Electrophilic Displacement Reactions. XI. Solvent Isotope Effects in the Protodeboronation of Areneboronic Acids[1-3]

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The effect of solvent hydrogen isotope composition (hydrogen and deuterium) on the rates of protodeboronation of p-methoxybenzeneboronic acid in 6.3 M sulfuric acid and of 2,6-dimethoxybenzeneboronic acid in 0.1 M perchloric acid have been studied. In the former case k_H/k_D is 3.7 and the rate constant variation with solvent isotope composition is nearly linear. In the latter case k_H/k_D is 1.7 and variation of rate constant with solvent isotope composition is non-linear. This rate behavior is in quantitative accord with that expected for a rate-determining proton transfer.

The acid-catalyzed replacement of the boronic acid group of an areneboronic acid by hydrogen (protodeboronation) is an example of aromatic substitution in which the proton functions as the electrophile. By appropriate choice of substituents on the benzene ring it is possible to study the kinetics of the reaction conveniently in the range from dilute aqueous acid to concentrated mineral acids. Consequently, a study of the mechanism of the reaction offers promise of bridging the gap between the fairly well understood characteristics of acid catalysis in dilute acid solutions and the little understood characteristics in strongly acid media.

In the preceding paper of this series[1] the results of kinetic studies on the protodeboronation of p-methoxybenzeneboronic acid and 2,6-dimethoxybenzeneboronic acid were reported. The kinetic behavior in concentrated phosphoric acid solution, in phosphoric acid–dihydrogen phosphate buffers and formic acid are those expected for a reaction subject to general acid catalysis. Therefore, the A-1 mechanism which involves a reversible proton transfer preceding a rate-determining unimolecular step, and would thus be subject to specific lyonium ion catalysis, is ruled out as the major pathway. On the other hand, several other mechanisms which differ substantially in detail require general acid catalysis. In order to narrow down the possibilities, the earlier work has been extended to include a study of the solvent isotope effect on the protodeboronation of the same substrates.

Results

The effect of solvent hydrogen isotope composition on the rate of protodeboronation of p-methoxybenzeneboronic acid in 6.31 M sulfuric acid at 25° was determined. Rate constants, k_n, in the pure isotopic solvents and mixtures are presented in Table I, and are plotted against n in Fig. 1. Two significant facts are revealed by the data: (1) the rate in the protium solvent is 3.7 times as fast as that in the deuterium solvent; (2) the dependence of rate constant on solvent hydrogen isotope composition is essentially linear.

(1) Preceding paper in this series: H. G. Kuivila and K. V. Nahabedian, J. Am. Chem. Soc., 83, 2159 (1961).

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(3) Based in part on the doctoral dissertation of K. V. Nahabedian, June, 1959.

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TABLE I

THE EFFECT OF SOLVENT HYDROGEN ISOTOPE COMPOSITION ON THE RATE OF PROTODEBORONATION OF p-METHOXYBENZENEBORONIC ACID AT 25.0° IN 6.31 M SULFURIC ACID

n^a	$k_n \times 10^4$, sec.$^{-1}$	n^a	$k_n \times 10^4$, sec.$^{-1}$
0	3.45	0.598	2.02
0.221	3.02	.799	1.54
.443	2.42	.799	1.45
.598	1.96	.995	0.940

^{a} n = atom fraction of deuterium = $D/(D + H)$.

A similar study was carried out with 2,6-dimethoxybenzeneboronic acid. In this case, because of the greater reactivity of the substrate, the kinetics could be examined in dilute aqueous perchloric acid solution. Results are summarized in Table II and plotted in Fig. 2. In addition to the experimentally observed rate constants in column three, second-order rate constants are presented in column four. The value of k_2 in the deuterium solvent is estimated to be 1.44 × 10^{-3} 1. mole^{-1} sec.$^{-1}$, yielding a value of 1.65 for k_{2H}/k_{2D}. The last three rows in the table show that the isotope effect does not change with change in acid concentration from 0.1 to 0.02 M. A non-linear dependence of rate constant on the solvent hydrogen isotope composition is observed in this case.

TABLE II

THE EFFECT OF SOLVENT HYDROGEN ISOTOPE COMPOSITION ON THE RATE OF PROTODEBORONATION OF 2,6-DIMETHOXYBENZENEBORONIC ACID IN AQUEOUS PERCHLORIC ACID AT 60.0°

C_{HClO_4}	n	$k \times 10^5$, sec.$^{-1}$	$k_2 \times 10^{-3}$, 1. mole^{-1} sec.$^{-1}$	Ionic strength
0.0975	0.0	23.5	2.41	0.50
.104	.198	24.4	2.35	.50
.104	.396	23.8	2.29	.50
.104	.595	22.3	2.15	.50
.104	.793	19.8	1.91	.50
.1013	.99	14.2	1.42	.50
.0507	.99	7.12	1.42(1.43)^a	.46
.0203	.99	2.95	1.47(1.49)	.43

^{a} Figures in parentheses obtained by extrapolating to ionic strength 0.50; see ref. 1.

Discussion

The solvent hydrogen isotope effect can be used as a criterion of mechanism in two ways: first, in terms of the magnitude of k_H/k_D and, second, in terms of how the rate constant changes with variation in the isotopic composition. At a given acid concentration a substrate will be converted into its
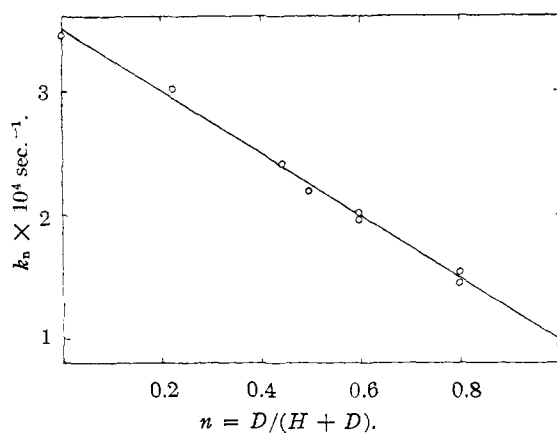
Fig. 1.—p-Methoxybenzeneboronic acid, dependence of k on solvent hydrogen isotope composition.

conjugate acid to a greater extent in deuterium oxide than in protium oxide.[5] As a result a reaction proceeding by the A-1 mechanism will go faster in the former solvent. If the proton transfer is the slow step, on the other hand, the normal kinetic isotope effect causes the reaction to go more slowly in the deuterium oxide, because the proton is usually more loosely bound in the transition state than in the ground state. The reverse state of affairs is conceivable, but has not been realized to our knowledge. The fact that proto-deboronation of p-methoxybenzene boronic acid is 3.7 times as fast in protium oxide as in deuterium oxide is clear-cut evidence for a rate-determining proton transfer. In the case of 2,6-dimethoxy-benzeneboronic acid the ratio is 1.65 at 60° which would correspond to about 2 at 25°.[5] Possible reasons for this difference in isotope effects will be discussed below.

The variation of rate with solvent isotope composition can be discussed in terms of the Gross–Butler equation.[6] As originally developed it applies to reactions dependent on protonation equilibria. Very recently, however, Gold has extended the treatment to apply to rate-determining proton transfers.[7] It begins with the known distribution of isotopes among neutral solvent molecules and an estimate of the distribution among lyonium ions arrived at from appropriate thermodynamic measurements. It is then assumed that the rate constant in a mixed solvent is given by eq. 1, where the superscripts refer to the isotope to be transferred from the lyonium ion

$$k_n C = k^H{}_{H_3O^+}[H_3O^+] + (k^H{}_{H_2DO^+} + k^D{}_{H_2DO^+})[H_2DO^+] +$$
$$(k^H{}_{H_2DO^+} + k^D{}_{H_2DO^+})[HD_2O^+] + k^D{}_{D_3O^+}[D_3O^+] \quad (1)$$

indicated in the subscript. The ability (acidity) of each ion to transfer a proton or deuteron is known, and the Brönsted catalysis law is assumed to apply after statistical corrections. Now, given the rate constants in the isotopically pure solvents, those for mixtures can be calculated for various values of α, and agreement with the experimental data sought. Both the equilibrium and kinetic approaches have been applied to the data for 2,6-

(5) K. B. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

(6) For a recent survey of its application see E. L. Purlee, *J. Am. Chem. Soc.*, **81**, 263 (1959).

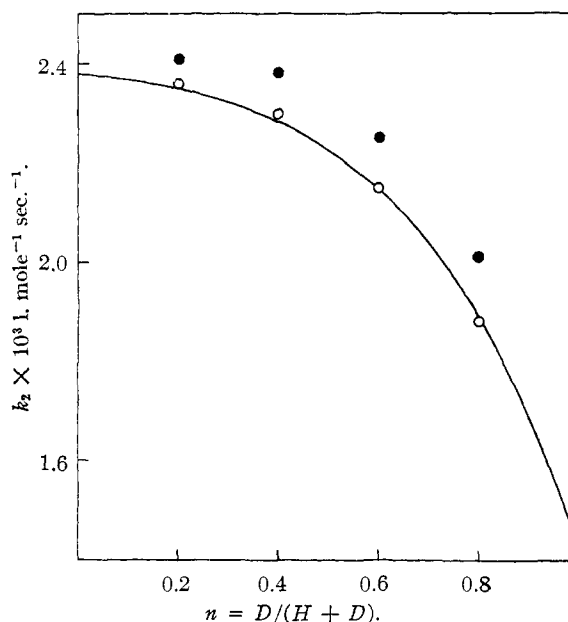(7) V. Gold, *Trans. Faraday Soc.*, **56**, 255 (1960).

Fig. 2.—2,6-Dimethoxybenzeneboronic acid, dependence of k_2 on solvent hydrogen isotope composition: solid circles, predicted by Gross–Butler theory; open circles, predicted by Gold theory; solid line, experimental values.

dimethoxybenzeneboronic acid. The solid circles in Fig. 2 are obtained on the assumption that a pre-equilibrium mechanism is involved. The deviations are far beyond experimental error. Data to fit the line can be obtained in two ways; first, if one assumes that the activity coefficient ratio $f_S f_+/f_\pm$, where the subscripts refer to substrate, lyonium ion and transition state decreases linearly with n by a total of 15% in going from protium oxide to deuterium oxide.[6] In view of the fact that the reaction is slower in the latter solvent, this agreement is considered to be fortuitous. Similar fit is also obtained by applying the slow proton transfer approach with α taken as 0.85. Specific values for $k_n \times 10^3$ calculated for values of n equal to 0.2, 0.4, 0.6 and 0.8 are 2.35, 2.30, 2.15 and 1.88, respectively. (For k_H the average value given in the preceding paper,[1] 2.38×10^{-3} l. mole^{-1} sec.$^{-1}$, was used.)

Of the mechanisms consistent with general acid catalysis indicated earlier[1] the A-2 mechanism can now be eliminated. Furthermore, those which invoke the special nature of phosphoric acid are not necessary. The A-S_E2 mechanism is the simplest one which is consistent with all of the data now available. As a matter of fact, the same can be said with slight modification for the available data on protodeuteration and protodetritiation[8,9] as pointed out by Kresge and Chiang[9] and for proto-decarbonylation as proposed by Schubert and his associates.[10]

The reactions can be compared with reference to eq. 2 and 3 where X represents a hydrogen isotope,

(8) V. Gold, R. Lambert and D. P. N. Satchell, *Chemistry & Industry*, 1312 (1959).

(9) A. J. Kresge and Y. Chiang, *J. Am. Chem. Soc.*, **81**, 5509 (1959); Abstracts of Papers, 137th Meeting of the American Chemical Society, April 5-14, 1960, p. 31-R.

(10) W. M. Schubert and P. C. Myhre, *J. Am. Chem. Soc.*, **80**, 1755 (1958), and earlier papers.

$$\text{(2)}$$

$$\text{(3)}$$
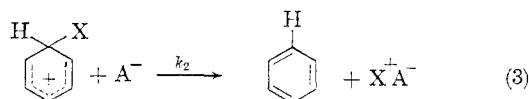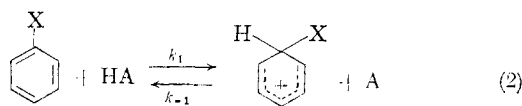
a formyl group or the boronic acid function. When X is an isotope of hydrogen the transition states for reaction 2 forward and reaction 3 should have nearly identical compositions and configurations. This means that A^- must contribute to both transition states to the same extent. For detritiation k_{-1} will be expected to exceed k_2 by a factor of ten or so because of the zero point energy difference in the carbon–hydrogen and carbon–tritium bonds. As a result, the mechanism falls in the A-2 category. General acid catalysis, greater rates in deuterium oxide than in protium oxide, and correlation of rates in isotopic solvent mixtures by the equilibrium Gross–Butler equation would be expected, and are observed. When X is the $-B(OH)_2$ function one would expect k_2 to exceed k_{-1} because of the lower energy of the carbon–boron bond as compared with the carbon–hydrogen bond. The proton transfer is now rate determining and the reaction should show a kinetic solvent isotope effect with $k_H > k_D$, correlation of rates in isotopic solvent, mixtures by the slow-proton-transfer Gross–Butler equation, and general acid catalysis; these are observed. When X is the formyl group the reaction may take on either set of characteristics depending on the structure of the substrate and on reaction conditions.

The fact that the rate of protodeboronation, which follows the A-SE2 mechanism, is correlated by the acidity function is not suprising in the present state of our knowledge.[1,11] According to the Zucker–Hammett hypothesis[11,12] one would expect rates of A-2 reactions like protodedeuteration to be correlated by the hydronium ion concentration, contrary to the fact that correlation with the acidity function is observed. However, doubts concerning the applicability of the hypothesis have arisen recently. Of particular significance is the observation of Archer and Bell[13] that the

(11) F. A. Long and M. A. Paul, *Chem. Revs.*, **57**, 935 (1957).

(12) L. Zucker and L. P. Hammett, *J. Am. Chem. Soc.*, **61**, 2791 (1939).

(13) G. Archer and R. P. Bell, *J. Chem. Soc.*, 3228 (1959).

rate of bromination of acetone, a well-established example of the A-2 mechanism, is correlated by the acidity function, contrary to earlier reports.

The reason for the change in the kinetic solvent isotope effect from 3.7 for p-methoxybenzeneboronic acid in 6.31 M sulfuric acid to 1.65 for 2,6-dimethoxybenzeneboronic acid in 0.1 M perchloric acid is not clear. One possible explanation follows from the observation of general acid catalysis. In dilute perchloric acid only the hydronium ion is present as an acid; in 6.31 M sulfuric acid a high concentration of bisulfate ion is present and can function as an acid. Indeed, it would be expected to participate because its ionization constant is only about 50% smaller than that of phosphoric acid. A greater isotope effect would be expected for a weak acid than for a strong acid. This has been clearly shown by Long and Watson[14] who found that in proton transfer to the anion derived from 3-methylpentane-2,4-dione the values of k_H/k_D for acetic acid and hydronium ion are 5.6, and 1.1, respectively.

Experimental

Isotope Effects in Sulfuric Acid.—Solutions of deuterium sulfate in deuterium oxide were prepared by the method of Schubert and Burkett.[15] The sulfur trioxide was obtained by distillation from oleum containing 20% sulfur trioxide. Despite precautions taken to keep moisture out, the sulfur trioxide condensed as a silky white crystalline solid. The solution of deuterio acid contained 43.85% deuterium sulfate; its density at 25° was 1.442, and its concentration 6.316 M. A sulfuric acid solution containing 45.73% sulfuric acid, density 1.354, hence 6.313 M in acid, was also prepared. Combination of equal volumes led to a contraction of 0.032%, so volume changes were neglected when these solutions were mixed.

In making up kinetic runs with these solutions, boronic acid was added to one or the other, and the mixture was shaken for a few minutes. Since the rate of solution was rather slow, supernatant was carefully removed with a pipet and added to an appropriate volume of the other solution for the kinetic experiment. Even though a significant amount of protodeboronation may have occurred by this time, it caused no complications. The remainder of the kinetic procedure was as previously described.[1]

Isotope Effects in Dilute Perchloric Acid.—Solutions of acid were prepared by adding concentrated perchloric acid (70.9%) to deuterium oxide (99.5%). Thus a very slight dilution of the deuterium with hydrogen resulted. The boronic acid was dissolved in water, appropriate volumes of the solutions were mixed at zero time, and the procedure described before was then followed.[1]

(14) F. A. Long and D. Watson, *ibid.*, 2019 (1958).

(15) W. M. Schubert and H. Burkett, *J. Am. Chem. Soc.*, **78**, 64 (1956).