ORGANIC AND BIOLOGICAL CHEMISTRY

Organoboron Compounds. XIV.[1,2] Polyfunctional Catalysis by 8-Quinolineboronic Acid

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8-Quinolineboronic acid was found to be a polyfunctional catalyst for hydrolysis of chloroethanol and 3-chloro-1-propanol in dimethylformamide solutions containing water and collidine. In the absence of 8-quinolineboronic acid the chloroalcohols underwent slow solvolysis in dimethylformamide solution to products that were not glycols. Both water and ethylene glycol inhibited the catalytic reaction when present in high concentration. It is proposed that the boronic acid group in 8-quinolineboronic acid functions as a binding site for the chloroalcohol and that the nitrogen participates in the reaction as a basic or nucleophilic transforming site.

Swain and Brown defined a polyfunctional catalyst as one "which uses concerted action by two or more groups, each acting on a different atom or point in the substrate."[3] Inherent in their concept was the idea that "basic and acidic functions in the catalyst operate simultaneously" at the points of net chemical change in the substrate. In such catalysts each active group serves directly as a *transforming site*. As an example of this type of catalysis, Swain and Brown showed that 2-hydroxypyridine was much more effective than a mixture of pyridine and phenol in accelerating the mutarotation of tetramethylglucose in benzene solution.[3]

The concept of polyfunctional catalysis may be extended to include substances in which one functional group serves as a transforming site and another as a *binding site*, the role of the latter being to hold the substrate in position for interaction with the transforming site. Polyfunctional catalysts of this type may exhibit selectivity in acting upon substrates which differ in structure at some position far removed from the points of net chemical change. Partially protonated poly-(4-vinylpyridine), a particularly effective catalyst for hydrolysis of nitrophenyl esters which bear a negative charge,[4] illustrates this category of reagents.

Although enzymes provide abundant evidence for the catalytic potentialities to be realized by exploiting cooperative functional group effects, relatively few simple systems exhibiting polyfunctional catalysis have as yet been studied. In searching for new examples we turned to compounds possessing boronic acid and amine functional groups. These substances appeared especially attractive since the boronic acid group could function either as a binding site (for alcoholic substrates) or as an acidic transforming site, while the amine could act as a basic or nucleophilic center.

Preliminary studies were made with 8-quinolineboronic acid and chloroethanol in dimethylformamide solution, on the assumption that quaternization at the nitrogen might be facilitated by esterification of the chloroalcohol with the boronic acid group. A marked synergetic effect of the neighboring boronic acid and amine groups was indeed found. As judged by the initial rate of appearance of chloride ion, 8-quinolineboronic acid reacted at least eighty times faster than a mixture of quinoline and benzeneboronic acid with chloroethanol.[5]

Investigation of the products revealed that the nitrogen in 8-quinolineboronic acid was in fact protonated rather than alkylated in the course of the reaction. This result indicated that chloroalcohols might be substrates in a reaction *catalyzed* by 8-quinolineboronic acid if a suitable base were incorporated in the reaction mixture to take up hydrogen ions. As a test of this idea experiments were carried out with equimolar amounts of 2,4,6-trimethylpyridine (collidine) and either chloroethanol or 3-chloro-1-propanol and 0.1 mole equivalent of 8-quinolineboronic acid. The reactions were followed by removing aliquots of the solution and titrating for chloride ion. Collidine was employed as a transfer base since it is a stronger base than 8-quinolineboronic acid yet it does not accelerate the rate of formation of chloride ion from chloroethanol in dimethylformamide solution. Control reactions in which 8-quinolineboronic acid was omitted from the recipe were also carried out. They provided a measure of the extent of non-catalyzed solvolysis of the chloroalcohols in the dimethylformamide solutions. As shown in Fig. 1 (expt. A and B) and Fig. 2 (expt. E and F), the reactions with 8-quinolineboronic acid proceeded several times faster than the controls and the high rates were maintained even after the number of moles of chloride ion formed exceeded the moles of boronic acid by a factor of four. It is therefore apparent that 8-quinolineboronic acid did "turn over" or function catalytically in these cases, in contrast to the results in the collidine-free system.[5] Numerical data on the rates of these and other reactions reported in this paper are summarized in Table I.[6]

Collidine hydrochloride was readily isolated from the products of the catalyzed reaction. In addition, essentially all of the 8-quinolineboronic acid was recoverable. No aldehydes or gaseous products, such as ethylene oxide or trimethylene oxide, were found. The principal substances derived from the chloroalcohols proved to be glycols, produced from water present in the dimethylformamide solutions.[7] 1,3-

(1) This work was supported by the National Science Foundation.

(2) For the previous paper in this series see R. L. Letsinger, T. E. Feare, T. J. Savereide and J. R. Nazy, *J. Org. Chem.*, **26**, 1721 (1961).

(3) C. G. Swain and J. F. Brown, *J. Am. Chem. Soc.*, **74**, 2538 (1952).

(4) R. L. Letsinger and T. J. Savereide, *ibid.*, **84**, 3122 (1962).

(5) R. L. Letsinger and S. H. Dandegaonker, *ibid.*, **81**, 498 (1959). The concentration of the boronic acids, quinoline and 2-chloroethanol was 0.16 *M* in these reactions.
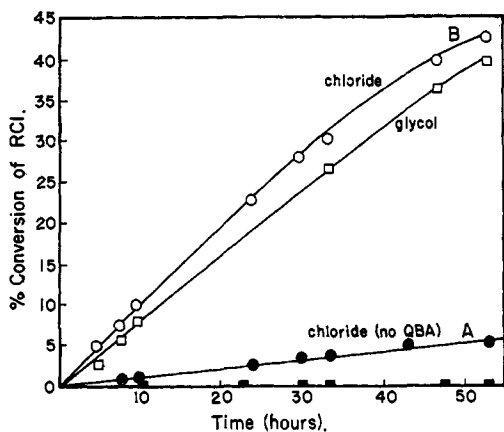
(6) The kinetics of the reactions with 8-quinolineboronic acid in dimethylformamide were complicated by the various equilibria involving water, chloroalcohol, glycol product, and the boronic acid and its anhydride; and the reaction rates did not depend in a simple way on the concentration of chloroalcohol and quinolineboronic acid. Within a given run, however, the amount of product was a linear function of time throughout several catalytic cycles of the boronic acid. Accordingly, the rates are expressed in terms of moles per liter of product (chloride ion or glycol) obtained per hour.

Dimethylformamide was a good solvent for the reaction and was used in the studies discussed in this paper; however, the properties of 8-quinolineboronic acid do not depend upon this solvent. 8-Quinolineboronic acid also functions in dimethylacetamide, sulfolane, and a mixture of butanol and chloroethanol (see papers XV and XVI in this series).

(7) Dimethylformamide contains considerable quantities of water unless special drying procedures have been employed to get an "anhydrous" sample. A. B. Thomas and E. G. Rochow, *J. Am. Chem. Soc.*, **79**, 1843 (1957), found that even dimethylformamide that had been dried by distillation of benzene was about 0.01 *M* in water.

Fig. 1.—B, reaction of chloroethanol (0.80 M) in dimethylformamide solution, 0.080 M in 8-quinolineboronic acid and 0.86 M in collidine: per cent chloride ion liberated, —O—; per cent glycol formed, —□—. A, same conditions, except no 8-quinolineboronic acid: per cent chloride ion liberated, —●—; per cent glycol formed, —■—

TABLE I

SUMMARY OF DATA OF REACTIONS OF CHLOROETHANOL AND
3-CHLORO-1-PROPANOL IN DIMETHYLFORMAMIDE SOLUTIONS
CONTAINING COLLIDINE[a]

Expt.	Quinoline-boronic acid, moles/liter	Water added, moles/liter	$10^4 k_{total}$ $_{Cl^-}$[b]	$10^4 k_{cat.}$ $_{Cl^-}$[c]	$10^4 k_{glycol}$[d]
A (E)[e]	...	...	8.8		0
B (E)	0.080	...	78.8	70.0	62.7
C (E)	.080	...	78.4	69.6	62.7
D (E)	.080	...	79.5	70.7	76.8
E (P)[e]	...	...	9.6		
F (P)	.079	...	35.6	26.0	
G (P)[f]	...	...	8.4		
H (P)[f]	.039	[0.2][g]	15.2	[7.8]	
I (E)	.032	...	23.6	14.8	16.8
J (E)	[h]	...	8.4	0	
K (E)[f]	...	...	8.0		
L (E)[f]	...	0.8	8.0		
M (E)[f]	...	8.0	18.4		
N (E)[f]	.080	...	82.3	74.3	
O (E)[f]	.080	0.8	33.2	25.2	
P (E)[f]	.080	8.0	22.0	3.6	
Q (E)	.080	[i]	34.4	25.6	

[a] Each solution was 0.800 M in the chloroalcohol and 0.864 M in collidine, and the temperature was 88.6°. [b] k_{total} $_{Cl^-}$ expresses the initial rate of appearance of chloride ion in terms of moles/liter/hour. [c] $k_{cat.}$ $_{Cl^-}$ expresses the initial rate of appearance of chloride ion that arises directly from the catalytic reaction, in terms of moles/liter/hour; $k_{cat.}$ $_{Cl^-}$ = k_{total} $_{Cl^-}$ — $k_{con.}$, where $k_{con.}$ is k_{total} $_{Cl^-}$ for a control reaction which does not involve 8-quinolineboronic acid (e.g., A is a control for B). [d] k_{glycol} expresses the rate of appearance of glycol (or substances which behave equivalently toward periodic acid), in terms of moles/liter/hour. [e] Reactions involving chloroethanol are designated by (E); those involving 3-chloro-1-propanol, by (P). [f] "Benzene-dried" dimethylformamide was used in these experiments. [g] For details, see Discussion section. The rate in expt. H is for the reaction after addition of water. [h] The solution contained benzeneboronic acid (0.032 M) and quinoline (0.032 M) in place of 8-quinolineboronic acid. [i] The solution was 0.80 M in ethylene glycol.

Propanediol, characterized by its physical properties and by preparation of solid derivatives, was isolated in 43% yield from the reaction of 3-chloro-1-propanol. Ethylene glycol was detected and quantitatively determined by titration with periodic acid. Since ethylene oxide and ethylene glycol behave similarly toward periodic acid, care was taken to establish the identity of the oxidizable substance. For this purpose the mixture of products from a reaction of 2-chloroethanol with 8-quinolineboronic acid in dimethylformamide was
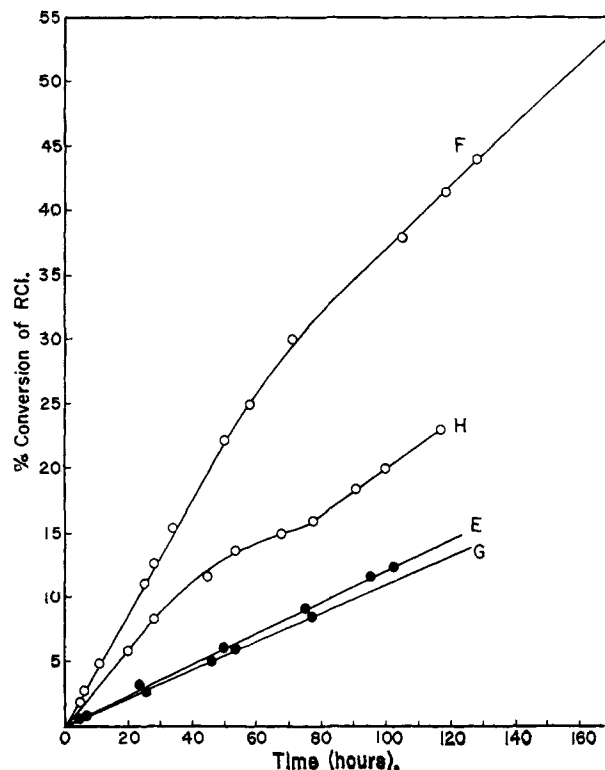

Fig. 2.—F, reaction of 3-chloro-1-propanol (0.80 M) in dimethylformamide with 8-quinolineboronic acid (0.079 M) and collidine (0.86 M). E, same, without 8-quinolineboronic acid. H, same as F except with 0.039 M 8-quinolineboronic acid in "benzene-dried" dimethylformamide (see Discussion for details). G, same initial conditions as in H, except no 8-quinolineboronic acid.

warmed at reduced pressure in order to distil out any ethylene oxide present. Titration of aliquots taken prior and subsequent to this treatment showed that none of the oxidizable substance was removed. By contrast, it was found in a control test that although some ethylene oxide would be retained by a solution of 8-quinolineboronic acid in dimethylformamide at 88.8°, most of the oxide was expelled when the pressure on the system was reduced (see Experimental section). It may therefore be concluded that the oxidizable substance from the chloroethanol reaction was not ethylene oxide and, in addition, that the rate of hydrolysis of ethylene oxide in dimethylformamide at 88.8° was too slow to be consistent with a mechanism involving ethylene oxide as an intermediate in the formation of ethylene glycol.

On following the reaction of chloroethanol by quantitative titration for glycol a striking result was observed: *ethylene glycol was a major product of the catalytic reaction, but it was not formed in a measurable amount in the non-catalytic contro' reaction* (Fig. 1.[8]) Furthermore, the rate of formation of chloride ion in the catalytic reaction (k_{cat} $_{Cl^-}$ = 70.1 ± 0.04 × 10^{-4} mole/liter/hour for expt. B and two duplicate experiments, C and D) was very close to the rate of production of glycol (k_{glycol} = 67.4 ± 6.3 × 10^{-4} mole/liter/hour for B, C, D). These data indicate that two independent reactions take place: (1) a solvolysis which is not influenced by 8-quinolineboronic acid and yields chloride ion but no ethylene glycol and (2) a specific hydrolysis, the rate of which is increased enormously by 8-quinolineboronic acid.

(8) In agreement with this result, no 1,3-propanediol could be isolated from the products of reaction of 3-chloro-1-propanol in dimethylformamide solutions of collidine.
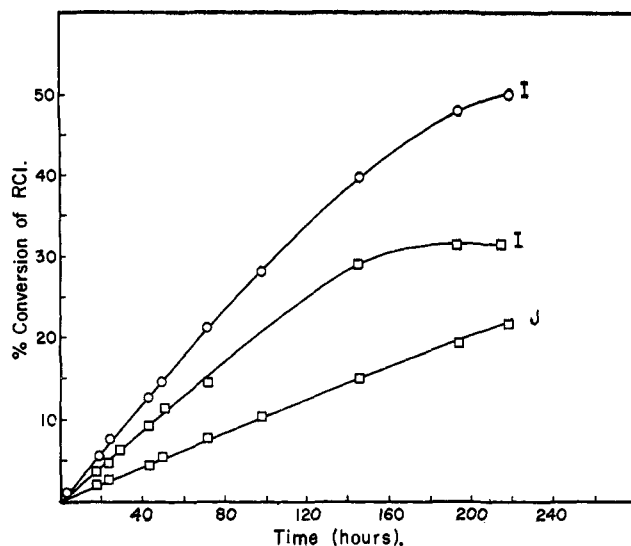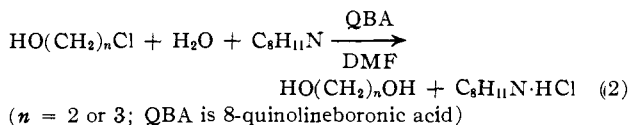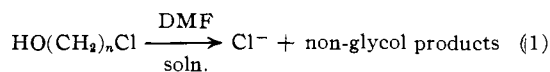
Fig. 3.—I, reaction of chloroethanol (0.80 M) in dimethylformamide with 8-quinolinebornic acid (0.032 M) and collidine (0.86 M): per cent chloride ion liberated, —O—; per cent glycol formed, —□—. J, same with benzeneboronic acid (0.032 M) and quinoline (0.032 M) in place of 8-quinolineboronic acid (extent of reaction expressed as per cent chloride ion liberated).

$$HO(CH_2)_nCl \xrightarrow[\text{soln.}]{\text{DMF}} Cl^- + \text{non-glycol products} \quad (1)$$

$$HO(CH_2)_nCl + H_2O + C_8H_{11}N \xrightarrow[\text{DMF}]{\text{QBA}}$$
$$HO(CH_2)_nOH + C_8H_{11}N \cdot HCl \quad (2)$$
(n = 2 or 3; QBA is 8-quinolineboronic acid)

It is interesting that OH of water rather than OH of the alcohol served as the nucleophile in the catalytic reaction even though the concentration of the alcohol was relatively quite high.

Figure 3 records data for a reaction in which the chloroethanol–quinolineboronic acid ratio was 25:1. In this case ethylene glycol was produced at a steady rate until the chloride ion yield was 30%, which corresponds to a turnover number of 7 for the boronic acid. Thereafter the rate of hydrolysis decreased rapidly, probably as a result of depletion of water in the system and inhibition by ethylene glycol (see later discussion). It may be noted for comparison that a mixture of benzeneboronic acid and quinoline did not increase the rate of reaction of chloroethanol (expt. J, Fig. 3, and Table I),[9] a fact which points up the polyfunctional character of the catalytic action of 8-quinolineboronic acid.

To learn more about the role of water, some experiments were carried out with 3-chloro-1-propanol in dimethylformamide which had been dried by distillation of benzene and by molecular sieves (expt. G and H, Fig. 2). The rate of a reaction, H, involving 8-quinolineboronic acid was initially faster than that for a control, G, as expected. However, after about 13% conversion of chloropropanol, the rate for H fell to that of the control. When a small amount of water (0.069 g., giving a solution 0.21 M in water) was then added to reaction H (at time = 79 hr.) the rate again increased. These results are consistent with the view that the catalytic reaction caused by 8-quinolineboronic acid in dimethylformamide requires water. Sufficient

(9) The ineffectiveness of a mixture of benzeneboronic acid and quinoline in causing hydrolysis was also demonstrated by heating 1.5 mmoles of chloroethanol with 4.0 mmoles each of benzeneboronic acid and quinoline in 10 ml. of dimethylformamide for 23.4 hours. At the end of this time 23.4% of the chloride had been liberated, but titration with periodic acid showed that no "glycol" had been formed.
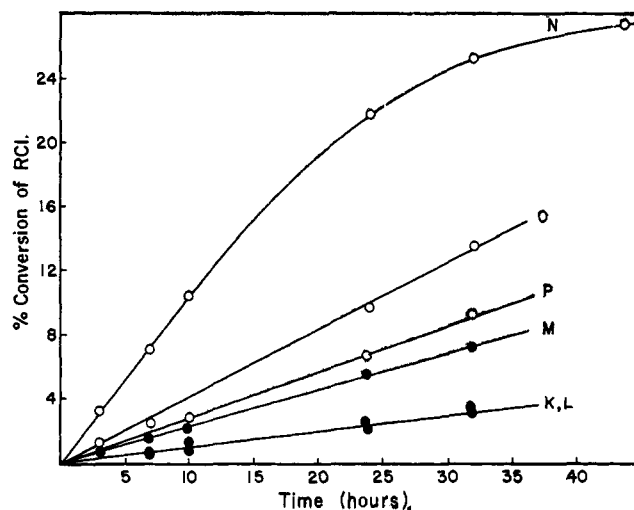

Fig. 4.—Reaction of chloroethanol (0.800 M) in "benzene-dried" dimethylformamide and collidine (0.86 M). Added reagents: N, 8-quinolineboronic acid (0.08 M); O, 8-quinolineboronic acid (0.08 M) and water (0.8 M); P, 8-quinolineboronic acid (0.08 M) and water (8.0 M); K, none; L, water (0.8 M), and M, water (8.0 M).

water would be available from esterification of the boronic acid to hydrolyze 9.7% of the chloropropanol, a value close to the 7.5% reaction observed in the initial catalytic phase.[10]

While some water appeared to be necessary for the catalytic reaction in dimethylformamide solution, water in relatively high concentration acted as an inhibitor. This fact may be seen by comparing expt. N, O and P in Fig. 4. In contrast, water did not retard the solvolysis of chloroethanol which occurred in the absence of 8-quinolineboronic acid; indeed, the solvolytic rate was greater in the solution 8 M in water (M) than in the solutions with lower water concentrations (K, L). The decrease in rate observed after 24 hours in expt. N, for which "benzene-dried" dimethylformamide was used and no water was added directly to the system, seems best explained, as in the case of expt. H for chloropropanol, on the basis of consumption of water introduced in the form of OH from the boronic acid group. In agreement with this explanation, the amount of chloride ion liberated in the accelerated reaction ($\sim$23%) was close to that calculated to be formed from the OH groups available from the boronic acid (20%).

Ethylene glycol also proved to be an inhibitor of the catalytic reaction. When present in the same concentration as chloroethanol, ethylene glycol reduced the rate of reaction by a factor of 2.7 (compare Q and B, Table I). Even more effective was cis-1,2-cyclopentanediol, which forms a relatively stable ester with 8-quinolineboronic acid. At a concentration equal to that of the boronic acid (0.08 M) this diol stopped the catalytic reaction completely.

The effectiveness of 8-quinolineboronic acid as a catalyst is strongly influenced by the geometry of the chloroalcohol. Chloroethanol and 3-chloro-1-propanol were good substrates, and the rate of reaction of 4-chloro-1-butanol[5] was also affected by 8-quinolineboronic acid. However, 8-quinolineboronic acid did not enhance the rate of formation of chloride from 6-chloro-1-hexanol or trans-2-chlorocyclohexanol.

Although a detailed description of the mechanism of the hydrolysis of chloroalcohols in the catalytic system is not possible at the present time, it is clear that the

(10) This value was estimated from the difference in curves G and H in the 60–79-hr. period in Fig. 2.

following reactions are involved: (a) esterification of 8-quinolineboronic acid by the chloroalcohol; (b) displacement of chloride from the chloroalkyl group of the ester; (c) transfer of a proton to a base such as collidine, and (d) ester interchange, in the course of which a chloroalkyl boronate ester is reformed. The boronic acid group is considered to function as a binding site for the chloroalcohol and the basic nitrogen, as a catalytic transforming site. Pertinent equilibria are represented in Chart I (R is left unspecified since it night be hydrogen, a substituted alkyl group or a quinolineboronic acid residue, such as [C_9H_6NBOH]).

CHART I

(or the cyclic ester)
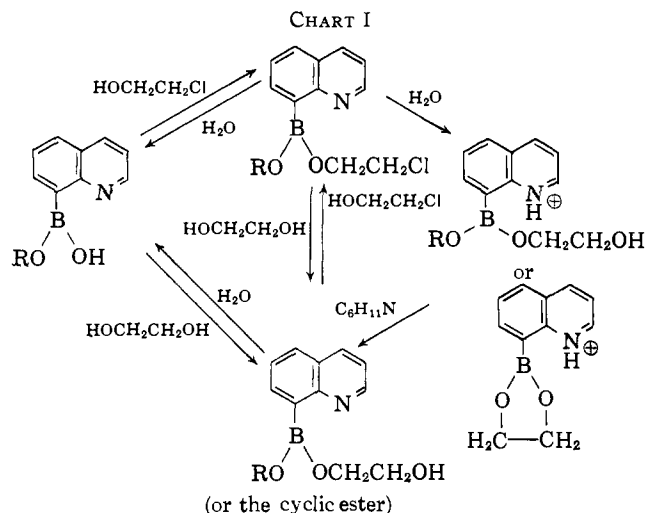
In support of this scheme, 8-quinolineboronic acid is known to form esters with chloroethanol and 3-chloro-1-propanol.[5] Direct involvement of a chloroalkyl ester in the catalytic reaction is indicated by the fact that both water and 1,2-diols inhibit the hydrolysis of chloroethanol. These substances would reduce the concentration of the chloroethyl ester, water by hydrolysis of the ester to the boronic acid, and the diols by ester interchange to produce the more stable cyclic esters. In consideration of the facile exchanges observed with borate esters and primary alcohols and the catalysis of these reactions by general bases,[11] one would expect interchange reactions involving esters of 8-quinolineboronic acid to occur readily. The necessity for a suitably oriented basic atom near the boronic acid groups is demonstrated by the fact that neither benzeneboronic acid nor mixtures of benzeneboronic acid and quinoline can duplicate the activity of 8-quinolineboronic acid. Furthermore, the requirement of a transfer base for catalytic activity shows that the nitrogen in quinolineboronic acid must be in the basic rather than the protonated form for activity in the hydrolytic reaction.

Experimental

Kinetic Experiments.—Appropriate quantities of collidine (b.p. 166°) and 8-quinolineboronic acid[5] were weighed into volumetric flasks (10 ml. or 25 ml.) and N,N-dimethylformamide (obtained from Matheson, Coleman and Bell; b.p. 32° at 3.8 mm.) was added until the flasks were about 0.75 full. The flasks were then placed in a water-bath at 88.6° and, after the 8-quinolineboronic acid had dissolved, the chloroalcohol and sufficient prewarmed dimethylformamide were added to fill the flasks to the mark. At intervals, 1-ml. aliquots of the solutions were removed and titrated for chloride ion or for ethylene glycol.

Chloride ion determinations were performed by adding the aliquot to 10 ml. of water, acidified with 10 drops of nitric acid, and titrating by the Volhard procedure, using silver nitrate and potassium thiocyanate solutions with nitrobenzene and a ferric alum indicator. It was shown in control tests that 8-quinolineboronic acid, the chloroalcohols, collidine and dimethylform-

(11) G. T. Perkins and T. I. Crowell, *J. Am. Chem. Soc.*, **78**, 6013 (1956).

amide did not interfer with the determination. In reactions carried to high conversions (greater than 0.3 M chloride, e.g., later points in expt. F and I) the mixtures became heterogeneous due to precipitation of collidine hydrochloride as fine crystals. By shaking the flasks prior to removal of the aliquots uniform sampling could be achieved.

Titrations for ethylene glycol were carried out as described by Siggia.[12] It was also shown that 8-quinolineboronic acid, the chloroalcohols, collidine and dimethylformamide did not interfere with the test.

For the experiments in the "anhydrous solvents," collidine was dried by distillation from barium oxide and dimethylformamide was dried by distillation of benzene from a dimethylformamide-benzene solution. The reagents were then stored over Linde Air Co. 4A Molecular Sieves.

8-Quinolineboronic acid could be recovered from the mixtures remaining after the Volhard titration by extracting with chloroform and then making the aqueous layer alkaline with ammonia. The boronic acid precipitated on standing and could be obtained in good form by a single recrystallization from alcohol-water.

Products from the Catalyzed Hydrolysis of 3-Chloro-1-Propanol. (a).—Isolation of collidine hydrochloride and recovery of 8-quinolineboronic acid. A mixture containing 9.45 g. (0.1 mole) of 3-chloro-1-propanol, 3.46 g. (0.02 mole) of 8-quinolineboronic acid, 12.1 g. (0.1 mole) of collidine and 20 g. of dimethylformamide was heated on a steam-bath for 39 hours. No volatile products collected in a Dry Ice trap which was connected to the reaction vessel. The mixture was then cooled and filtered to remove the collidine hydrochloride which had precipitated; weight 5.0 g. (31% yield). Titration of the filtrate indicated chloride ion corresponding to 16% yield; therefore the total conversion of chloropropanol amounted to 47%. The filtrate was concentrated by vacuum distillation (14 g. of organic liquid removed at 18 mm.) and poured into water. 8-Quinolineboronic acid precipitated and it was collected by filtration; weight 3.36 g. (97%). The aqueous layer was extracted several times with ether. Distillation of the extracts yielded 3-chloro-2-propanol (2 g., b.p. 28° (0.8 mm.).

In a parallel control reaction, in which 8-quinolineboronic acid was omitted from the mixture, no collidine hydrochloride precipitated from the solution. Titration indicated the conversion to chloride ion to be only 7.0%.

(b). Isolation of 1,3-Propanediol.—Since the product derived from chloropropanol was too soluble in water to be extracted with ether, an alternate isolation procedure was investigated. In this case the reaction was carried out by heating 9.45 g. (0.1 mole) of 3-chloro-1-propanol, 12.1 g. (0.1 mole) of collidine and 1.73 g. (0.01 mole) of 8-quinolineboronic acid in 40 g. of dimethylformamide on a steam-bath for 109 hr. Titration of a 1-ml. aliquot indicated that 37% of the chloropropanol had reacted. On cooling, 2.75 g. of collidine hydrochloride precipitated. After filtration, triethylene glycol (11 g.) was added to the liquid to liberate any propanediol which might be present as an ester of the boronic acid, and the mixture was distilled at reduced pressure. After removal of dimethylformamide, chloropropanol and collidine, a liquid was obtained which, on redistillation at 1 mm., afforded three fractions: (i) b.p. 34–40°, 0.5 g.; (ii) b.p. 60–70°, 1.0 g.; and (iii) b.p. 70–84°, 1.2 g. The infrared spectrum of ii was identical with that of 1,3-propanediol; the spectrum of iii was the same, except for a band in the carbonyl region indicative of some impurity. A phenylurethan derivative of fraction ii had the same melting point (139–140°) and infrared spectrum as the phenylurethan derivative prepared from 1,3-propanediol, and the mixture melting point showed no depression.

Anal.[13] Calcd. for $C_{17}H_{18}O_4N_2$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.85; H, 5.59; N, 8.92.

The identity of the product was further confirmed by preparation of a mono-3,5-dinitrobenzoate derivative from fraction iii. It exhibited the same melting point (56.0–56.5°) and infrared spectrum (λ_{max}^{KBr} 2.97, 5.82 and 7.41 μ, indicating hydroxyl, carbonyl and nitro groups) as the derivative prepared from 1,3-propanediol.

Anal.[13] Calcd. for $C_{10}H_{10}O_7N_2$: N, 10.37. Found: N, 10.4.

Fraction ii corresponds to a 43% yield of 1,3-propanediol, based on the amount of chloride ion formed in the reaction. The yield was actually considerably higher since fraction iii was largely 1,3-propanediol as well.

A control reaction was run which was similar to the catalytic reaction just described except that 8-quinolineboronic acid was omitted and the time of reaction was 164 hr. Titration indicated 22% conversion of chloropropanol to chloride; however, no propanediol could be found on distillation of the mixture. The reaction product (4 g.) remained as a non-distillable oil.

(12) S. Siggia, "Quantitative Organic Analysis," John Wiley and Sons, Inc., New York, N. Y., 1949, p. 8.

(13) Carbon, hydrogen and nitrogen analyses were performed by H. Beck.

Behavior of Ethylene Oxide in a Dimethylformamide Solution. Ethylene oxide (25 ml., measured at 0°) was cooled to −60° and added over a 12-min. period to a well stirred solution containing 1.384 g. of 8-quinolineboronic acid and 0.8 ml. of 1-butanol in 100 ml. of dimethylformamide at 88.8°. The reaction flask was equipped with a Dry Ice trap to collect volatile material. In the course of the addition and for about 5 min. afterward a gas (ethylene oxide) could be observed boiling out of the solution. Approximately 20 ml. of ethylene oxide condensed in the cold trap; after an hour it was added back to the reaction mixture. The solution was stirred for 2 hr., and then three 5-ml. aliquots were withdrawn over a period of 4.5 hr. for titrations with periodic acid. The results of the titrations were consistent in indicating the concentration of ethylene oxide to be 0.090 M. The pressure on the system was then reduced to where dimethylformamide began to distil, at which point the ethylene oxide concentration was 0.007 M. On repetition of the vacuum treatment 12 hr.

later the concentration of oxidizable substance was only 0.004 M. These experiments show that some ethylene oxide is retained by a dimethylformamide solution containing 8-quinolineboronic acid at 88.8° and that, at most, only a very small amount (0.004 M) is converted to ethylene glycol. The oxidizable substance which remained after the pressure reductions corresponded to less than 5% of the 8-quinolineboronic acid present.

Evidence that the Product of Reaction of Chloroethanol and 8-Quinolineboronic Acid was not Ethylene Oxide.—8-Quinolineboronic acid (1.39 g.) and chloroethanol (0.648 g.) were heated together in 50 ml. of dimethylformamide at 88.8° for 4 hr. A titration with periodic acid indicated the concentration of reducing agent (ethylene glycol or its ester or ethylene oxide) to be 0.0388 M. After the reduced pressure treatment described in the previous experiment, a titration showed the concentration of reducing agent to be 0.0394 M. Since none of the reducing agent was lost under these conditions, it must have been the glycol (or a glycol ester of the boronic acid) and not ethylene oxide.

Organoboron Compounds. XV.[1] Stereochemistry of the Reaction of 8-Quinolineboronic Acid with Chloroalcohols

BY ROBERT L. LETSINGER AND JAMES D. MORRISON[2]

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The reaction of 8-quinolineboronic acid with two pairs of stereoisomeric chlorohydrins was investigated. In two-step reactions, involving treatment of the chlorohydrin with 8-quinolineboronic acid and hydrolysis of the cyclic esters thereby produced, trans-2-chloro-1-indanol was converted to cis-1,2-indandiol and erythro-2-chloro-1,2-diphenylethanol was converted to dl-hydrobenzoin in good yield. cis-2-Chloro-1-indanol did not undergo carbon–chlorine fission when treated with 8-quinolineboronic acid under the conditions used for reaction of the trans isomer, and threo-2-chloro-1,2-diphenylethanol afforded in a very slow reaction a low yield of meso-hydrobenzoin. The mechanistic implications of the stereoselectivity of the reaction of 8-quinolineboronic acid are discussed.

It was shown in the previous paper that 8-quinolineboronic acid is a polyfunctional catalyst for hydrolysis of chloroethanol and 3-chloro-1-propanol in dimethylformamide solutions containing water and collidine.[3] Several features relevant to the mechanism of the transformation were noted. The most interesting reaction in the proposed, generalized scheme is the one in which the carbon–halogen bond is broken, for it is in this step that the coöperative action of the neighboring boron and nitrogen should play a decisive role. The work described in the present paper was undertaken with the objective of learning more about this process.

The various mechanisms that may be envisaged for the substitution reaction may be classified into two categories: (1) those in which halogen is displaced by nitrogen and (2) those in which halogen is displaced by oxygen, the nucleophilicity of which has been increased by a neighboring nitrogen. In the former, the borono group would function as a binding site and nitrogen would act as a nucleophilic transforming site.[3] The carbon–oxygen bond would be formed by attack of water on an intermediate quaternary ammonium salt. Several pathways for the latter case (2) seem plausible. In each, boron would serve as a binding site and also participate in activation of oxygen. Sequence 2a illustrates a pathway of this type.

Since each displacement on carbon should occur with preponderate inversion of configuration, the stereochemical consequence at an asymmetric carbon would be net retention of configuration if the reaction followed sequence 1 and inversion of configuration if it went by sequence 2. The likelihood that displacement by water in sequence 1 proceeds with retention of configuration in an S_Ni type mechanism, via an intermediate
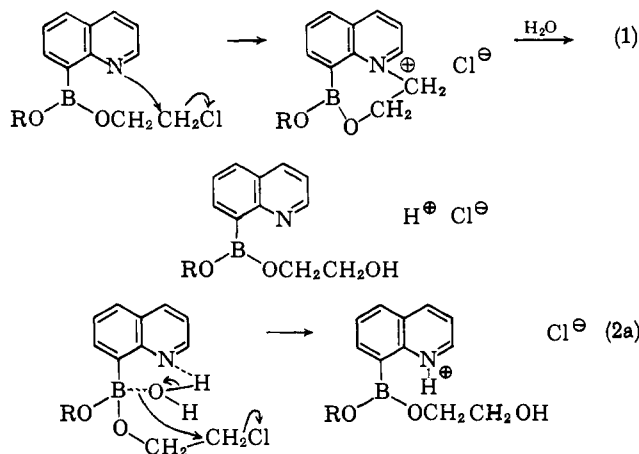
such as (a), is remote since the geometry of the groups about boron would be very unfavorable for such a process.

(a)
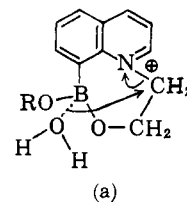
As a means of distinguishing between sequences 1 and 2 we therefore investigated the stereochemistry of the reaction of 8-quinolineboronic acid with two pairs of isomers: trans-2-chloro-1-indanol (I) and cis-2-chloro-1-indanol (II), and erythro-2-chloro-1,2-diphenylethanol (III) and threo-2-chloro-1,2-diphenylethanol (IV).

The stereoisomeric 2-chloroindanols were obtained by hydrolysis of 1,2-dichloroindane.[4] Based on the

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(3) R. L. Letsinger, S. Dandegaonker, W. J. Vullo and J. D. Morrison, J. Am. Chem. Soc., **85**, 2223 (1963).

(4) C. M. Suter and G. A. Lutz, ibid., **60**, 1360 (1938).