

ing the solution at -15° with 1 *N* methanolic NaOH solution (phenolphthalein). The salt was recovered by evaporation of the solvent and vacuum drying overnight at 60° . The finely powdered salt, 3.5 g, was heated with 60 cc of aniline in an oil bath at $100-105^{\circ}$ for 5 hr. After cooling, 10 cc of 1 *N* NaOH solution was added and excess aniline extracted three times with ether. The aqueous phase was acidified with concentrated HCl to pH 4. Crystals mixed with oil separated; the oil was found to be unreacted XIII. The crystals were filtered off and recrystallized from EtOH-water. A yield of 310 mg of colorless crystalline XIV was obtained, $[\alpha]^{25D} - 86.0^{\circ}$ (1.2% in EtOH).

N-2-Nitrophenylvaline (XV), 2-Fluoronitrobenzene, 10 g, was suspended in a solution of 5 g of L-valine and 10 g of NaHCO_3 in 200 cc of EtOH and 100 cc of water and the mixture heated at reflux for about 3 hr. The solution was filtered, excess 2-fluoronitrobenzene extracted with ether, and the filtrate acidified with concentrated HCl. A dark yellow oil was obtained which was extracted with ether. The ether solution was dried and the solvent evaporated. The product crystallized on standing at room tem-

perature for several hours, mp 85° , $[\alpha]^{25D} + 60.0^{\circ}$ (2.5% in EtOH). *Anal.* Calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_4$: C, 55.5; H, 5.9; N, 11.8. Found: C, 55.4; H, 6.0; N, 11.7.

N-2-Nitrophenylvaline (XVI), A mixture of 0.5 g of XIII and 4 g of 2-nitroaniline was heated in an oil bath at $100-105^{\circ}$ for 1 hr. A clear, red solution was obtained after this time. After cooling 6 cc of 1 *N* NaOH solution was added and excess 2-nitroaniline extracted three times with ether. Concentrated HCl was added until the initially dark yellow solution was nearly colorless and a yellow oil separated. The oil was extracted with ether, the ether solution dried, and the solvent evaporated. The yellow oily residue was trimethylsilylated with bis(trimethylsilyl)acetamide and was found to be a mixture of XVI and unreacted XIII as determined by vpc (comparison with authentic samples). The more volatile silylated XIII was removed by heating at $40-50^{\circ}$ (0.1 mm) for 30 min. At a bath temperature of 80° , a yellow liquid distilled which was identical with silylated XV by vpc. The product was hydrolyzed with EtOH; concentration gave crystalline XVI, $[\alpha]^{25D} + 57.3$ (1.2% in EtOH).

The Mechanism of Reaction of Benzylboronic Esters with Mercuric Chloride, a Concerted Electrophilic Displacement^{1a}

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Contribution from the Department of Chemistry, Washington State University, Pullman, Washington 99163. Received July 19, 1968

Abstract: The kinetics of the reaction of benzylboronic esters with mercuric chloride have been followed by a titration method involving complexing of the remaining mercuric chloride with EDTA. In aqueous ethanol in the presence of glycerol, sodium acetate, sodium chloride, and acetic acid, the rate law appears to be $-d[\text{HgCl}_2]/dt = k[\text{RB(OR)}_2][\text{HgCl}_2][\text{OH}^-]$. We have also prepared benzylboronic esters with *p*- CH_3 , *p*-Cl, and *m*- CF_3 substituents. A Hammett correlation of the four rates yielded $\rho \cong +0.93$. If the relative acidities of the boronic esters are taken into account so that reactions of their hydroxide complexes with mercuric chloride are correlated, ρ becomes ~ -0.5 . These results are consistent with a concerted electrophilic displacement mechanism.

Electrophilic displacements of boron from saturated carbon by mercury have convenient characteristics for mechanistic studies. We have found previously that the transannular displacement of boron from norborneneboronic acids by mercuric chloride proceeds with preferential inversion of the configuration of the carbon from which the boron departs² and we have studied the mechanism.³ Direct displacement of boron from 1-phenylethaneboronic acid by mercuric chloride proceeds with retention.⁴ Attempts to study the mechanism of this reaction yielded disappointing results, due to the inaccuracy of the analytical method and the instability of the product, 1-phenylethylmercuric chloride.⁵

In the present work we have obtained much more accurate kinetics by the use of the simpler benzylboronic acids and an improved analytical technique. The effects of substituents in the benzene ring have provided information about the electron density at the benzyl carbon in the transition state.

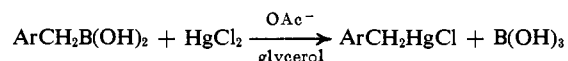
(1) (a) Supported by National Science Foundation Grant GP 6069. (b) Alfred P. Sloan Foundation Research Fellow, 1966-1968.

(2) D. S. Matteson and J. O. Waldbillig, *J. Am. Chem. Soc.*, **85**, 1019 (1963); **86**, 3778 (1964).

(3) D. S. Matteson and M. L. Talbot, *ibid.*, **89**, 1119, 1123 (1967).

(4) D. S. Matteson and R. A. Bowie, *ibid.*, **87**, 2587 (1965).

(5) D. S. Matteson, R. A. Bowie, and G. Srivastava, *J. Organometal. Chem.* (Amsterdam), in press.



Results

Our analytical method was based on the fact that mercuric chloride forms a strong complex with ethylenediaminetetraacetic acid (EDTA), but benzylmercuric chloride does not. We were thus able to follow the concentration of unconsumed mercuric chloride by a simple titration method.⁶

The reaction conditions were those which had evolved from earlier experience with related reactions.^{3,5} The solvent consisted of 8% water, 4% glycerol, and the remainder ethanol, and the solution was buffered with sodium acetate and acetic acid. Sodium chloride was included to prevent ionization of the mercuric chloride, which would lead to more complicated kinetics. The reactions were run under nitrogen, and the butyl ester of the boronic acid was injected into the reaction flask through a rubber septum, as described previously.³ Samples were withdrawn at intervals by means of a hypodermic needle and were added to a solution of EDTA, which stops the reaction immediately, and then titrated.

(6) G. Schwarzenbach, "Complexometric Titrations," Interscience Publishers, New York, N. Y., 1957, p 87.

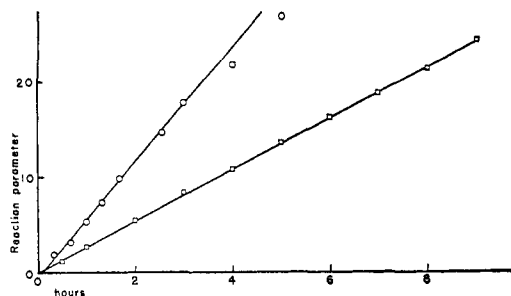


Figure 1. Plot of $A \ln [a/(a-x)] + B \ln [b/(b-x)] + C \ln [c/(c-x)]$ ("reaction parameter") against time for the reaction of mercuric chloride with benzylboronic esters: circles, *p*-chlorobenzylboronic ester; squares, unsubstituted benzylboronic ester.

As in analogous previous work, it was necessary to assume a rate law in order to obtain reasonably linear plots.³ We began by assuming that

$$dx/dt = k[\text{RB}(\text{OH})_2][\text{HgCl}_3^-][\text{AcO}^-]/[\text{Cl}^-] \quad (1)$$

The integrated law is then

$$kt = A \ln [a/(a-x)] + B \ln [b/(b-x)] + C \ln [c/(c-x)] \quad (2)$$

where x is the molarity of mercuric chloride consumed and a , b , and c are the initial concentrations of boronic ester, mercuric chloride, and acetate ion. The constant A is $(a+d)/[(a-b)(a-c)]$, B is $(b+d)/[(b-a)(b-c)]$, and C is $(c+d)/[(c-a)(c-b)]$, where d is $[\text{NaCl}]_0 - [\text{HgCl}_2]_0$.³ Typical plots based on this equation are shown in Figure 1.

This rate law is based on the assumption that the active electrophile is HgCl_2 , which is present in small amounts in equilibrium with HgCl_3^- and Cl^- .³

$$[\text{HgCl}_3^-] = K[\text{HgCl}_2][\text{Cl}^-] \quad (3)$$

This assumption is accurate when the solvent is aqueous acetone, where K is on the order of 1000, but is not true in aqueous ethanol, where our data suggest that K is probably between 10 and 100, which is several times greater than in water.⁷ We also obtained linear plots if we chose d as $[\text{NaCl}]_0$, only a slight and insignificant curvature being apparent, and these correspond to assuming that the active electrophile is HgCl^+ or a species having the same equilibrium relationships. Varying the initial sodium chloride concentration revealed that neither assumption leads to a constant value for k , as shown in Table I.

Table I. Effect of Sodium Chloride on k for the Reaction of Benzylboronic Ester with Mercuric Chloride in Aqueous Ethanol at 40°

$[\text{NaCl}]_0^a$	$10^3 k^b$	$[\text{NaCl}]_0 - [\text{HgCl}_2]$	$10^4 k^c$
0	1.36	<0	...
0.040	1.97	<0	...
0.079	2.19	0.013	7.08
0.092	2.44	0.026	9.86

^a Other initial concentrations: HgCl_2 , 0.066; NaOAc , 0.043; HOAc , 0.070; $\text{PhCH}_2\text{B}(\text{O}i\text{Bu})_2$, 0.05–0.06 *M*. ^b $d = [\text{NaCl}]$. ^c $d = [\text{NaCl}]_0 - [\text{HgCl}_2]_0$.

(7) L. G. Sillén and A. Martell, "Stability Constants of Metal-Ion Complexes," Special Publication No. 17, The Chemical Society, London, 1964, p 293.

Varying the mercuric chloride concentration had little effect on the observed rate constant. When $[\text{HgCl}_2]_0$ was 0.132 *M* (double the usual 0.066), $[\text{NaCl}]_0$ was 0.079 and calculated as equal to d , and dimethyl benzylboronate was used, k remained 2.09×10^{-3} at 40°. (The methyl ester was used in a number of our earlier experiments, and it generally yielded k 's 5–10% higher than those of the butyl ester,⁸) Doubling the boronic ester concentration did not affect k . The reproducibility of our data is illustrated by a set of four k values obtained at 40° at the usual concentrations (see Table I, line 3, right-hand column), 7.08, 7.12, 7.09, and 7.03×10^{-4} .

The dependence on acetic acid and sodium acetate is shown in Table II. The approximate reciprocal-order dependence of the rate on acetic acid concentration corresponds to first-order dependence on hydroxide (or ethoxide) ion rather than on acetate ion. At constant acetic acid concentration, the equation used for plotting the data should yield a k value independent of the initial sodium acetate concentration if the reaction is first order in either hydroxide or acetate. The partial failure of this constancy, corresponding to a fractional-order dependence on base, is similar to previous observations in another system³ and will be considered in the Discussion section.

Table II. Effect of Acetic Acid and Sodium Acetate Concentrations on k for the Reaction of Benzylboronic Ester with Mercuric Chloride

$[\text{HOAc}]_0^a$	$[\text{NaOAc}]_0$	k (rel)
0.035	0.043	1.78
0.070	0.043	1.00
0.140	0.043	0.63
0.280	0.043	0.33
0.070	0.015	2.01
0.070	0.086	0.64

^a Other initial concentrations: NaCl , 0.079; the rest the same as in Table I.

Increasing the water content of the solvent mixture to 10% (compared to the usual 8%) increased the rate constant by a factor of 1.76. Replacing the 4% glycerol in the solvent mixture entirely by water (*i.e.*, using aqueous 88% ethanol) reduced the rate constant by a factor of about 20 and increased the apparent pK_a of benzylboronic ester from 9.24 to 11.1, showing that glycerol catalyzes the reaction by converting the boron compound to a more acidic derivative, believed to be the cyclic glycerol ester.⁹

The range of substituents available for obtaining a Hammett correlation is limited by the usual synthesis of boronic esters, which requires a Grignard reagent as an intermediate.¹⁰ We prepared *p*-chloro-, *p*-methyl-, and *m*-trifluorobenzylboronic esters in this way, and also prepared the corresponding benzylmercuric chlorides under conditions used in the kinetic runs. Wurtz

(8) Our interest in the possibility of using the methyl esters for kinetic studies prompted us to develop a general synthesis for these compounds, consisting of heating the boronic acid with 2,2-dimethoxypropane and a catalytic amount of zinc chloride and distilling out methanol and acetone. However, the easily prepared butyl esters proved more convenient for our purposes.

(9) H. G. Kuivila, *J. Am. Chem. Soc.*, **76**, 870 (1954); H. G. Kuivila and R. M. Williams, *ibid.*, **76**, 2679 (1954).

(10) E. Khotinsky and M. Melamed, *Ber.*, **42**, 3090 (1909).

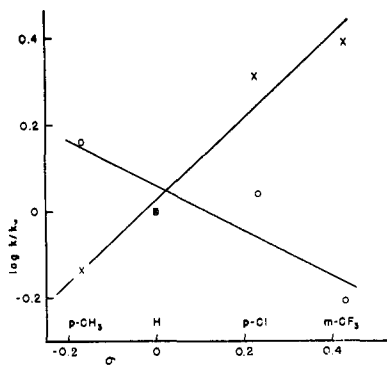


Figure 2. Hammett correlation of rates of reaction of benzylboronic esters with mercuric chloride. X's are measured k 's, O's are k 's derived by taking pK_a 's into account.

coupling of the Grignard reagents prevented synthesis of the *p*-methoxybenzylboronic ester. Several attempts to nitrate benzylboronic acid or its butyl ester under a variety of conditions failed,

Kinetics for the substituted benzylboronic esters were followed at 30 and 40°, "Dissociation constants" of the boronic esters, which are acidic because they add hydroxide ion in base,¹¹ were also determined by means of potentiometric titration with standardized sodium hydroxide in the same ethanol-water-glycerol solvent mixture used for the kinetics. The results are summarized in Table III,

Table III. Substituted Benzylboronic Esters: pK_a 's and Rate Constants for Reaction with Mercuric Chloride

Substituent	pK_a	10^4k , 30°	10^4k , 40°
<i>p</i> -CH ₃	9.54	2.36	5.35
H	9.24	3.19	7.08
<i>p</i> -Cl	8.97	6.74	15.2
<i>m</i> -CF ₃	8.64	7.94	17.2

The k values reported are all averages of two or more runs and were determined by least squares. Standard deviations are in the 2–5% range and agreement between runs was within 2%. The approximate Arrhenius activation energies are all in the range 14.5–15.5 kcal/mol and show no consistent trend because of experimental error.

When these data are correlated with a Hammett plot the rates at 30° yield $\rho = +0.93 \pm 0.08$ and the pK_a 's yield $\rho = +1.47 \pm 0.05$. Derived rates of attack of mercuric chloride on the boronic ester-hydroxide ion complex, the difference between these two slopes, correlate with $\rho = -0.55 \pm 0.17$. Hammett plots of the rate constants are shown in Figure 2,

We also studied the kinetics of mercuri-deboronation with mixtures of mercuric chloride and mercuric acetate, in other words, a deficiency of chloride ion. Under these conditions, the reaction was complete in a few minutes instead of requiring many hours. We arbitrarily plotted the data according to a second-order rate law, first order each in boronic ester and in chloro-

(11) M. J. S. Dewar and R. Jones, *J. Am. Chem. Soc.*, **89**, 2408 (1967), have obtained definitive nmr evidence that boronic acids normally ionize by combination with hydroxide ion, not loss of a proton, confirming the generally accepted interpretation of boronic acid and ester ionization.

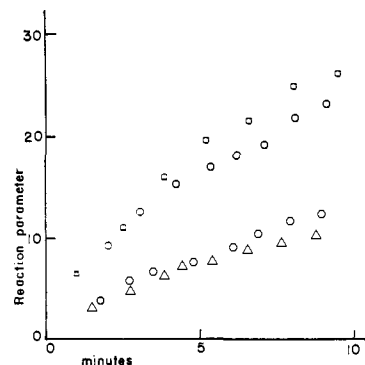


Figure 3. Second-order plot of reactions of substituted benzylboronic esters with chloromercuric acetate. The "reaction parameter" is $(a - b)^{-1} \ln [a/(a - x)] + (b - a)^{-1} \ln [b/(b - x)]$. Substituents: squares, H; circles, *p*-CH₃; hexagons, *m*-CF₃; triangles, *p*-Cl.

mercuric acetate (assumed to be twice the amount of mercuric chloride used). The plots obtained were sharply curved as shown in Figure 3. The standard initial concentrations were HgCl₂, 0.040; Hg(OAc)₂, 0.025; and boronic ester, 0.065 *M*,

Because of the curvature of the plots, it was not possible to make numerical correlation of data. Third-order plots based on [ClHgOAc]² still yielded curved lines. From inspection of the second-order plots it appeared that introduction of 0.043 *M* sodium acetate had almost no effect on the rate. However, increasing the HgCl₂ from 0.04 to 0.07 *M* increased the rate (still based on ClHgOAc) by a factor of 2 or 3, both for the unsubstituted and the *p*-chlorobenzylboronic ester. When all three reactants were reduced to half the standard concentrations, the apparent rate constant was increased by a factor of 1.5 to 2.0. Attempts to measure a salt effect yielded inconsistent results, 1 *M* lithium nitrate leaving the rate of benzylboronic ester reaction unaffected but apparently doubling the rate of the *p*-chloro compound. Because the rate law appears to be complex and the data not very accurate, we abandoned further attempts to determine kinetics under these conditions. From Figure 3, taking time to a given per cent reaction into account, it can be seen that the *p*-methyl and unsubstituted boronic esters react about three times as fast as the *p*-chloro and *m*-trifluoromethyl compounds,

Discussion

We conclude that the actual rate law for the reactions with excess chloride ion present is

$$dx/dt = k'[\text{ArCH}_2\text{B(OR)}_2][\text{HgCl}_2][\text{OH}^-] \quad (4)$$

An analogous rate law has been reported for the attack of phenylmercuric ion on benzenboronic acid in the presence of buffers.¹²

There is no simple mathematical relationship between eq 4 and the observed kinetics, though all deviations can be rationalized at least qualitatively. The actual concentration of HgCl₂ is unknown and is not a simple function of mercury(II) and chloride ion. The data in Table I imply that the stability constant of HgCl₃⁻ is in the 10–100 range, just enough to cause some inhibition by chloride ion, one of the reaction products.

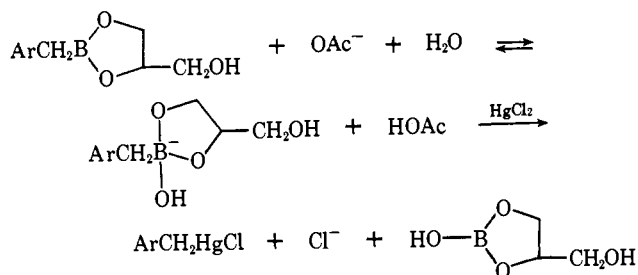
(12) H. G. Kuivila and T. C. Muller, *ibid.*, **84**, 377 (1962).

However, our initial assumption that the order in chloride would be -1 is incorrect, and zero order might be a better approximation in the region of most interest. (Aqueous acetone gave a higher, mathematically tractable stability constant,³ but we changed to ethanol after getting some unexplained erratic behavior in acetone.⁵)

On the other hand, eq 4 requires (by the usual equilibrium relationship) that the reaction be of order -1 in acetic acid, another reaction product. Linear plots (and identical Hammett correlations) were obtained whether we assumed that the initial "chloride" concentration was 0.013 or 0.079 *M* at our "standard" set of conditions. (Curved plots resulted if the reciprocal-order term was omitted.) The "standard" acetic acid concentration was 0.07 *M*, between the tested "chloride" values. Thus, the absolute values of the *k*'s in all tables are based on a false assumption, but the relative values are correct in Table III and informative in the other tables, and we considered it unnecessary to replot the data to obtain absolute *k*'s based on acetic acid.

The remaining discrepancy is that the data of Table II show a less-than-first-order dependence on the initial sodium acetate concentration, together with a somewhat less than reciprocal inhibition by acetic acid. This suggests that mercuric chloride may be acting as a weak acid, either by forming ClHgOH or by complexing with acetate or some other base. The $\text{p}K_a$ of acetic acid in the medium is 7.1, with the pH remaining within 0.1 unit of the theoretical titration curve. We were unable to measure the pH of solutions containing mercuric chloride because this compound rapidly inhibited the available pH electrodes. However, an insoluble precipitate formed when attempts were made to dissolve mercuric chloride and sodium acetate in ethanol-water-glycerol without acetic acid. If the effective $\text{p}K_a$ of the mercuric chloride were about 8, which seems likely, then our imperfect kinetic results would be expected. The linearity of our kinetic plots may result partly from compensating errors, though the region emphasized by the method of plotting, 50–75% completion, may show little deviation from first-order behavior in acetate as a consequence of prior release of enough acetic acid to overcome partially the perturbing effect of the mercuric chloride. Sodium acetate was normally the limiting reagent in our kinetic runs, and there is no doubt that the kinetics are approximately first order in this reagent when its concentration becomes small.

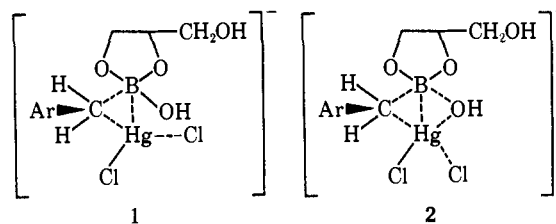
The simplest mechanism consistent with eq 4 involves attack of mercuric chloride on the hydroxide complex of the glycerol ester of the boronic acid, which is formed in equilibrium with the buffer. It would be



mathematically equivalent if Cl_2HgOH^- (but not Cl-HgOH) attacked the uncomplexed boronic ester and

transferred OH^- from mercury to boron in the transition state.

The Hammett correlation indicates that the benzyl carbon atom at which the displacement occurs is slightly more negative in the transition state than in the starting boronic ester ($\rho = +0.93$), or slightly less negative than in the hydroxylated boronic ester ($\rho = -0.55$). For 1-phenylethaneboronic esters, the over-all ρ is negative.⁵ Steric effects are small, the rate of reaction of 1-phenylethaneboronic ester⁵ being roughly 0.5 that of benzylboronic ester at 40°. Entropies of activation are in the -20 to -30 eu range. These results are consistent with a concerted front-side displacement of boron by mercury, similar to what we have suggested for 1-phenylethaneboronic ester.^{4,5} Possible transition states include structures 1 and 2.



The incomplete data obtained with chloromercuric acetate suggest a similar mechanism, but in place of HgCl_2 there is an electrophile which reacts much faster (by a factor of 100 or more). The kinetic data suggest HgCl^+ or a closely related species. The rate retardation by electron-withdrawing groups ($\rho \sim -1$) is in accord with the increased electron demand of the attacking species.

The lack of carbanion character in these electrophilic displacement transition states contrasts with some previous cases which have been studied,^{13,14} though it has a precedent in the reaction of benzylmercury compounds with iodine¹⁵ as well as in a number of metal replacements which seem to involve little if any charge development at carbon.¹⁶ (However, comparisons based on methyl, ethyl, and higher alkylmetallics¹⁶ seem to us to be more ambiguous as indicators of the "polarity" of a reaction than is a Hammett correlation.) Many so-called electrophilic displacements¹⁶ actually involve intramolecular migration of carbon from the metal to an electron-deficient atom.⁹ In a broad sense, all migrations to electron-deficient atoms are electrophilic displacements, and where the migrating group is aryl, they tend to have ρ values in the -1 to -3 range.¹⁷

We have drawn a dotted line between B and Hg in the transition-state structures 1 and 2, representing some direct bonding interaction. Our primary justification is that it seems sterically difficult to bring the vacant orbital of the mercury atom close to the front side of the carbon without forcing some overlap with the emptying orbital of the departing boron. This overlap

(13) O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **163**, 909 (1965).

(14) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 137; W. T. Ford and D. J. Cram, *J. Am. Chem. Soc.*, **90**, 2612 (1968), and 39 preceding papers by Cram, *et al.*

(15) I. P. Beletskaya, T. P. Fetisova, and O. A. Reutov, *Dokl. Akad. Nauk SSSR*, **155**, 1095 (1964).

(16) Review: M. H. Abraham and J. A. Hill, *J. Organometal. Chem.* (Amsterdam), **7**, 11 (1967).

(17) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 334–339.

Table IV. Properties of Substituted Benzylboronates

Substituent	Bp, °C (mm)	Calcd, %				Found, %			
		C	H	B	Hal ^a	C	H	B	Hal ^a
None	90 (0.1)	72.60	10.15	4.36	...	72.75	10.09	4.46	...
<i>p</i> -CH ₃	120 (1)	73.29	10.38	4.12	...	73.40	10.83	4.57	...
<i>p</i> -Cl	106–108 (0.1)	63.75	8.56	3.83	12.55	63.86	8.11	3.70	12.53
<i>p</i> -CF ₃	83–84 (0.1)	60.78	7.65	3.42	18.03	60.54	7.78	3.67	18.37

^a Hal = halogen.

Table V. Properties of Substituted Benzylmercuric Chlorides

Substituent	Reaction time, hr	Mp, °C	Calcd, %				Found, %					
			C	H	Cl	Hg	F	C	H	Cl	Hg	Cl
<i>p</i> -CH ₃	2	145	28.16	2.66	10.39	58.79	...	28.03	2.57	10.27	58.72	...
<i>p</i> -Cl	3	148	23.25	1.67	19.61	55.47	...	23.08	1.64	19.52	55.54	...
<i>m</i> -CF ₃	20	185	24.31	1.53	8.97	50.76	14.42	24.22	1.47	8.83	50.98	14.43

makes a three-membered ring which has two bonding electrons, quantum mechanically analogous to H₃⁺ or cyclopropenium ion, and is therefore favorable. The carbon atom would lose some electron density in such a transition state, which seems in accord with the observed, slightly negative ρ for reaction of the hydroxylated boronic ester with mercuric chloride. This type of cyclic interaction is definitely present and, of course, much stronger in intramolecular migrations to electron-deficient atoms, mentioned in the preceding paragraph. In contrast, if there were no boron-mercury bonding, the central carbon atom should not lose electron density in the transition state, according to the simple Hückel model. In fact, steric and other factors tend to increase the *s* character of the involved carbon orbital in the transition state, and it should take on a considerable degree of carbanion character, contrary to observations.

The possibility of direct electrophile-electrophile bonding was pointed out in a pioneering study of electrophilic displacement stereochemistry by Winstein, Traylor, and Garner.¹⁸ However, it seems fashionable in recent publications to emphasize discussion of electrophile-ligand-electrophile cyclic interaction (included in transition state 2) and its role in promoting retention of configuration, with little² or no^{4,16} mention of possible direct electrophile-electrophile bonding. This emphasis is no doubt correct for carbanion-type transition states,¹⁴ but electrophile-electrophile bonding seems likely to be highly significant in concerted electrophile displacement reactions of organometallic compounds and ought to be evaluated with respect to the experimental evidence in any serious mechanistic study in this field. In some systems where all such cyclic interactions should be weak, preferred inversions have been observed.^{2,3,14,19} Direct metal-metal bonding may prove to play a related and significant role in neighboring-group effects on electrophilic displacement, such as the abnormally rapid replacement of both boron atoms of ethane-1,1-diboronic acid by mercuric chloride.²⁰ We will discuss and review these mechanistic concepts more fully elsewhere.²¹

(18) S. Winstein, T. G. Traylor, and C. S. Garner, *J. Am. Chem. Soc.*, **77**, 3741 (1955).

(19) D. E. Applequist and G. N. Chmurny, *ibid.*, **89**, 875 (1967).

(20) D. S. Matteson and J. G. Shdo, *J. Org. Chem.*, **29**, 2742 (1964).

(21) D. S. Matteson, *Organometal. Chem. Rev.*, in press.

Experimental Section

Benzylboronic Esters. Grignard reagents were prepared from the appropriate commercially available substituted benzyl chloride or bromide. With *p*-methylbenzyl bromide, it was necessary to put the magnesium in a Soxhlet extractor with a glass wool plug in the siphon to maintain a smooth flow and add the benzyl halide solution slowly through the magnesium in order to prepare the Grignard reagent without excessive Wurtz coupling. The Grignard solution was added to trimethyl borate below -30°, then treated with aqueous acid and butanol and worked up in the usual way.²² The products were distilled twice through a 15-cm Vigreux column. Their properties are summarized in Table IV; yields were 40–60%.

Dimethyl Benzylboronate. This compound, bp 34° (0.1 mm), was first obtained by inadvertent methanolysis of tetramethyl phenylmethanediboronate.²³ We have since developed a rational synthesis of methyl esters of boronic acids. Boronic acid (0.5 mol), 200 ml of 2,2-dimethoxypropane, and 0.1 g of zinc chloride were heated, and the mixture of methanol, acetone, and 2,2-dimethoxypropane was distilled through a packed column. The boronic ester was distilled under vacuum.

Anal. Calcd for C₆H₁₃BO₂: C, 65.91; H, 7.99; B, 6.59. Found: C, 65.68; H, 8.02; B, 6.78.

Dimethyl *p*-methylbenzylboronate was similarly prepared, bp 53° (0.2 mm).

Anal. Calcd for C₁₀H₁₅BO₂: C, 67.46; H, 8.49; B, 6.07. Found: C, 67.04; H, 8.53; B, 6.21.

Substituted Benzylmercuric Chlorides. A solution of 6.25 mmol of mercuric chloride and 6.25 mmol of mercuric acetate in 10 ml of glycerol, 20 ml of water, 1 ml of acetic acid, and enough ethanol to make 250 ml was treated with 12.5 mmol of the substituted dibutyl benzylboronate. After the solution stood for a few hours the substituted benzylmercuric chloride crystallized, was filtered, and was recrystallized from acetone. Reaction times and properties are listed in Table V; yields were 50–65%. Benzylmercuric chlorides obtained from kinetic runs (with excess chloride present) had the same melting points. Benzylmercuric chloride has been reported previously.⁷

Kinetics. The general conditions of the kinetic runs have been described previously.³ Weighed amounts of mercuric chloride, sodium chloride, and sodium acetate were dissolved in 20 ml of water, 1 ml of acetic acid, 10 ml of glycerol, and enough absolute ethanol to make 250 ml; 25 ml of this stock solution was measured into a side-arm flask equipped with a magnetic stirrer and a rubber septum for transfers with a hypodermic needle. The contents of the flask were kept under a nitrogen atmosphere and thermostated ($\pm 0.02^\circ$). A weighed amount of boronic ester was introduced by hypodermic syringe. (A volume correction should be made for the added boronic ester. This was done in all cases for computing the mercuric chloride analyses, but was neglected in subsequent calculation of our reported *k* values. Appropriate correction would increase each tabulated *k* by 5–10%.) Analyses were carried out by withdrawing samples of measured volume at convenient intervals

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and adding the sample to an excess of EDTA in a pH 10 buffer solution. The remaining EDTA was back-titrated with 0.005 *M* magnesium sulfate with Eriochrome Black T as the indicator.⁸ In

preliminary experiments we had verified that EDTA does not complex with benzylmercuric chlorides and that accurate values for mercuric chloride can be obtained in their presence.

The Acid-Catalyzed and Mercuric Ion Catalyzed Hydrolysis of 2-(*para*-Substituted phenyl)-1,3-oxathiolanes

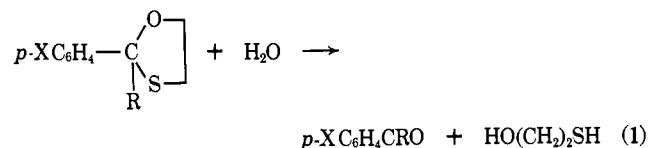
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Abstract: The hydrolysis of 2-(*para*-substituted phenyl)-1,3-oxathiolanes to give *para*-substituted benzaldehydes and mercaptoethanol is hydronium ion catalyzed and mercuric ion catalyzed. Mercuric ion catalysis is from 300 to 1600 times more efficient than hydronium ion catalysis. For the acid-catalyzed reactions, $\rho = -1.66$, $\Delta S^\ddagger = -17.8$ eu, and the deuterium solvent kinetic isotope effect $k_D/k_H = 2.15$, results consistent with an A2 mechanism involving solvent water in the transition state.

Although there is considerable information concerning the acid-catalyzed hydrolysis of acetals,^{1b,2,3} ketals,³ oxides,⁴ ortho esters,^{5,6} *para*-substituted phenyl acetals,⁷ 2-(*para*-substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes,⁸ and 2-(substituted phenyl)-3-ethyl-oxazolidines,⁹ relatively little is known about the details of the acid-catalyzed hydrolysis of 2-(*para*-substituted phenyl)-1,3-oxathiolanes (eq 1). Thus the hemithioketal

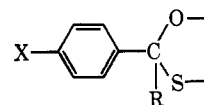


group has been studied primarily from the viewpoint of its synthetic utility as a carbonyl protective group.^{10,11} Of biochemical interest is the report of a mammalian thioglycosidase which is capable of catalyzing the hydrolysis of 6-mercaptapurine- β -D-glycothiopyranosides to 6-mercaptapurine and pyranoses.¹² This enzymic reaction is catalyzed by a variety of substances including cupric and mercuric ions and is inhibited by some substances including ethylenediaminetetraacetic acid, results which suggest that the enzyme may have a metal ion requirement and further that the metal ion may function as a super acid in the hydrolysis reaction. This investigation was undertaken in order to gain

information about the mechanisms of hydrolysis of oxathiolanes as well as to determine the relative catalytic efficiency of the proton *vs.* mercuric ion in hydrolytic reactions of these substances.

Experimental Section

Reagents. Inorganic salts were Fisher ACS certified reagent chemicals. Organic reagents were purchased from Fisher Co. and were distilled or crystallized before use. Tap-distilled water was redistilled from a Corning AG1a still. Deuterium oxide (99.8%) and deuterium chloride in D₂O were purchased from Ciba Co. 2-(Substituted phenyl)-1,3-oxathiolanes were synthesized by the method of Djerrasi, *et al.*¹³ A mixture of equimolar quantities of appropriate aldehyde with 2-mercaptoethanol was refluxed in benzene with a trace of *p*-toluenesulfonic acid until the calculated amount of water was collected. The solution was cooled, washed successively with dilute sodium bicarbonate solution and water, and dried with MgSO₄. The benzene was distilled out and the residue was purified by vacuum distillation or crystallization from methanol. The physical constants of oxathiolanes are given in Table I.



Apparatus. A Gilford Model 2000 spectrophotometer equipped with thermospacers through which water ($\pm 0.1^\circ$) from a Tamson T9 water bath was circulated, was used for kinetic measurements. pH measurements were made with a Radiometer PH M22 pH meter with a PHA 630 scale expander and a Radiometer GK2021 B electrode. Ultraviolet spectra were scanned using a Beckman Model DBG spectrophotometer.

Kinetics. Stock solutions of compounds 1-6 were prepared in redistilled acetonitrile. All the reactions were carried out in redistilled water and at a calculated ionic strength of 1 *M* (KCl) unless otherwise stated. The values for the rate constants for the acid and mercuric ion catalyzed reactions were unaffected by changes in μ from 0.1 to 1.0. pH was determined before each run and sometimes after some runs to ensure constancy of pH ± 0.02 units. Reactions were started by addition of a microdrop of the appropriate substrate in acetonitrile to a 3-ml cuvette filled to the stopper level with the proper solutions equilibrated at appropriate temperatures (final concentration of substrate = $3\text{--}5 \times 10^{-6}$ *M*).

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