Kinetic Isotope Effects upon the Hydrolysis of Pyridine Arylboranes[1]

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Abstract: The deuterium kinetic isotope effect for the hydrolysis of a series of pyridine arylboranes was measured. The results indicate that both a normal (>1) primary and an inverse (1<) secondary isotope effect are probably involved in the rate-determining process. A correlation was found between the boron-hydrogen stretching frequency of the arylborane and the kinetic isotope effect on the hydrolysis of pyridine *p*-$XC_6H_4BH_2$. The k_H/k_D values and the stretching frequencies are *p*-Cl, $k_H/k_D = 0.924 \pm 0.002$, $\nu_{B-H} = 2353$; *p*-H, $k_H/k_D = 0.966 \pm 0.008$, $\nu_{B-H} = 2345$; *p*-CH_3, $k_Hk_D = 1.147 \pm 0.006$, $\nu_{B-H} = 2331$; *p*-CH_3O, $k_H/k_D = 1.406 \pm 0.022$, $\nu_{B-H} = 2326$ cm^{-1}. The value of k_H/k_D increases as the strength of the boron-hydrogen bond (or the stretching frequency) decreases.

The primary kinetic isotope effect for the breaking of an X–H *vs.* the breaking of an X–D bond in the transition state of a reaction will be generally greater than one. This is because of the differences in vibrational energies of the ground and transition states.[3,4] The inverse isotope effect (<1) first was encountered in the hydrolysis of sodium borohydride.[5–9] The isotope effect of 0.70 in water at 25° was ascribed to the presence in the transition state of a *large inverse secondary deuterium* isotope effect.

An attempt was made by Kibby[6,10] to determine the kinetic isotope effect for the hydrolysis of trimethylamine borane. The value of k_H/k_D as determined from *separate determinations* of the uptake of acid on a pH-Stat of both the hydrogen and deuterium compounds was 1.0. It was found by mass spectral evidence that

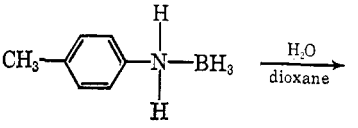
$$(CH_3)_3NBH_3 \xrightarrow[H_2O]{H^+} (CH_3)_3NH^+ + H_3BO_3 + 3H_2 \quad (1)$$

$$(CH_3)_3NBD_3 \xrightarrow[H_2O]{H^+} (CH_3)_3NH^+ + H_3BO_3 + 3H_2 \quad (2)$$

(deuteride is exchanged into the bulk of the hydrogens of the solvent)

the gas produced in the reaction of undeuterated trimethylamine borane[11] with D_2O–DCl *was* D_2, *not HD*. Pure trimethylamine borane-d_3 could be extracted from the reaction mixture. The kinetic isotope effect of *one* was due to rapid exchange of the deuterated trimethylamine borane. This ruled out the previous postulation[10] that it was due perhaps to fortuitous canceling of the primary and secondary isotope effects.

Kelly[12] has found k_H/k_D for *p*-toluidine borane hydrolysis was 1.0 at 25° in dioxane-water solvent. Under the conditions of no added acid, the rates of *p*-toluidine borane hydrolysis and that of *p*-toluidine borane-d_3 were identical as measured by separate experiments. Isolation of material from the reaction of *p*-toluidine borane-d_3 after 50% reaction allowed the determination by infrared analysis that no boron–hydrogen stretching frequency absorptions were detectable while the B–D stretching frequencies were strong.



$$CH_3\text{–}C_6H_4\text{–}NH_2 + H_3BO_3 + 3H_2 \quad (3)$$

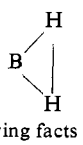
The lack of exchange under the hydrolysis conditions outlined is not true at lower pH. In 0.14 *M* acid (after 35% solvolysis) the ratio of boron hydride to boron deuteride stretching absorptions was 0.8. The results were interpreted to mean that no boron–hydrogen bond breaking was occurring in the transition state. A mechanism consistent with the kinetic isotope effect was proposed by Kelly to involve the heterolytic cleavage of the boron–nitrogen bond in an irreversible rate-determining step.

The hydrolysis of pyridine diphenylborane was investigated by Lewis.[13] The reaction has a primary isotope effect of $k_H/k_D = 1.4$ in aqueous acetonitrile solution.

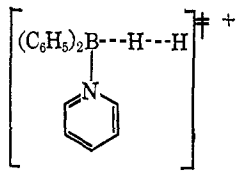
$$(C_6H_5)_2BH\cdot C_5H_5N \xrightarrow{H_2O} (C_6H_5)_2BOH + H_2 + C_5H_5N \quad (4)$$

The value of ρ for the reaction[14] was found to be -1.52. The reaction rate expression is consistent with a hydride transfer[15] occurring in the transition state (5). The

(1) Boron Hydrides. XIII. Paper XII: R. E. Davis and R. E. Kenson, in press.
(2) (a) Alfred P. Sloan Fellow 1962–1966; (b) Purdue Research Foundation XL Fellow, 1964–1965. Taken from the Ph.D. thesis, June 1965.
(3) K. E. Wiberg, *Chem. Rev.*, **55**, 713 (1955).
(4) F. H. Westheimer, *ibid.*, **61**, 265 (1961).
(5) R. E. Davis and C. G. Swain, *J. Am. Chem. Soc.*, **82**, 5949 (1960).
(6) R. E. Davis, C. L. Kibby, and C. G. Swain, *ibid.*, **82**, 5950 (1960).
(7) R. E. Davis, E. Bromels, and C. L. Kibby, *ibid.*, **84**, 885 (1962).
(8) R. E. Davis, *ibid.*, **84**, 892 (1962).
(9) R. E. Davis and J. A. Gottbrath, *ibid.*, **84**, 895 (1962).
(10) C. L. Kibby, Ph.D. Thesis, Purdue University, 1964.
(11) R. E. Davis, A. E. Brown, R. Hopmann, and C. L. Kibby, *J. Am. Chem. Soc.*, **85**, 487 (1963).
(12) H. C. Kelly, F. R. Marchelli, and M. B. Giusto, *Inorg. Chem.*, **3**, 431 (1964).
(13) E. S. Lewis and R. H. Grinstein, *J. Am. Chem. Soc.*, **84**, 1158 (1962).
(14) M. F. Hawthorne and E. S. Lewis, *ibid.*, **80**, 4296 (1958).
(15) It is generally assumed[16] that hydride transfer reactions have triangular transitions states. In the present case the two extremes would be B–H–H and



We wish to point out the following facts which have not received much comment.

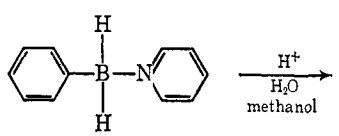


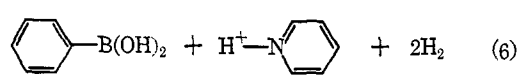
(5)

value of k_H/k_D is that of a primary boron hydride deuterium iosotope effect of the proper direction and magnitude expected for a partial transfer of the hydride in the transition state. The isotope effect was found to be independent of temperature over a 50° temperature range. However, the technique of measuring the thermal conductivity of the gases released by the reaction probably contains a degree of error that may obscure small changes in the isotope effect with temperature.

The Present Study

The kinetic isotope effects in borane hydrides are quite remarkable. Sodium borohydride has a k_H/k_D value of 0.70. Trimethylamine borane has a value of 1.00. Pyridine diphenylborane has a value of 1.4. To assume that the increase in the effect is related *only* to the decrease of the number of hydrogens atoms (4, 3, and 1) is very naive. Kibby[10] studied the hydrolysis





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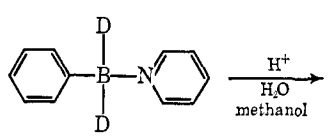
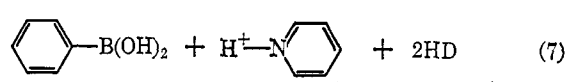




(7)

(mass spectrum)

of pyridine phenylborane. The k_H/k_D value, as determined by Kibby by separate measurements of the acid uptake during hydrolysis on a Radiometer pH-Stat instrument, was 0.95 ± 0.04. The gas was HD from reaction 7. These intriguing results led to the present study.

The bending force constant[17] of the linear B-H-H system would be quite small in the transition state, perhaps as low[18] as (0.01 to 0.03) × 10^5 dynes/cm. Since the force constant measures the second derivative of the energy surface, a *very low force constant* means a *very shallow potential energy surface* with only slowly rising sides. Therefore, the amplitude of the motion of that central H atom would be so large and the motion of the terminal H so large that *most of the time* the "linear B-H-H" would be a distorted triangle. It is still true that the energy minimum for the system would be the linear form.

(16) E. S. Lewis and M. C. R. Symons, *Quart. Rev.* (London), 12, 230 (1958); see pp 244–247.

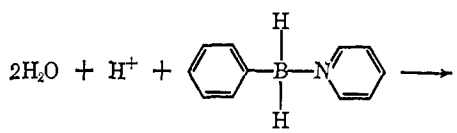
(17) G. Herzberg, "Infrared and Raman Spectra of Polyatomic Molecules," D. van Nostrand Co., Inc., New York, N. Y., pp 168–183, 192–209.

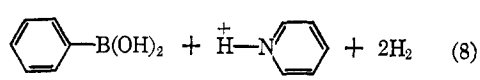
(18) Detailed calculations on the borohydride transition state using the force fields of BH_4^- and of BH_5 are in good agreement with observed isotope[10] effects and the temperature dependence from −100 to + 50°. The B-H-H bending force constant is 0.01 × 10^5 dynes/cm (R. E. Kenson and R. E. Davis, unpublished data reported in the Ph.D. thesis of R. E. Kenson).

The pyridine arylborane system was used then to examine the interaction of the primary and secondary deuterium isotope effects for boron hydride hydrolysis reactions. The pyridine *p*-X-phenylboranes (where X is chloro, hydro, methyl, and methoxy) were prepared in high purity by procedures of Hawthorne.[19] The deuterium compounds were also prepared. Thereby the electronic effect of these groups *para* to boron upon the kinetic isotope effect could be examined to determine more about the nature of the secondary isotope effect for a single boron–hydrogen or boron–deuterium bond stiffening. Arguments can be presented against the determination of isotope effects by separate measurements for small isotope effects as the error limits may be higher than the deviation of the isotope effect from unity; therefore, all isotope effects were measured by competitive means. To ensure accurate results, the relative rates were determined mass spectrometrically by analysis of the gases evolved from the H_2/HD ratio.

Results

The hydrolysis reaction of pyridine phenylborane has a stoichiometry





(8)

and a rate expression

$$\text{rate} = k_2[H^+][\text{borane}] \quad (9)$$

The rates were determined using the ultraviolet absorption. Typical raw data are presented in Table I. The activation energy of 8.9 kcal/mole for the hydrolysis reaction of pyridine phenylborane was calculated from the rate constant of the reaction at 10, 30, and 45°. In Table II the data are reported. The plot of log k_1 against $1/T$ was linear. The plot of log k_1 of X against Hammett σ_X, the slope of which is the ρ value for the hydrolysis reaction, is a curved line with the same curvature (Figure 1) as in Figure 2.

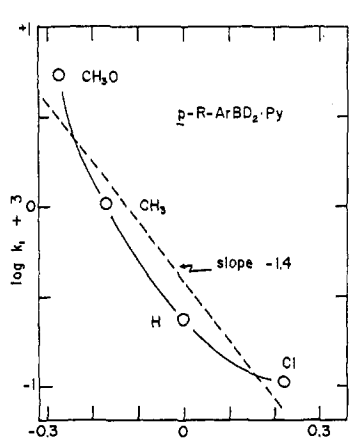


Figure 1. Plot of log k *vs.* the Hammett σ constants.

(19) M. F. Hawthorne, *J. Am. Chem. Soc.*, 80, 4292 (1956).

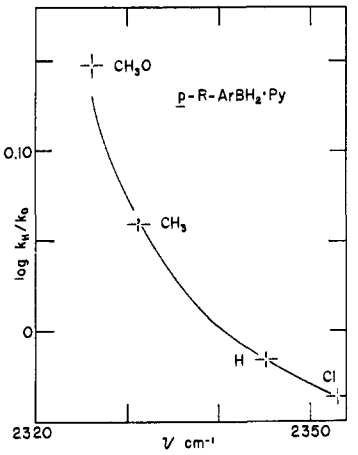


Figure 2. Plot of log k_H/k_D *vs.* the B–H stretching frequency.

The nonvolatile products of the hydrolysis reaction are pyridine and phenylboronic acid. Hawthorne[14] identified the acid by the melting point of material extracted from a reaction mixture. The ultraviolet spectra of the products of a hydrolysis reaction and a mixture of pyridine and phenylboronic acid are superimposable.

For the determination of k_H/k_D values for the pyridine arylboranes, the competitive method obviates there being error in k_H/k_D due to a difference of conditions of the two reactions. Only three quantities are required, the H_2/HD ratio for the total mixture (R_0), the ratio (R_i) for the product gases up to the time t and to

Table I. Rates of Reaction of Pyridine Phenylborane-d_2[a]

Time, sec	A	$A_\infty - A$
340	0.758	0.392
420	0.780	0.392
660	0.790	0.360
800	0.817	0.333
1000	0.841	0.309
4800	1.034	0.125
4850	1.035	...
∞	1.150	...

[a] Typical raw data obtained at λ 280 mμ at 30° at pH 6.86.

infinity (R_t). Time t is an arbitrary time period which does not have to be an initial rate time period, and does not appear in the k_H/k_D expression of Bigeleisen and Wolfsberg.[20]

$$k_H/k_D = 1 + \frac{\log (R_t/R_0)}{\log [(R_i - R_0)/(R_i - R_t)]} \quad (10)$$

Enough measurements of each R value were made to determine a standard deviation for the measurements. These error limits were used to calculate the maximum error of k_H/k_D by substituting the extreme values of the R's into the k_H/k_D expression and determining k_H/k_D. The deviations in each direction were averaged, and the error limits of the k_H/k_D values were thereby established. Table III contains the R_0, R_i, and R_t values for typical kinetic experiments, the standard deviation of each value of R, the value of k_H/k_D calculated, and its error limits.

(20) J. Bigeleisen and M. Wolfsberg, *Advan. Chem. Phys.*, 1, 15 (1958).

Table II. Kinetic Results for Pyridine Phenylborane Hydrolysis

	Temp, °C[b]	k sec^{-1} [c]	pH[d]
Pyridine phenylborane[a]	30	2.44×10^{-4}	6.86
	10	8.40×10^{-5}	6.86
	45	4.82×10^{-4}	6.86
	30	1.61×10^{-3}	5.89
Pyridine *p*-chlorophenylborane	30	1.1×10^{-4}	6.86
	30	1.02×10^{-3}	5.87
Pyridine *p*-methylphenylborane	30	1.05×10^{-3}	6.86
	30	2.53×10^{-4}	7.50
Pyridine *p*-methoxyphenylborane	30	5.44×10^{-3}	6.86
	30	2.5×10^{-3}	7.20
	30	1.01×10^{-3}	7.55

[a] k_1 at 25° for pyridine phenylborane at pH 6.86 is 1.9×10^{-4} sec^{-1} and E_a is 8.9 kcal/mole. ρ value for reaction is −1.40. [b] ±0.02° (NBS). [c] First-order rate constants: ±4%, average σ. Each number is an average of numerous trials. [d] pH in the buffer with some THF added. Plots of log k *vs.* pH are linear with slopes of −1; thus the rate expression is rate = $k_2(H^+)$(arylpyridine borane).

The determination of k_H/k_D's in this manner overcame problems that were encountered in noncompetitive means of following the rates of the pyridine arylboranes and their deuterated analogs. Volumetric means of measuring the amount of gas produced on a Warburg apparatus failed to give consistent results. The small order of magnitude of the isotope effects illustrates why noncompetitive techniques will not be as precise as competitive measurements. The difference between the isotope effects of pyridine phenylborane and pyridine *p*-chlorophenylborane is only 4%.

The infrared spectra of the pyridine arylboranes were obtained and are presented in Table IV. The boron–hydrogen and boron–deuterium stretching modes correlate with the values of k_H/k_D while no such correlation exists for the bending modes. Figure 2 is a free energy plot of the log of k_H/k_D for the pyridine arylboranes against the boron–hydrogen stretching frequency for each arylborane. As k_H/k_D *increases*, the strength of the boron–hydrogen or boron-deuterium bond decreases, as does the frequency of vibration of the bond. The plot is not linear, but describes a gently curving line. The curvature is rather like that in Figure 1.

Discussion

The isotope effect for the hydrolysis of the pyridine arylboranes varies over a small range from 0.92 to 1.41. An inverse isotope effect (less than one) is found for the pyridine *p*-chloro- and *p*-hydrophenylboranes. The shift to a normal isotope effect (greater than one) begins with pyridine *p*-methylphenylborane and the isotope effect is highest for pyridine *p*-methoxyphenylborane. The value of 1.41 for k_H/k_D of pyridine *p*-methoxyphenylborane equals the pure primary isotope effect for the hydrolysis of pyridine diphenylborane.[13] The trend of k_H/k_D follows the order of Hammett σ constants for the *para* substituents. For σ greater than that of hydrogen (>0.0) the isotope effect is less than one, while for σ less than that of hydrogen (<0.0) the isotope effect is greater than one. The kinetic isotope effect trend for this system indicates a fine balance of electronic and vibrational effects upon the transition state of the hydrolysis reaction.

The hydrolysis reaction of the arylboranes has a ρ value of about −1.4, indicating a need for increased

Table III. The k_H/k_D Values for the Hydrolysis of the Pyridine Arylboranes[a]

X	H[b]	Cl[c]	CH_3[d]	CH_3[e]	CH_3O[f]
R_0	0.6990 ± 0.0027	1.159 ± 0.002	1.055 ± 0.004	1.004 ± 0.004	0.2662 ± 0.0006[g]
R_i	0.6802 ± 0.0028	1.116 ± 0.013	1.177 ± 0.004	1.160 ± 0.005	0.3366 ± 0.0091
R_t	0.7112 ± 0.0005	1.288 ± 0.001	1.005 ± 0.004	0.9463 ± 0.004	0.2087 ± 0.0022
k_H/k_D	0.966 ± 0.008	0.924 ± 0.002	1.141 ± 0.004	1.153 ± 0.006	1.408 ± 0.022[h]

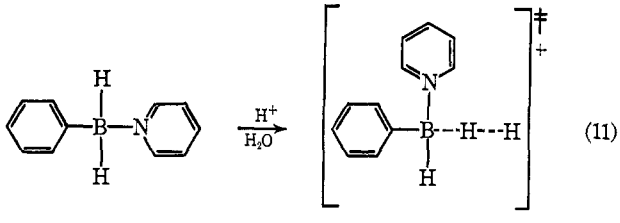
[a] Typical experimental data for pyridine *p*-X-phenylboranes; temperature 25.00 ± 0.01° (NBS). [b] Typical results. Each number is the average of 27 measurements. [c] Average of 23 measurements. [d] Average of 25 measurements. [e] Same experiment as *d* only another gas sample was taken much later in the reaction, average of 25 measurements. [f] Average of 16 measurements. [g] Standard deviation of each measurement is reported following the measurement. [h] Method of calculation of the uncertainty for the isotope effect is discussed in the text. It is best described as equivalent to a 95% confidence limit.

Table IV. Infrared Spectra of the Pyridine Arylboranes in CCl_4 for the B^{11} Isotope

Pyridine *p*-X-phenylborane	B-H stretch[a]	B-H bend[a]
Cl	2353	1109
H	2345	1107
CH_3	2331	1110
CH_3O	2326	1110
Pyridine *p*-X-phenylborane-d_2	**B-D stretch[a]**	**B-D bend[a]**
Cl	1786-1701[b]	901-876
H	1781-1694	899-874
CH_3	1776-1689	901-879
CH_3O	1773-1688	903-876

[a] Frequencies are in wavenumbers (cm^{-1}). [b] Each band is a doublet. Spectra were recorded with the compounds (1% by mass) dissolved in carbon tetrachloride. The instrument was a Perkin-Elmer 221 high-resolution instrument and calibrated against the standard gases (HCl, HBr, and CO_2). We wish to thank Professor W. Edgell and the spectroscopy laboratory for obtaining these precise values.

electron density at the reaction center in the transition state. The fastest rate for this acid-catalyzed reaction is for pyridine *p*-methoxyphenylborane. This compound has the most hydridic boron–hydrogen bonds. The value of ρ and k_H/k_D for the reactions is evidence



(11)

for the transition state. The correlation of the stretching frequency (*rather than the bending frequency*) of the boron–hydrogen bonds with k_H/k_D indicates the transition state *may involve a linear B–H–H configuration.*[15] The least hydridic boron–hydrogen bonds would be found in pyridine *p*-chlorophenylborane, which, of course, has the slowest rate of hydrolysis.

If the log of k_H/k_D is plotted against the boron–hydrogen stretching frequency (in cm^{-1}), a gently sloping curve is obtained (Figure 2). Thus the isotope effect is correlated with the strength of the boron–hydrogen bond. The same effect is noted for the boron–deuterium stretching frequencies. As the stretching frequency *increases*, the k_H/k_D value *decreases*. The effect of a *para* group is therefore an electronic effect upon the vibrations of the boron–hydrogen and boron–deuterium bonds. This effect is illustrated in the diagrams where the resonance and bond polarization effects of the *para* groups upon the ground and transition states are given for both pyridine *p*-chlorophenylborane and pyridine *p*-methoxyphenylborane. The over-all isotope effects can be explained on the basis of these models if we assume that the primary isotope effect by itself is affected very slightly by the *para* substituent. The electronic effect would then be upon the secondary isotope effect, where the stiffening of this secondary bond causes the inverse kinetic isotope effect. In the case of the parent compound (pyridine phenylborane) the secondary isotope effect is predominant. The electron-withdrawing *p*-chloro group (eq 12 and 13) would give a more inverse isotope effect if the contribution of the secondary bond stiffening were increased by the presence of this group. The effect of the boron–hydrogen bond weakening *p*-methoxy group is to minimize the stiffening of the secondary bond in the transition state. The k_H/k_D value for this borane (1.41) is very close to the value obtained by Lewis[13] for the hydrolysis of pyridine

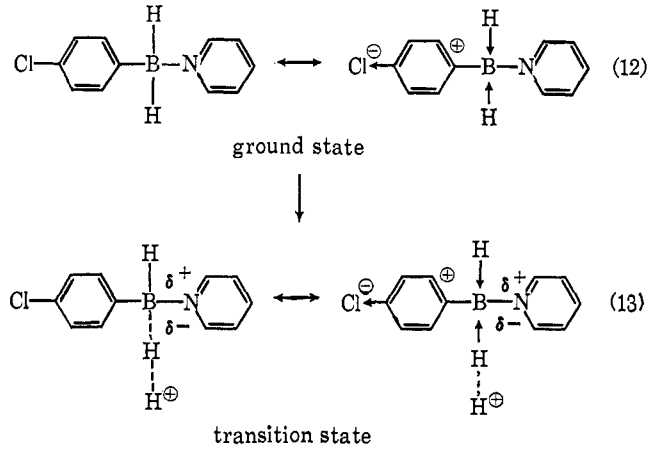


Table V. Preparation and Properties of Pyridine Arylboranes

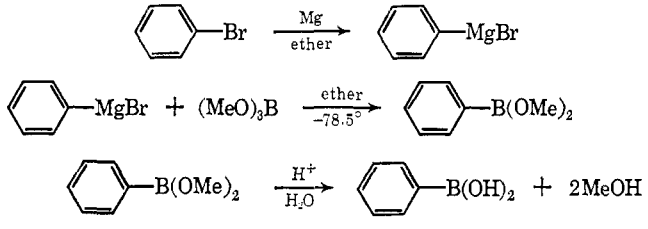
Compound	Ester used, g	Product, g	Yield, %	Mp, °C[a]	Isotopic purity, %[b]	Ultraviolet spectra, λ_{max}, mμ
Pyridine phenylborane	9.8	3.0	33	80		228, 256, 260, 268, 287
Pyridine phenylborane-d_2	10.0	3.2	32	81	98	
Pyridine *p*-chlorophenylborane	17.1	9.0	45	61		230, 255, 261, 268, 298
Pyridine *p*-chlorophenylborane-d_2	10.1	0.65	6	63	99	
Pyridine *p*-methylphenylborane	*c*			65.5		230, 256, 262, 268, 300
Pyridine *p*-methylphenylborane-d_2	*c*			64	99	
Pyridine *p*-methoxyphenylborane	17.5	3.94	20	75		230, 256, 260, 268, 300
Pyridine *p*-methoxyphenylborane-d_2	24.6	5.8	21	76	96	

[a] Capillary tube method. Melting rage 0.5–0.7° (on calibrated thermometers checked against our NBS thermometers). Temperature reported is the midpoint of this narrow melting range. Satisfactory carbon, hydrogen, and nitrogen analyses were obtained on all of these compounds. However, these represent a good judge of purity in these compounds. [b] Based on deuterium analysis of the HD and H_2 produced upon hydrolysis. [c] Prepared previously in this laboratory by C. L. Kibby.[10]

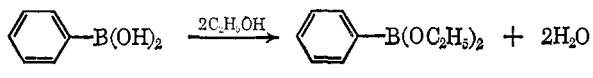
diphenylborane (k_H/k_D = 1.4) where a pure primary boron–hydrogen, bond-breaking, isotope effect is involved in the transition state. If it is assumed that the transition states are very similar (ρ is −1.4 for the hydrolysis of pyridine phenylboranes, −1.5 for pyridine diphenylboranes), then the *p*-methoxy group decreases the activation energy difference between the boron–hydrogen and boron–deuterium secondary bond stiffening in the transition state so that the predominant isotope effect is the primary one.

Experimental Section

Materials. The pyridine arylboranes were prepared by procedures of Hawthorne.[14,19] For pyridine phenylborane, bromobenzene (78 g, 0.5 mole) was treated with 12 g (0.5 g-atom) of magnesium turnings in 250 ml of dry ether. The Grignard reagent was added dropwise under dry nitrogen with vigorous stirring to a solution of 52 g of methyl borate in 250 ml of dry ethyl ether at −78°. After addition, the reaction was warmed to room temperature by allowing the coolant to evaporate overnight. The reaction was cooled to 0° and 2 *M* hydrochloric acid was added. The ether solution was separated, washed three times with water, and dried over magnesium sulfate. The ether was evaporated *in vacuo* with a Rinco flash evaporator to yield the crude phenylboronic acid (35 g, 57% of theory). The same procedures were followed with 96 g of 4-chlorobromobenzene to yield 49.2 g of 4-chlorophenylboronic acid or 62% of theory; 85 g of 4-methylbromobenzene yielded 42.4 g of 4-methylphenylboronic acid, 55% of theory; and 93 g of 4-bromoanisole yielded 48.6 g of 4-methoxyphenylboronic acid, 64% of theory.



Phenylboronic acid (30 g, 0.25 mole) was refluxed for 24 hr with 160 g of dry benzene and 70 g of absolute ethanol. The azeotrope of benzene, water, and ethanol was distilled. After the azeotrope was removed, the pressure was reduced and the ester (diethyl phenylboronate) distilled. The yield of ester was 10.6 g (23% of theory). The same procedure was followed using 36 g of *p*-chlorophenylboronic acid to yield 17.1 g of diethyl *p*-chlorophenylboronate, 33% of theory; 21 g of *p*-tolylboronic acid to yield 0.27 g of diethyl *p*-tolylboronate, 0.2% of theory; and 35 g of *p*-anisylboronic acid to yield 6.7 g of diethyl *p*-anisylboronate, 13% of theory.



Lithium aluminum hydride (2.5 g) was dissolved in 500 ml of dry ether at reflux under dry nitrogen. The solution was cooled to −78° and 10 ml of dry pyridine was added. Diethyl phenylboronate (0.06 mole) dissolved in 70 ml of dry ether was added slowly with vigorous stirring. After addition, the coolant was removed and the reaction brought to room temperature. A solution of 5 ml of pyridine and 12 ml of water was added with cooling by an ice bath. The solid was removed by filtration and the solvent removed *in vacuo* with a Rinco flash evaporator. The solid material was removed and recrystallized from an ether–pentane solution. The yield of pyridine phenylborane was 3 g, or 33% of theory. The same procedure and amount of diethyl phenylboronate was used with 2.7 g of lithium aluminum deuteride to prepare 3.2 g of pyridine phenylborane-d_2. Table V is a tabulation of the amount of ester used for the preparation of each pyridine arylborane, the yield, and the melting point of the pyridine arylborane.

The purity of the compounds was checked by two techniques. The reducing power of the borane was measured by a method of Jensen[21] and the purity of the compound expressed as the percentage of the theoretical reducing power that the borane possessed. The deuterated compounds were hydrolyzed in light water. The isotopic purity from the H_2/HD ratio was determined by mass spectral analysis. The results of these determinations are given in Table V. The infrared spectra of the compounds were analyzed on a Perkin-Elmer 221 infrared, high-resolution spectrophotometer under identical conditions.

Mixtures of the deuterated and hydrogenated pyridine arylboranes were prepared by dissolving equal amounts of each in a 1:1 mixture of ether–pentane and recrystallizing to obtain a homogeneous mixture of the two. The white crystals were filtered, ground with a mortar and pestle to a fine powder, and then dried *in vacuo*.

Tetrahydrofuran was Baker Analyzed reagent or Mallinckrodt reagent grade containing less than 0.01% water and peroxide free. Buffers were prepared from reagent grade potassium dihydrogen phosphate and potassium hydroxide solution which was standardized by titration with standard potassium acid phthalate. The buffers were made up to μ = 0.440. Standard perchloric acid was prepared from 85% perchloric acid (G. Frederick Smith and Co.) diluted to 1 *M* and titrated with potassium hydroxide solution.

Procedures. The kinetic procedure for k_H/k_D was to weigh out a sample of the mixed isotopic boranes of about 5 mg on a Cahn Electrobalance to ±0.01 mg. This was placed in a reaction vessel and 5 ml of tetrahydrofuran added to dissolve the sample. Two side arms to the reaction vessel contained 15 ml of phosphate buffer (pH 6.66 or 6.72) and 10 ml of 1 *M* base, respectively. The vessel was attached to a vacuum line and the system degassed by freeze–thaw techniques.

The temperature of the solutions was brought to 25.00 ± 0.01°. The buffer was transferred *in vacuo* into the tetrahydrofuran and the reaction stirred by a magnetic stirrer. After a time *t*, the reaction was quenched with the base solution. After freezing the solution, the gas evolved during the reaction was pumped into a sample bulb, then analyzed on a CEC Model 201-21 isotope ratio mass spectrometer. The reaction was brought to completion by addition of 0.15 ml of perchloric acid to the side arm, degassing again by the freeze–thaw method, and mixing the solutions. After an appropriate time the solution was frozen and another gas sample

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taken for mass spectral analysis. For fast-reacting pyridine arylboranes 3 hr was sufficient, while 8 hr were taken for the slow-reacting pyridine arylboranes. Enough measurements were taken for each sample to determine a standard deviation of the measurement.

The same procedure was followed for total hydrolysis reactions, except the solution in the first side arm was 15 ml of 1 *M* perchloric acid, and the reaction was run to completion. The solution was frozen and a gas sample taken for mass spectral analysis.

The ultraviolet spectra of the compounds were examined in base solutions containing 25% tetrahydrofuran. The spectra were determined on a Perkin-Elmer Spectronic 505 recording ultraviolet spectrophotometer and are given in Table V. The rates of the hydrolysis of the pyridine arylboranes were studied using a Beckman DU ultraviolet spectrophotometer. This spectrphotometer was equipped with a brass cooling block for the cells through which water from a constant temperature flowed to maintain the proper temperature (±0.02°). The change of the pyridine arylborane absorption at 275 to 280 mμ was used to follow the reaction. Plots of log $(A_\infty - A)$ gave (*vs.* time) straight lines for runs in buffer solutions, thus showing first-order dependence in substrate.

Samples were dissolved in Eastman tetrahydrofuran that was distilled from calcium hydride and run through alumina to remove peroxides. The solution of 1–4 ml was diluted to 25 ml with a buffer of pH 6.86 prepared from 0.025 *M* each of potassium dihydrogen phosphate and disodium hydrogen phosphate.

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Neighboring N-Carboxyalkyl Group Participation in the Hydrolysis of Phthalimide[1]

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Contribution from the Chemistry Department of the Florida State University, Tallahassee, Florida. *Received March 18, 1966*

Abstract: A number of new 3- or 4-nitrophthaloyl-ω-amino acids have been synthesized. The effect of N-carboxyalkyl substitution on intramolecular hydrolysis of imides near neutrality has been investigated. A pH-rate profile for phthaloylglycine revealed that the rate of hydrolysis between pH 2 and 7 depends upon the degree of ionization of the carboxyl group. The magnitude of the enhancement of the rate of hydrolysis of an imide linkage by a neighboring carboxylate indicates that the neighboring group can be an intramolecular catalyst for hydrolysis of imide.

Intramolecular catalysis of the hydrolysis of phthalimide by a carboxyl group has been established for *o*-carboxyphthalimide by Zerner and Bender.[4] Neighboring carboxyl groups may influence the hydrolysis of polyimides generated by thermal copolymerization of aspartic acid with amino acids.[5,6] Because the kinetics of hydrolysis of such polyimides is complex, we selected phthaloyl derivatives of some amino acids as models for investigating the influence of an N-alkylcarboxy group on the hydrolysis of a cyclic imide. Intramolecular catalysis of ester hydrolysis by a neighboring carboxyl group has received considerable attention for some time.[7–12] Carboxyl groups have also been assigned roles in the mechanisms of action of several enzymes.[11,13,14]

This report will show that a carboxylate group linked through an alkyl group to the phthalimide nitrogen atom may participate as an anionic intramolecular catalyst in the hydrolysis of the imide ring.

Experimental Section

Characterization. Uncorrected melting points were determined with the Mel-Temp apparatus. Elemental analyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Acids were titrated potentiometrically with potassium hydroxide solution. Imide linkages were quantitatively hydrolyzed at constant pH with the same base, using a pH-Stat. When hydrolysis of an imide interfered with titration of an acid, total base consumed for neutralization of the carboxyl group and for hydrolysis of the imide was used for characterization.

Materials. A general procedure was employed for synthesis of imides.[15–17] An equimolar mixture of dicarboxylic acid anhydride and amino acid was fused under reduced pressure above 150° for about 1 hr. In Table I are listed the nitrophthaloylamino acids synthesized. The following derivatives were prepared: phthaloylglycine, mp 194–195° (lit.[18] 192–194°); phthaloyl-β-

(1) Contribution No. 082 of the Institute for Space Biosciences, The Florida State University, Tallahassee, Fla.

(2) From the Ph.D. dissertation of P. D. Hoagland, 1964.

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