] complexations concluded that substitution of the dianion and monoanion proceeded normally. Some alkyl substituted malonic acids have also been shown to react with normal rates.[20] In continuing studies of the details of chelate ring closure, it has been shown that as the dicarboxylate chelate rings become larger either slower rates are observed[21] or the ligand may bind at only one site.[22]

The results of the oxalate and malonate complexations mentioned above contrast with reactions of other ligands containing only oxygen donor atoms where chelate rings of the same size are formed. In particular, slower rates have been observed for reactions of β-diketones[23] and hydroxy acids.[22,24,25] Ligand acidity is certainly an important factor related to this difference. However, one other consideration may be significant. The diketones and hydroxy acids require that the coordination process directly involves the protonated oxygen atom. This is not true in the case of dicarboxylic acids where primary coordination could occur through a carbonyl oxygen with loss of ligand proton on the other side of the ligand, away from the metal. In the boron substitution reactions where OH^- is lost, the ligand may preferentially lose the proton on the side of the molecule coordinating to boron for the reasons presented above.

In summary, the reaction rates of fully protonated ligands with $PhB(OH)_2$ increase with ligand acidity. The acid anions may react more rapidly with $PhB(OH)_2$ than with $B(OH)_3$ due to an interaction of the carboxylate anion with the phenyl ring in $PhB(OH)_2$. Finally, the lack of reactivity of the dianion suggests that protonation of the ligand donor atom is necessary to minimize repulsion between the incoming carboxylate anion and the leaving hydroxide.

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Appendix

The coefficients in the expression for the relaxation time are given as follows

$$\alpha = (E - AF)/(CE - BF)$$

$$\beta = (B - AC)/(BF - CE)$$

$$\epsilon = 1 - \alpha - \beta$$

$$\varphi = (\epsilon - \alpha)/\gamma$$

where

$$A = \overline{[H^+]} + (\overline{[Ox^{2-}]}/\gamma)$$

$$B = \overline{[H^+]} + (2\overline{[OX^{2-}]}/\gamma)$$

$$C = (K_{a1}\gamma/\overline{[HOx^-]}) + 2$$

$$E = K_{a2} + \overline{[H^+]} + (\overline{[Ox^{2-}]}/\gamma)$$

$$F = 1 - (\overline{[H^+]}\gamma/\overline{[HOx^-]})$$

$$\gamma = 1 + \frac{\overline{[OH^-]}}{\overline{[H^+]}} + \frac{\overline{[In^-]}}{K_{HIn} + \overline{[H^+]}}$$

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