[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Kinetics and Mechanism of the Reaction of Hydrogen Bromide with Ethanol

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The reactivity of alcohols toward halogen acids has been investigated by several authors[1-3] and shows qualitatively the same variation with structure as the rate of solvolysis of alkyl halides in the presence of dilute base.[4] The operation of a bimolecular mechanism A and of a unimolecular mechanism B just as for alkyl halides[4] seems logical.

$$ROH + HX = ROH_2^+ + X^-$$

$$(A)\quad X^- + ROH_2^+ \xrightarrow{k_2} X{-}R + OH_2$$

$$(B)\quad ROH_2^+ \xrightarrow[k_1]{\text{slow}} R^+ + OH_2$$

$$R^+ + X^- \xrightarrow{\text{fast}} R{-}X$$

The existing data, particularly the sensitivity of the rate to the nature of X and to steric hindrance[5] in R, strongly suggest the predominance of mechanism A in the reaction of primary alcohols with halogen acids. However, apparently there is no clear-cut kinetic verification of this mechanism recorded in the literature to date.

In connection with other work on the alcoholysis of halides[6] we had occasion to measure the rate of disappearance of hydrogen bromide in dry ethanol at 54.95°. The results of these measurements are significant with respect to the above general question and are reported in the present article.

The kinetic work of previous investigators[1-3,7,8] shows that in the kinetic analysis of the reaction of halogen acids with alcohols, there are the following difficulties: (1) the decrease in ionic strength during the reaction; (2) the production of water during the reaction; (3) the solvolysis of the alkyl halide produced in the reaction. Since the present measurements deal with very dilute solutions of hydrogen bromide, the effect of the small amount of water produced during the reaction (less than 0.007 M) may be neglected. On the other hand, the alcoholysis of ethyl bromide (specific rate k_3) occurs at a rate comparable to that of the main reaction and must be considered in the kinetic analysis. Fortunately the specific rate k_3 can be determined independently so that this reaction does not introduce an additional parameter into the kinetic expression.

The pertinent kinetic data are summarized in Table I. Here as well as in all subsequent Tables, concentrations have been corrected for solvent expansion. The initial first-order rate constants for the alcoholysis of ethyl bromide (calculated as described in a later section) are listed in Table II. It is clear from this Table that k_3 increases but slightly with ionic strength, in good agreement with the results of McCleary and Hammett[9] on the hydrolysis of ethyl bromide in aqueous dioxane.

TABLE I

REACTION OF HYDROGEN BROMIDE WITH ETHANOL SOLVENT, 54.95°

Run 1. a = 0.01491 M		Run 2. a = 0.00576 M	
t, hr.	10^3y	t, hr.	10^3y
0.00	14.91	0.00	5.76
15.66	13.29	18.32	5.25
39.59	11.42	42.25	4.83
64.20	10.00	64.05	4.40
107.3	8.07	109.8	3.77
134.3	7.13	136.9	3.47
156.3	6.51	187.6	3.00
184.0	5.96	210.4	2.85
228.0	5.22	231.6	2.71

TABLE II

SUMMARY OF SPECIFIC RATES OF ETHANOLYSIS OF ETHYL BROMIDE, 54.95°

C_2H_5Br, b	$NaClO_4$, M	$10^7 k_3$, sec.$^{-1}$
0.1004	....	2.38
.1768	....	2.36
.0911	0.0706	2.49

Equations 1 and 2 are rate-laws applicable under our experimental conditions in case of the

$$-dy/dt = k_2y^2 - k_3(a - y) \quad (1)$$

$$-dy/dt = k_1y - k_3(a - y) \quad (2)$$

exclusive operation of mechanisms A and B, respectively. In these equations, a and y are the concentrations of hydrogen bromide initially and at time t. The slow step of mechanism B is of such a charge-type[4a] that k_1 is expected to decrease slightly with increasing ionic strength μ. On the other hand, k_2 is the specific rate of reaction between two oppositely charged univalent ions ($Br^- + C_2H_5OH_2^+$) and is expected to decrease markedly with ionic strength, the slope $d(\log k_2)/d\mu^{1/2}$ approaching the limiting value predicted by the Debye–Brönsted theory[10] at low ionic strengths.

In order to deduce whether the mechanism of the reaction is predominantly bimolecular (A) or

(1) Levene and Rothen, *J. Biol. Chem.*, **81**, 359 (1929).
(2) (a) Bennett and Mosses, *J. Chem. Soc.*, 2956 (1931); (b) Bennett and Reynolds, *ibid.*, 131 (1935).
(3) Norris, *Rec. trav. chim.*, **48**, 887 (1929).
(4) (a) Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941); (b) Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1269 (1937).
(5) Dostrovsky, Hughes and Ingold, *ibid.*, **173**, (1946).
(6) Winstein and Grunwald, THIS JOURNAL, in press (1947).
(7) Kilpi, *Z. physik. Chem.*, **141A**, 424 (1929); **166A**, 285 (1933).
(8) Hinshelwood, *J. Chem. Soc.*, 599 (1935).
(9) McCleary and Hammett, THIS JOURNAL, **63**, 2260 (1941).
(10) Glasstone, "Textbook of Physical Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1940, pages 942, 1096.

unimolecular (B) values of k_2 and k_1 were calculated at various hydrogen bromide concentrations from equations 1 and 2. The derivative dy/dt was obtained with satisfactory precision for a number of values of y from the nearly linear plot of $1/y$ *vs.* t with the aid of a tangent meter. For k_3, the value 2.37×10^{-7} was used (Table II). The results of the calculation are summarized in Table III.

TABLE III

KINETICS OF REACTION OF HYDROGEN BROMIDE WITH ETHANOL, 54.95°

$10^3\ y$	$10^6\ k_1$, sec.$^{-1}$	$10^4\ k_2$, sec.$^{-1}\ M^{-1}$	$10^3\ y$	$10^6\ k_1$, sec.$^{-1}$	$10^4\ k_2$, sec.$^{-1}\ M^{-1}$
14.91	1.95	1.31	5.76		2.37
12.14		1.39	5.03	1.19	2.36
10.24		1.57	4.47		2.46
8.74		1.79	4.02		2.70
7.57		1.96	3.63		2.84
6.69	1.32	1.98	3.31		2.94
6.03		2.01	3.05		2.97
5.50		2.23	2.84	0.89	3.14

The great increase in the values of k_1 with hydrogen bromide concentration (Table III) indicates that the reaction is not predominantly unimolecular (mechanism B). On the other hand, the decrease in the values of k_2 with hydrogen bromide concentration is qualitatively correct for a bimolecular mechanism. A plot of $\log k_2$ *vs.* $y^{1/2}$ is linear, and equation 3—obtained by the method

$$\log k_2 = -3.185 - 6.14y^{1/2} \qquad (3)$$

of least squares using the data in Table III for which $y^{1/2}$ is less than 0.1—fits the experimental values of k_2 with a mean deviation corresponding to an experimental error of 3%. The observed slope $d(\log k_2)/dy^{1/2}$ of -6.14 agrees well with the limiting slope $d(\log k_2)/d\mu^{1/2}$ of -6.76 predicted by the Debye–Brönsted theory.[10,11] The small discrepancy between the two slopes, *ca.* 10%, is in the expected direction and of a reasonable order of magnitude. Thus the conductance data of Bezman and Verhoek[12] in ethanol at 25° indicate that hydrogen chloride in 4×10^{-3} M solution is only about 90% dissociated and that at this ionic strength the activity coefficients of the dissociated ions deviate slightly from values calculated by the limiting theory.

Although the data are not sufficiently accurate, and the ionic strengths employed not sufficiently low, to definitely rule out the presence of a small amount of unimolecular reaction, the preceding discussion indicates that the reaction proceeds very predominantly by the bimolecular mechanism A.

Experimental

Materials.—Dry ethanol was prepared from commercial absolute alcohol by the ethyl formate method.[13] It contained less than 0.02% of water by Robertson's paraffin-oil test.[13]

Hydrogen bromide was generated by dropping bromine into refluxing tetralin. The gas was passed through a cold-trap, a naphthalene tower, and a drying tower filled with anhydrous calcium sulfate.

Ethyl bromide was fractionated through an efficient column; b.p. 37.7–37.8° (750 mm.).

Rate Measurements.—Rates were measured by the usual sealed ampule technique. Titrations were carried out with 0.05 N base from a 5-ml. microburet, using brom thymol blue as indicator. The probable error of the titrations is estimated at 0.008 ml. Special precautions were taken in the ethyl bromide runs to keep the vapor space in the ampules less than 1 ml. The initial concentrations of ethyl bromide were obtained by treating aliquots of the reaction mixture with 2 M sodium hydroxide and titrating the liberated bromide ion argentimetrically.

Kinetics of Alcoholysis of Ethyl Bromide.[14]—In Table IV are given typical kinetic data on the initial rate of alcoholysis of ethyl bromide in dry ethanol at 54.95°. K_3 calculated by equation 4

TABLE IV

ETHANOLYSIS OF ETHYL BROMIDE AT 54.95°, b = 0.1004 M

t, hr.	$10^3\ y$	$10^7\ K_3$, sec.$^{-1}$
19.88	1.637	2.29
27.80	2.336	2.35
43.97	3.61	2.32
49.0	3.94	2.27
68.1	5.00	2.08
73.1	5.39	2.10

for a first-order reaction (b = initial concentration of ethyl bromide), drops slightly during the run due to the reaction of the liberated hydrogen

$$K_3 = -\frac{1}{t}\ln\left(1 - \frac{y}{b}\right) \qquad (4)$$

bromide with the ethanol. The specific rate of alcoholysis, k_3, was obtained by extrapolation of the K_3 values to $y = 0$. It was found that a plot of K_3 *vs.* y^2 is linear to a fair approximation, and the intercept k_3 was obtained from the data with the aid of equation 5 by the method of least

$$K_3 = k_3 - my^2 \qquad (5)$$

squares. It is evident from the data in Table II that values of k_3 are satisfactorily reproducible.

Summary

The kinetics of the reaction of hydrogen bromide with ethanol solvent at 54.95° were investigated. The reaction was found to be of the second order, first order with respect to both $C_2H_5OH_2^+$ and Br^-. The variation of the specific rate with ionic strength was shown to be in

(11) The dielectric constant of ethanol at 54.95° was calculated from the equation of Akerlof, THIS JOURNAL, **54**, 4125 (1932).

(12) Bezman and Verhoek, *ibid.*, **67**, 1330 (1945).

(13) Robertson, "Laboratory Practice of Organic Chemistry," The Macmillan Co., New York, N. Y., 1943, pages 178, 296.

(14) The assistance of Howard H. Hopper and Irwin H. Linden in these measurements is gratefully acknowledged.

quantitative accord with predictions based on the Debye–Brönsted limiting theory at ionic strengths less than 0.01 *M*.

The ethanolysis of the ethyl bromide produced in the main reaction was shown to proceed at a comparable rate at 54.95° and was considered in the kinetic analysis. The specific rate of ethanolysis of ethyl bromide was measured in independent experiments and found to be quite insensitive to changes in the ionic strength of the medium.

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Some Basically Substituted Diaryl Sulfides and Sulfones

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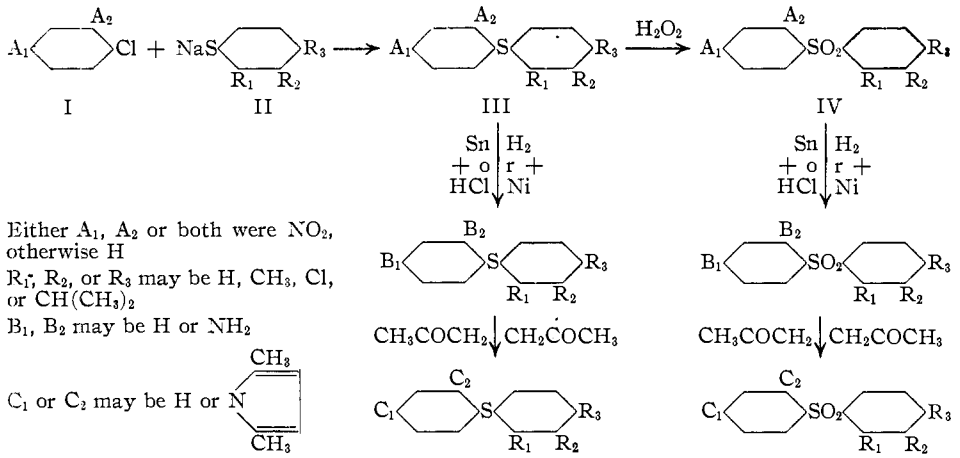
Studies on the treatment of tuberculosis by chemotherapeutic agents have disclosed that among the compounds of most promise are Diasone,[1] Promin,[2] and Promizole.[3,4] The first two of these are derivatives of 4,4′-diaminodiphenyl sulfone whereas in the last, one of the *p*-aminophenyl groups is replaced by the 2-aminothiazolyl-5 group. Moreover, early trials on the treatment of experimental avian and simian malaria with 4,4′-diaminodiphenyl sulfone[5] derivatives had been promising. It seemed likely, therefore, that other basically substituted derivatives of diphenyl sulfide and diphenyl sulfone might display activity against tuberculosis and malaria.

Accordingly, a number of 4-amino-, 2-amino- and 2,4-diaminodiphenyl sulfides and sulfones and some of their 2,5-dimethyl-1-pyrryl derivatives were prepared and submitted to chemotherapeutic tests. The other, unsubstituted, benzene ring was varied by the introduction of methyl, chloro and isopropyl groups.

By the time the compounds were ready for testing, there appeared little likelihood that a sulfanilamide type of compound would show promise as an antimalarial; therefore, these compounds were given only *in vitro* tests for potential antituberculous activity.[6]

The general scheme by which these compounds were prepared is outlined below.



The nitrochlorobenzenes, thiophenols and the thiocresols were obtained from the Eastman Kodak Company. The preparation of *o*-, *m*- and *p*-chlorothiophenol was patterned after a modification of Leuckhardt's method[7] for converting arylamines to thiophenols through the S-aryl ethyl xanthates. They were obtained in 67, 65 and 49% yields, respectively. *p*-Isopropylthiophenol was prepared from the corresponding sulfonyl chloride,[8] which has never been isolated in the pure form, by reduction with zinc and sulfuric acid in 63.5% over-all yield from cumene.

The general procedure of Bourgeois and Huber[9] was followed in condensing I and II to form III. 2-Nitrochlorobenzene generally requires one-half to one hour for complete reaction, 4-nitrochlorobenzene requires two to three hours, and 2,4-dinitrochlorobenzene requires about fifteen minutes. In the last case, more prolonged refluxing often

(1) Raiziss, *Science*, **98**, 350 (1943).

(2) Feldman, Hinshaw and Moses, *Proc. Staff Meeting, Mayo Clinic*, **15**, 695 (1940); **16**, 187 (1941).

(3) Bambas, THIS JOURNAL, **67**, 671 (1945).

(4) Feldman and Hinshaw, *ibid.*, **19**, 25 (1944).

(5) Coggeshall, Maier and Best, *J. Am. Med. Assoc.*, **117**, 1077 (1941).

(6) These tests for tuberculocidal activity were performed by Dr. Guy P. Youmans of the Northwestern University Medical School, Chicago, Illinois, and will be reported elsewhere.

(7) Schwarzenbach and Egli, *Helv. Chim. Acta*, **17**, 1176 (1934).

(8) Huntress and Autenrieth, THIS JOURNAL, **63**, 3446 (1941).

(9) Bourgeois and Huber, *Rec. trav. chim.*, **31**, 38 (1912).