observations previously reported by Crandall and Keyton[5] concerning the reaction of 6-bromo-1-phenyl-1-hexyne with lithium biphenyl.

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial support of this research. Rui-lian Shao was a visiting research scholar from 1980 to 1982 under auspices of the Indiana University–Nankai University (The People's Republic of China) Exchange Program.

Registry No. Hg, 7439-97-6; $C_4H_9C{\equiv}C(CH_2)_4\cdot$, 40215-73-4; $C_4H_9C{\equiv}C(CH_2)_4Hg\cdot$, 86669-18-3; $C_4H_9C{\equiv}C(CH_2)_4I$, 42049-41-2; $C_4H_9C{\equiv}C(CH_2)_4Br$, 35843-78-8; $C_4H_9C{\equiv}CC_4H_9$, 1942-46-7; $C_4H_9C{\equiv}C(CH_2CH{=}CH_2$, 82511-32-8; $C_4H_9C{\equiv}C(CH_2)_4OH$, 68274-97-5; $[C_4H_9C{\equiv}C(CH_2)_4]_2Hg$, 86669-20-7; diethyl 5-decynylmalonate, 86669-19-4.

Solvent Isotope Effects on the Kinetics of Nucleophilic Addition of Water to a β-Nitrostyrene

Thomas I. Crowell

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

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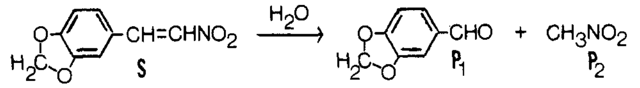
The hydrolysis rate of 3,4-(methylenedioxy)-β-nitrostyrene (S) has been measured in H_2O and in 99% D_2O buffer solutions from pH −0.9 to 10.6. The kinetic solvent isotope effect (KSIE), $k(H_2O)/k(D_2O)$, is 6.2 at pH 2.5, where k is independent of pH in both solvents and attains a higher value, approximately 22, at about pH 6.2. The isotope effects $k_i(H_2O)/k_i(D_2O)$ on the rate constants for the individual steps of the mechanism have been determined and their contributions to the overall KSIE evaluated. Accordingly, the KSIE on the pH–rate plateau at pH 1–4 can be separated into two factors: 5.0 for K_{12}, the ionization constant of S as a pseudo-base in water; and 1.4 for k_3^H, the rate constant for rate-controlling protonation of the resulting anion by H_3O^+. At pH 6.2, the higher KSIE (7.6) on $k_3^{H_2O}$ becomes important while the uncatalyzed addition of water to the double bond is partly rate controlling. The rate at the midpoint of a proton-inventory plot (49.5% D_2O) shows a negative deviation from linearity of 18%.

When β-nitrostyrenes act as substrates in nucleophilic addition reactions in aqueous solutions, the retro-Knoevenagel process, hydrolytic cleavage, takes place.[1-5] In our last paper,[4] we reported the rate of hydrolysis of 3,4-(methylenedioxy)-β-nitrostyrene (S), at pH 1-11, to the products P_1 and P_2.



The anion[6] T_{OH^-} (Scheme I), readily formed by addition of hydroxide ion to S, was identified by its reversion to S after a pH jump. The nitro alcohol T_{OH} was prepared and used for direct observation of some of the intermediate reactions. The rate of condensation of the products P to form T_{O^-} was determined.[4]

In D_2O, the hydrolysis of S shows a rather large kinetic solvent isotope effect (KSIE). The object of this research was to measure the KSIE over a wide pH range and to separate the overall effect into KSIE's for the successive steps in the mechanism. The results support the previously proposed mechanism in which hydration of S occurs prior to the steps involving acid–base catalysis.

Results

In all experiments except one at pH 12, noted below, the rate of disappearance of the olefin S was followed by the decrease in its UV absorption. We define the initial rate coefficient[7] k by $dS/dt = -kS$. Above pH 6, k is easily obtained since the reaction is first order. At lower pH, the cleavage of the intermediate T_{OH} is no longer fast compared with its reversion to S and the kinetics are characteristic of first-order consecutive reactions (eq 1).

$$S \underset{k_{-123}}{\overset{k_{123}}{\rightleftharpoons}} T_{OH} \xrightarrow{k_{45}} P \tag{1}$$

The uppermost set of points in Figure 1, for example, shows the decrease in nitrostyrene concentration with time, plotted as $\ln(S_0/S)$, in 0.0032 M HCl. The value of k can be obtained by estimating the initial slope of the curve, by approximation methods[8] or by programming and fitting the exact solution[9] to the rate equations for eq 1. Since the last procedure is necessary for D_2O solutions, which cause an earlier decrease in slope than H_2O, it was used in all three parallel runs at $[L^+] = 0.0032$, pL 2.5,[10] shown in Figure 1. The same value of k_{45}, 1.5×10^{-7} s^{-1}, sufficed to fit all three, suggesting that the KSIE on the rate of cleavage of T_{OH} is small, though this could be more reliably determined by using the nitro alcohol T_{OH} itself as the substrate.[4] The equilibrium constant k_{123}/k_{-123} for the best fit was approximately 0.46 in H_2O and 0.15 in D_2O;[11] the mean value 0.30 was chosen for HDO. The rate constants k_{123} for these three particular runs were then computed: 1.64×10^{-7} s^{-1} in H_2O, 7.5×10^{-8} s^{-1} in HDO, and 2.5 ×

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(1) Stewart, R. *J. Am. Chem. Soc.* **1952**, *74*, 4531.
(2) Boileau, J. Thesis, University of Paris, 1953.
(3) Crowell, T. I.; Francis, A. W. *J. Am. Chem. Soc.* **1961**, *83*, 591.
(4) Crowell, T. I.; Kim, T.-R. *J. Am. Chem. Soc.* **1973**, *95*, 6781.
(5) Bernasconi, C. F.; Carré, D. J.; Kanavarioti, A. *J. Am. Chem. Soc.* **1981**, *103*, 4850.
(6) The notation of Bernasconi (ref 5 for example) is used in place of our previous notation (ref 4): T_{OH^-} for A_1^-, T_{OH} for 2, $T_{OH}^{O^-}$ for A_2^- and $T^{\pm}$ for $A^{\pm}$.
(7) k is the same as k_ψ in ref 4; k_{123} is the rate constant encompassing steps 1–3 in Scheme I, etc.
(8) McDaniel, D. H.; Smoot, C. R. *J. Phys. Chem.* **1956**, *60*, 966.
(9) Frost, A. A.; Pearson, R. G.; "Kinetics and Mechanism"; Wiley: New York, 1953; pp 162–163.
(10) L represents hydrogen, whether H or D.
(11) "D_2O" used as solvent throughout this work was 99.0% D_2O, 1.0% CH_3OH; "HDO" was 49.5% D_2O, 49.5% H_2O, 1.0% CH_3OH.

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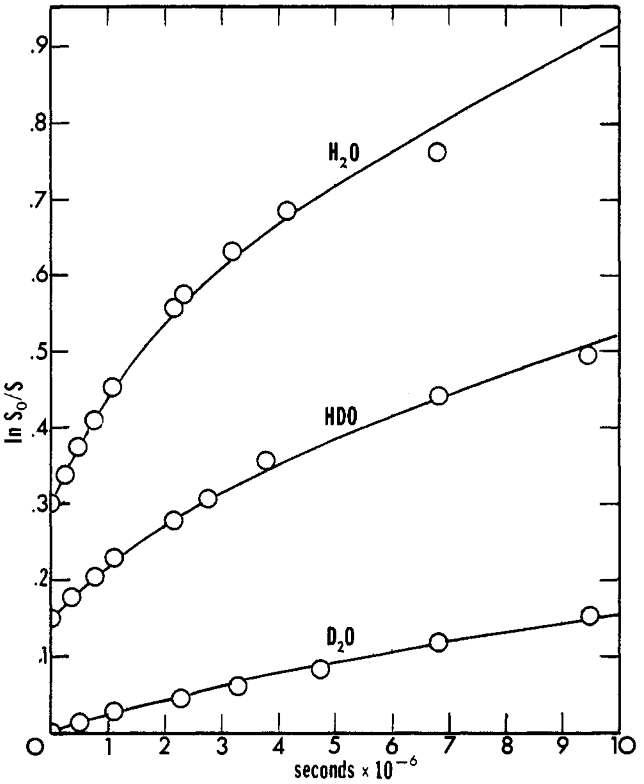

Figure 1. Solvent isotope effect on rate of decrease of nitrostyrene concentration at pL 2.5. Curves fitted to the experimental points by the rate equation for eq 1 as described in text. The HDO set is displaced upward 0.15 log unit, the H_2O set 0.30 log unit.

10^{-8} s^{-1} in D_2O. The curves in Figure 1 are calculated[9] with these rate constants for comparison with the experimental points shown.

Three runs with each of these three solvent compositions gave the following average values of k (s^{-1})[12] at 25 °C: H_2O 1.61×10^{-7}, HDO 7.7×10^{-8}, and D_2O 2.60×10^{-8}. The average deviations from the mean were 2%, 4%, and 5%, respectively. The KSIE, $k(H_2O)/k(D_2O)$, is 6.2 at pL 2.5.

The upper curve in Figure 2 shows our previous results[3,4] (open circles) for log $k(H_2O)$ as a function of pH and several new ones (half-shaded circles) used to check and extend the data. The dark circles represent the values of log k in 99% D_2O at the given pD (Table I). The points on both curves at pL 2.5 are the log k's calculated from the runs of Figure 1 as described above.

Below pH 2, the hydrolysis shows acid catalysis in D_2O to the extent that log k in 3.6 M D_2SO_4 is within 0.1 log unit of log k in 3.6 M H_2SO_4. No further work was done on the acid-catalyzed reaction. (In 3.6 M H_2SO_4, λ_{max} was increased from 372 nm to 377 nm in the UV spectrum of S, due either to a medium effect or to protonation of an appreciable fraction of the substrate.)

Buffer catalysis was observed in D_2O at pH 4–8.5 as it was in H_2O. The rate constants plotted in Figure 2 in this range have been extrapolated to zero buffer concentration. The slope of a plot of k vs. acetate ion concentration at pD 4.3 is 4×10^{-5} M^{-1} s^{-1} in D_2O as compared with 2×10^{-4} M^{-1} s^{-1} in H_2O,[3] a KSIE of about 5 on the catalytic constant.

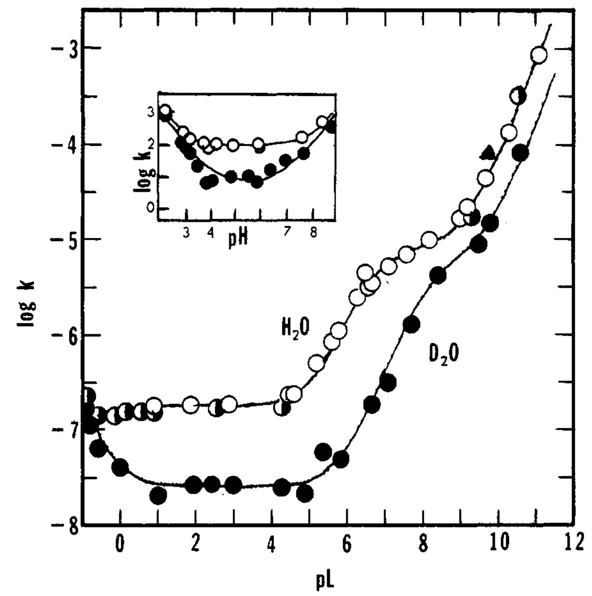

Figure 2. Log k vs pL for the nitrostyrene S in D_2O (dark circles) and in H_2O (shaded circles, this research; open circles, ref 3 and 4). The inset shows the similar plot for the exchange of methoxide between methanol and methyl borate (ref 20, the dark circles designating rates with CH_3OD).

Table I. Rate Constants for Addition of Water to 3,4-(Methylenedioxy)-β-nitrostyrene in 99% D_2O at 25 °C

pD	buffer	molarity	k, s^{-1}
−0.9	D_2SO_4	3.6	1.7×10^{-7}
−0.8	D_2SO_4	2.9	1.2×10^{-7}
−0.6	D_2SO_4	1.8	6.3×10^{-8}
0.0	D_2SO_4	0.50	4.0×10^{-8}
1.0	DCl	0.10	2.0×10^{-8}
1.9	DCl	0.13	2.6×10^{-8}
2.5	DCl	0.0031	2.6×10^{-8}
3.0	DCl	0.0010	2.6×10^{-8}
4.3	acetate	1–20[a]	2.6×10^{-8}
4.9	phthalate	1–5	2.2×10^{-8}
5.4	acetate	1–5	6.0×10^{-8}
5.86	acetate	1–3	5.0×10^{-8}
6.65	phosphate	0.9–1.8	1.8×10^{-7}
7.10	phosphate	0.9–1.8	3.2×10^{-7}
7.70	phosphate	0.9	1.3×10^{-6}
8.42	borate	1.7–10	4.3×10^{-6}
9.50	borate	10	9.1×10^{-6}
9.80	borate	4–10	1.5×10^{-5}
10.60	borate	10	8.3×10^{-5}

[a] Range of buffer base concentrations, mmol/L; k extrapolated to zero buffer concentration.

Above pH 9 both curves rise with slopes of 1 due to nucleophilic attack of hydroxide ion on S to form T_{OH^-}. Although the rate in D_2O at any pD is lower than in H_2O at that pH, this is irrelevant to the interpretation involving hydroxide ion: the concentrations of OH^- and OD^- are different at the same pL, due to the variation of pK_W with isotopic composition of the solvent (14.00 in H_2O and 14.88 in D_2O at 25 °C).[13] The triangle in Figure 2 shows the pD 10.6 value of log $k(D_2O)$ plotted against 14 + log $[OD^-]$ as abscissa. This has moved the point 0.88 log unit to the left from its position on the log k vs pD plot so that it now has the same abscissa (9.78) as points in the H_2O set with the same hydroxide ion concentration (6.0×10^{-5} M) rather than the same hydrogen ion concentration. Because the triangle is above the H_2O line the KSIE on k_1^{OH} for the nucleophilic addition of hydroxide ion to S is inverse though small.

At pH 12, conversion of S to T_{OH^-} is practically complete in 600 s. The rate of the ensuing protonation of T_{OH^-} to

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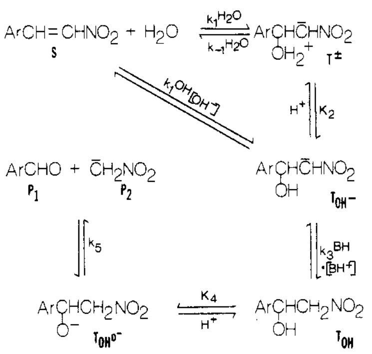
[12] k is equal to k_{123} at low pH, where nucleophilic addition by OL^- is negligible.

[13] Bell, R. P. "The Proton in Chemistry", 2nd ed.; Chapman and Hall: London, 1973; p 233.

Scheme I



T_{OH} can then be measured by following the increase in piperonal (P_1) concentration, since T_{OH} cleaves extremely rapidly at this pH.[14] The first-order rate constant for the formation of P_1 from S, interpreted as $k_3^{H_2O}$, the specific rate of protonation of T_{OH^-} by water molecules, was found to be 1.40×10^{-3} s^{-1}, in agreement with our published value based on the same experiment.[4] Duplicate determinations in D_2O gave $k_3^{D_2O} = 1.84 \times 10^{-4} \pm 0.04$ s^{-1} and $k_3^{H_2O}/k_3^{D_2O} = 7.6$.

Discussion

We have interpreted the kinetics of hydrolysis of S at low pH as a preequilibrium with water, followed by protonation of anion T_{OH^-} to the nitro alcohol (Scheme I).[4] The assumption that the hydration step, with rate constant $k_1^{H_2O}$, can become rate controlling when protonation step 3 is fast explains the fact that the slope of a plot of k vs. buffer base concentration progressively decreases.[3] The limiting value of k in such a plot corresponds to the height of the shoulder in the pH–log k profile.[4] Since there seems to be no reason why acetate buffers in aqueous solution should inherently give rise to nonlinearity,[15] we continue to assume that addition of water takes place in two steps and must determine whether this is consistent with the observed KSIE.

The rate constant k for the decrease in S by the mechanism of Scheme I is given by the steady-state eq 2, provided $T^{\pm}$ and T_{OH^-} do not accumulate. The data points above pH 1 for D_2O solutions were fitted by eq 2 to give the lower curve in Figure 2. The separately determined value of $k_3^{D_2O}$ was fortunately available and the rates at high pD gave k_1^{OD}, leaving three constants to be derived from the level of the plateau and the shape of the curve from pH 5 to 9.5: $k_1^{D_2O}$, the forward rate constant for attack of water on the α-carbon atom; k_3^{D}, the specific rate of protonation of T_{OD^-} by D_3O^+; and the ratio $k_{-1}^{D_2O}/K_2$. The constants so obtained are given in Table II for comparison with the previously published values for H_2O solutions. A term $k_6[H^+]$ with $k_6 = 2 \times 10^{-8}$ M^{-1} s^{-1} accounts for the observed acid catalysis below pH 1 in D_2O.

$$k = k_1^{OH}[OH^-] + \frac{k_1^{H_2O}(k_3^{H}[H^+] + k_3^{H_2O})}{(k_{-1}^{H_2O}/K_2)[H^+] + k_3^{H}[H^+] + k_3^{H_2O}} \tag{2}$$

Each of these rate constants for D_2O shows a KSIE comparable with known or expected values: (a) $k_1^{H_2O}$ for formation of the unionized hydrate $T^{\pm}$ would show only a secondary isotope effect, in agreement with the observed ratio 1.39. (b) The ratio k_3^{H}/k_3^{D} for protonation of T_{OH^-} is 1.44. Similar low isotope effects for proton transfers from L_3O^+ to delocalized anions were first noted by Maron and LaMer;[16] Bernasconi, Carré, and Kanavarioti found k_3^{H}/k_3^{D} to be 1.85 for the carbon protonation of the T_{OH^-} species derived from 1,1-dinitro-2,2-diphenylethylene.[5] (c) The much higher KSIE for protonation of T_{OH^-} by water, $k_3^{H_2O}/k_3^{D_2O} = 7.6$, is of the magnitude expected for proton transfers and may be compared with 5.5 for the corresponding value in the system cited above.[5]

Table II. Rate Constants for Nitrostyrene Hydrolysis in H_2O and D_2O

rate constant, k_i	k_i-(H_2O)	k_i-(D_2O)	KSIE	Δ_i log k[a] pL 3	Δ_i log k[a] pL 6.2
k_1^{OH}, M^{-1} s^{-1}	0.69	1.25	0.55	0.00	0.00
$10^6 k_1^{H_2O}$, s^{-1}	8.2	5.9	1.39	0.14	0.14
$10^2 k_3^{H}$, M^{-1} s^{-1}	1.80	1.25	1.44	0.16	0.00
$10^3 k_3^{H_2O}$, s^{-1}	1.40	0.184	7.6	0.00	0.61
$10^3 k_{-1}/K_2$, M^{-1} s^{-1}	0.80	2.84	0.28	0.54	0.40
				0.84[b]	1.15[b]
$10^7 k$, s^{-1} (pL 3)	1.82[c]	0.26	7.0[c]	0.84[d]	
(pL 6.2)	19.0	0.87	22		1.34[e]

[a] The change in log k produced by substituting $k_i(H_2O)$ for $k_i(D_2O)$ in eq 2. [b] Sum of Δ_i log k at given pL. [c] Calculated from eq 2; differs slightly from experimental value at pL 2.5. [d] Log 7.0. [e] Log 22.

The last quantity to be discussed is (d) the observed KSIE of 0.28 on $k_{-1}^{H_2O}/K_2$. To rationalize this result, we divide $k_1^{H_2O}/K_w$ by $k_{-1}^{H_2O}/K_2$, obtaining $(k_1^{H_2O}K_2)/(k_{-1}^{H_2O}K_w)$, which is equivalent to K_{12}^{OH} for the nucleophilic addition of hydroxide ion to S. Performing the corresponding operation on the KSIE's, using 7.5 for the solvent isotope effect on the ionization constant of water,[13] we find $1.39/[(7.5)(0.28)] = 0.66$ for the SIE on K_{12}^{OH} calculated from the observed isotope effect on $k_{-1}^{H_2O}/K_2$. This inverse SIE on the *equilibrium* constant for eq 3 is compatible with the observed KSIE of 0.55 on the *rate* constant for the same process, since the transition state for the addition of the strong nucleophile has undergone considerable electron reorganization and resembles the product.

$$S + OH^- \overset{K_{12}^{OH}}{\rightleftharpoons} T_{OH^-} \tag{3}$$

The foregoing comparisons show that the variation of the solvent isotope effect on the overall k can be explained in terms of the mechanism of Scheme I. In particular, observation a provides additional evidence for the uncatalyzed hydration step $k_1^{H_2O}$.

The large KSIE on log k shown in Figure 2 may be regarded as arising from contributions, Δ_i log k (Table II), from the component rate constants. For example, at pL 3 in the region of pH independence the chief contribution, 0.54 log unit, is from k_{-1}/K_2 with smaller ones from $k_1^{H_2O}$ and k_3^{H}. The combination of these three isotope effects is responsible for the large difference in log k in the two solvents on the low-pH plateaus. At this pH, moreover, step 3 is rate controlling so that

$$k = K_{12}^{H_2O}k_3^{H}$$

where the KSIE's on the last two constants are 5.0 and 1.44.

At pL 6.2, the KSIE on $k_3^{H_2O}$ assumes major importance while k_3^{H} is negligible in its effect on k. Fairly large contributions from k_{-1}/K_2 and $k_1^{H_2O}$ bring the isotope effect on the overall k to 22. While this value is so high as to be unusual, especially for a *solvent* isotope effect, it is easily

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(14) Reference 4, eq 3.

(15) Hand, E. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1975**, *97*, 6221.

(16) Maron, S. H.; LaMer, V. K. *J. Am. Chem. Soc.* **1938**, *60*, 2538.

understood in terms of its component rate constants, which are of more fundamental significance than the experimentally visible k.

The inset in Figure 2 shows the pH dependence of a large KSIE for another reaction involving nucleophilic addition to a moderately electrophilic center: the exchange of methoxide between methyl borate and methanol.[17] In this case also, the largest KSIE, which is between the regions of lyonium and lyate catalysis, appears where k is less pH dependent.

In 49.5% D_2O, the value of k, 7.7×10^{-8} s^{-1}, is 18% lower than the mean of the rate constants in H_2O and in D_2O, all at pL 2.5. This negative deviation from linearity of the Gross–Butler plot is not unexpected, since the transition state involves more than one transient proton.[18]

Experimental Section

Materials. 3,4-(Methylenedioxy)-β-nitrostyrene (S) was prepared according to Lange and Hambourger[19] and recrystallized from ethanol. Deuterium oxide (Aldrich Chemical Co. Gold Label, 99.8 atom % deuterium) was used without further purification.

Procedure. Kinetic runs were started by adding 1 mL of a 3×10^{-5} M solution of S in reagent-grade CH_3OH (containing 10^{-3} M hydrochloric acid to inhibit solvolysis) to the H_2O or D_2O buffer and diluting to 100 mL or equivalent proportions. The volumetric flask was sealed with Parafilm before it was placed in the thermostat. Fast runs were performed in the temperature-controlled compartment of a Beckman Model DU spectrophotometer. The nitrostyrene concentration was followed at its absorption maximum, 372 nm.

The pH meter was calibrated by adding measured quantities (up to 0.36 mL) of 0.11 M sodium hydroxide to 25 mL of boiled H_2O or D_2O, under a stream of nitrogen, in a Pyrex three-necked flask previously treated with boiling nitric acid. The glass electrode was introduced and a reading taken for each increment of sodium hydroxide. The measured pH for 10^{-4} to 10^{-3} M sodium hydroxide solutions was within 0.07 pH unit of the correct value, $14.00 + \log [OH^-]$. In D_2O, the measured pD (0.4 + pH meter reading)[18] differed from the calculated value of $14.88 + \log [OD^-]$ by 0.07 unit (average of four determinations). These observations confirmed the relationship between pH meter reading and hydroxide ion concentration in the buffer solutions.

Acknowledgment. I appreciate the advice and encouragement of Dr. Thomas H. Cromartie.

Registry No. S, 1485-00-3; D_2D, 7789-20-0; D, 7782-39-0; D_2SO4, 13813-19-9; DCl, 7698-05-7; OH, 14280-30-9; acetate, 71-50-1; phthalate, 3198-29-6; phosphate, 14265-44-2; borate, 14213-97-9.

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[17] Hutton, W. C.; Crowell, T. I. *J. Am. Chem. Soc.* **1978**, *100*, 6904.

[18] Schowen, K. B. J. In "Transition States of Biochemical Processes"; Gandour, R. D., Schowen, R. L., Eds., Plenum: New York, 1978; Chapter 6.

[19] Lange, N. A.; Hambourger, W. E. *J. Am. Chem. Soc.* **1931**, *53*, 3865.

Decarboxylative Ipso Halogenation of Mercury(II) Pyridinecarboxylates. Facile Formation of 3-Iodo- and 3-Bromopyridines[1]

Sakae Uemura, Sakuya Tanaka, and Masaya Okano*

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

Masatomo Hamana

Faculty of Pharmaceutical Sciences, Kyushu University, Maidashi, Fukuoka 812, Japan

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Treatment of mercury(II) nicotinate with iodine and bromine in nitrobenzene at 180–185 °C for 2 h afforded 3-iodo- and 3-bromopyridines in 44% and 27% yields, respectively, without any regioisomers and dihalopyridines. From mercury(II) picolinate only 2–3% of 2-bromopyridine was obtained under similar reaction conditions, while the reaction using mercury(II) isonicotinate did not give any products. When a mixture of nicotinic acid and HgO was used in place of mercury(II) nicotinate, the halodecarboxylation occurred with similar ease. An ionic pathway involving the initial attack of electrophilic Hg(II) species on the ring-C bearing carboxyl group to afford a 3-pyridylmercury(II) compound and the subsequent replacement of the Hg(II) moiety by electrophilic iodine and bromine was proposed for this reaction.

Electrophilic halogenation of pyridine itself with halogens is known to be difficult because of the electron-deficient nature of the pyridine ring.[2] Very high temperature and/or strong acidic conditions are generally required for the reaction, and in most cases the desired 3-halopyridines are formed in low yields and are accompanied by considerable amounts of 3,5-dihalopyridines.[2,3] During the study of developing a facile method for halopyridines we found that the treatment of mercury(II) nicotinate, out of various metal salts of pyridinecarboxylic acids, with iodine and bromine in nitrobenzene afforded 3-iodo- and 3-bromopyridines, respectively, in moderate yields under comparatively mild conditions without the formation of any of regioisomers and dihalopyridines. A similar reaction also proceeded by using nicotinic acid, HgO, and halogen. We report here the details of this decarboxylative ipso halogenation and discuss its probable reaction scheme briefly.

Results and Discussion

Reaction of Mercury(II) and Thallium(I) Pyridinecarboxylates with Halogens. Various metal salts of picolinic, nicotinic, and isonicotinic acids and nicotinic acid

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[1] Presented in part at the 13th Congress of Heterocyclic Chemistry, Shizuoka, Japan, 1980.

[2] See, for example: (a) "Rodd's Chemistry of Carbon Compounds", 2nd ed.; Coffey, S., Ed.; Elsevier: Amsterdam, 1976; Vol. IV, Part F, p 84. (b) Acheson, R. M. "An Introduction to the Chemistry of Heterocyclic Compounds", 3rd ed.; Wiley: New York, 1976; pp 236–239.

[3] Recently, a facile method for bromination and chlorination of pyridine by using pyridine-$PdCl_2$ complex was reported, although we could not reproduce the experimental data: Paraskewas, S. *Synthesis* **1980**, 378.