[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Mechanism of Addition Reactions. A Kinetic Study of the Addition of Methyl Hypobromite to Stilbene

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In many cases the photochemical halogenation of compounds containing an ethylenic double bond is known to be a chain reaction controlled by the production of halogen atoms or excited halogen molecules.[1] Much less is known about the mechanism of the dark halogenation reaction. Recent quantum mechanical calculations[2] indicate that in the gas phase a direct addition of a bromine or iodine molecule in one step to the double bond is a plausible mechanism, leading to calculated activation energies of the right order of magnitude.

For brominations in solution, in the dark or in diffused light as carried out in organic chemical practice, neither of these mechanisms is capable of accounting for the rate of the reaction and the character of the products. In the first place, the number of cases of *trans* addition of halogens on record[3] definitely rules out the simple one-step addition as a general mechanism. In the second place, it is clear from the high energy of formation of the bromine-to-bromine linkage that bromine atoms are equally ineligible as initiators of the bromination (usually extremely rapid) of olefins in the dark.

According to the theory which has been current for some years among English organic chemists,[4] the point of attack in an ethylenic linkage is an "aninoid," "nucleophilic," or electron-donating center which exists either permanently or at the moment of reaction at one or the other of the carbon atoms attached to the double bond. With this the halogen molecule reacts as a "cationoid" or "electrophilic" reagent, the net result of the rate-controlling step being the transfer of a halogen atom with a sextet of electrons from the halogen molecule to the organic molecule. The formation of dihalide is completed by the taking up of a halide ion by the positive organic intermediate, the halide ion being either from the original halogen molecule or from some other source in the solution.

The evidence supporting this theory is largely of the cumulative sort; it takes account of the types of reagents which will and will not add to the ethylenic linkage, the orientation of their addition, the catalysts which promote such addition, the occurrence of *trans* addition, and the directing influence of substituents upon aromatic substitution. For many reasons this theory, and the new language which has developed with it, has only gradually received a hearing in this country. One of these reasons is undoubtedly the lack of specific instances in which the necessity for this type of mechanism can be clearly demonstrated. The present work arises out of a search for a case in which a kinetic study can afford definite evidence for or against a two-step mechanism for a simple addition reaction to an ethylenic double bond.

It has been observed[5] that a solution of bromine in methyl alcohol functions analogously to bromine water in that it adds the elements of methyl hypobromite to the ethylenic linkage. A careful study of this reaction was made by Meinel,[6] who applied it to a number of ethylenic compounds and studied especially the effect of the structure of the ethylenic compound upon the relative amounts of methoxy bromide and dibromide formed. Meinel established that the methoxy bromide is a primary product, in that it cannot owe its origin to a reaction between methyl alcohol and ready-formed dibromide. Meinel therefore adopted the explanation that the methoxybromide results from the action on the double bond of methyl hypobromite in equilibrium with bromine, the solvent, and hydrogen bromide. Meinel strengthened this hypothesis by showing

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(1) J. Eggert, F. Wachholtz and R. Schmidt, *Z. Elektrochem.*, **33**, 542 (1927); F. Wachholtz, *Z. physik. Chem.*, **125**, 1 (1927); Berthoud and Porret, *Helv. Chim. Acta*, **17**, 237 (1934); Bauer and Daniels, THIS JOURNAL, **56**, 378 (1934); Purkayastha and Ghosh, *J. Indian Chem. Soc.*, **2**, 261 (1925); **4**, 553 (1927).

(2) Sherman and Sun, THIS JOURNAL, **56**, 1096 (1934); Eyring, *Science*, **77**, 158 (1933); Eyring, Sherman and Kimball, *J. Chem. Phys.*, **1**, 586 (1933).

(3) Chavanne, *Compt. rend.*, **154**, 776 (1912); Kuhn and Wagner-Jauregg, *Ber.*, **61**, 519 (1928); Holmberg, *Svensk Kem. Tid.*, 1912, no. 5; *J. prakt. Chem.*, **84**, 145 (1911); Lossen and Bergau, *Ann.*, **348**, 341 (1906); Terry and Eichelberger, THIS JOURNAL, **47**, 1067 (1925).

(4) Robinson, "Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions," Institute of Chemistry of Great Britain and Ireland, London, 1932; Ingold, *Chem. Rev.*, **15**, 225 (1934).

(5) Dimroth, Schultze and Heinze, *Ber.*, **54**, 3035 (1921); Conant and Jackson, THIS JOURNAL, **46**, 1727 (1924).

(6) Meinel, *Ann.*, **510**, 129 (1934); **516**, 237 (1935).

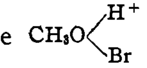
that the almost colorless solution resulting when a methyl alcoholic bromine solution is treated with silver nitrate reacts immeasurably fast with unsaturated hydrocarbons with the production of methoxy bromide. It is clear then that methyl hypobromite exists in these solutions and that it is an active addition reagent for the ethylenic linkage. It does not follow, however, without a study of the kinetics of the process, that all the methoxy bromide found actually owes its orgin to a direct addition of methyl hypobromite, rather than to a process analogous to that pictured by Robinson[4] (p. 18) for the formation of chlorohydrins. To test this point we have investigated the case of the reaction between stilbene and bromine in methyl alcohol solution, since this reaction leads to a high fraction of methoxybromide in the product (about 83% in the presence of 0.2 *M* sodium bromide and 99% in the absence of added bromide) and proceeds at a conveniently measurable rate at 0°. In non-polar solvents oxygen has been found to inhibit bromination reactions strongly.[7] An experiment showed that this is not the case with the present reaction, and no special effort was made to eliminate oxygen from the runs here described.

The addition is irreversible, neither stilbene dibromide nor stilbene methoxy bromide showing any color after some fifteen hours' standing at room temperature with potassium iodide in methyl alcohol solution. The effect of added bromide ion upon the kinetics was investigated in solutions whose ionic strength was made uniformly equal to 0.20 by supplementing the bromide present with lithium benzenesulfonate. The reaction in the absence of bromide ion is very rapid, and slows up as it progresses much more rapidly than if it were a simple bimolecular reaction. Addition of as much as 0.01 *M* sodium bromide (when the concentrations of the reactants were of the order of 0.003 *M*) diminished the reaction rate strongly and caused the reaction to follow normal second order kinetics. Further additions of sodium bromide up to 0.50 *M* steadily decreased the rate of the reaction, the total diminution in rate due to this highest concentration of sodium bromide being more than twenty-fold.

From the equation

$$Br_2 + CH_3OH \rightleftarrows CH_3OBr + H^+ + Br^-$$

it appears that if the concentration of methyl hypobromite controls the reaction rate, then an increased concentration of bromide ion, by shifting this equilibrium toward the left, would have such a retarding effect as is observed. However, since the hydrogen ion and the bromide ion enter symmetrically into this equilibrium, an increased concentration of hydrogen ion should likewise diminish the rate of reaction. We have measured the reaction rate in the presence of both sulfuric acid and hydrochloric acid of $\mu = 0.2$, and neither of these acids exhibits the expected retarding effect upon the reaction, which is of the same complex order with these acids as in the presence of lithium benzenesulfonate or in the absence of any added salt. Hydrogen bromide at 0.2 *M* concentration has approximately the same effect as sodium bromide of the same strength. These results are completely incompatible with the idea that the concentration of methyl hypobromite controls the rate of this addition reaction, and therefore also with the idea that methyl hypobromite is responsible for the formation of stilbene methoxybromide. To ascribe any role at all in this reaction to methyl hypobromite, one of two assumptions would seem to be necessary: (1) that hydrogen ion catalyzes the addition of methyl hypobromite to stilbene through a trimolecular reaction; (2) that the active addition reagent is the conjugate acid of methyl hypobromite



$CH_3O{<}^{H^+}_{Br}$

Assumption (1) is unlikely because a trimolecular reaction cannot proceed as rapidly as this one does without an extraordinarily low energy of activation, which there is no reason to expect in this case; also because it is difficult to assign any function to the hydrogen ion in such a process in the light of modern knowledge concerning acid catalytic reactions. Assumption (2) is highly improbable since it implies that methyl hypobromite is a strong enough base so that minute amounts of it can compete with the solvent, methyl alcohol, for protons. In fact, this assumption is thermodynamically equivalent to postulating an ionization of bromine into positive and negative ions, since the conjugate acid in question is in no way different from a solvated positive bromine ion. The idea that halogenation processes proceed by way of positive halogen ions has been frequently discussed,[8] but we know of no reaction for which this

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(7) Bauer and Daniels, THIS JOURNAL, **56**, 2014 (1934).

(8) Francis, *ibid.*, **47**, 2340 (1925); **48**, 1631 (1926); Taylor, Maas and Hibbert, *Can. J. Research*, **4**, 119 (1931); Soper and Smith, *J. Chem. Soc.*, 1582 (1926); W. A. Noyes and Lyons, THIS JOURNAL, **23**, 463 (1901), and later papers; Stieglitz, *ibid.*, **23**, 797 (1901).

is the only admissible mechanism. In the present case the kinetics is definitely inconsistent with this mechanism, as will be shown presently.[9]

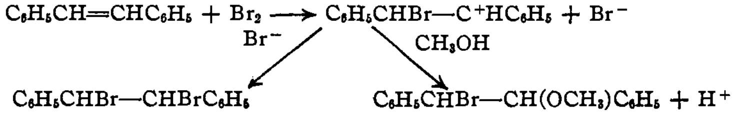
With methyl hypobromite, catalyzed or uncatalyzed, ruled out as an active participant in this reaction, it follows that the initiator of the reaction is some molecular species whose concentration is reduced by the addition of bromide ion but not by the addition of hydrogen ion. This species is evidently bromine itself, which is known to form the tribromide ion in aqueous solution

$$Br_2 + Br^- \rightleftarrows Br_3^-$$

The equilibrium constant for the dissociation of the tribromide ion in water at 0° is 0.051.[10] The instability of bromine solutions in methyl alcohol prevented our measuring this constant accurately under the conditions of our experiments, but a series of approximations using the Jones equilibrator[11] shows that this constant has a value between 0.0021 and 0.0042, the most probable value being 0.0024. The effect of added substances upon the order and rate of the reaction can be explained satisfactorily if both bromine and tribromide ion are capable of reacting with stilbene, bromine being considerably more active than the tribromide ion. When the solution contains at the beginning much more bromide ion than is formed during the reaction, the reaction will show second order kinetics, unaffected by accumulating products. However, since hydrogen bromide is a by-product of the formation of stilbene methoxy bromide, the original ratio of Br_2 and Br_3^- will be greatly altered during reaction, if the solution contains no added bromide ion at the beginning. According to this picture of the reaction mechanism, which is satisfactory both qualitatively and quantitatively, the changing ratio of methoxybromide to dibromide in the product, produced by the addition of bromide ion, is due to increasingly successful competition of bromide ion with the solvent in reaction with the intermediate

$$C_6H_5CHBr\text{-}C^+HC_6H_5$$

Unless this intermediate is given an electrical charge, as the theory of Robinson demands, no consistent explanation can be given of the part played by bromide ions in determining the nature of the reaction products. Apparently we have here a reaction which can be represented satisfactorily only in the following manner[12]



$$C_6H_5CH{=}CHC_6H_5 + Br_2 \longrightarrow C_6H_5CHBr{-}C^+HC_6H_5 + Br^-$$
$$\xrightarrow{Br^-} C_6H_5CHBr{-}CHBrC_6H_5 \qquad \xrightarrow{CH_3OH} C_6H_5CHBr{-}CH(OCH_3)C_6H_5 + H^+$$

There are three sets of quantitative facts about this reaction which a satisfactory theory must explain: (1) the ratio of products as a function of the bromide ion concentration in the solution, (2) the rate of the bimolecular reaction as a function of the bromide ion concentration in the solution and (3) the kinetic order of the reaction with no added bromide ion. The applicability of our mechanism to these three sets of data is tested as follows.

Derivation of Kinetic Equations

In the following formulations, K is the dissociation constant of the tribromide ion in methyl

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(9) Granting the assumption that the bromine positive ion, if present in solution, will be practically entirely solvated, and therefore identical with the conjugate acid of methyl hypobromite, we can make an approximate calculation which will show the maximum possible degree of ionization of bromine into positive and negative ions. In a series of colorimetric measurements we were unable to detect any conversion of bromine in methyl alcoholic solution into a colorless form at a concentration as low as 0.00392 *M*. Even granting an experimental error as high as 10%, this means that K_{Br}, defined by the equation

$$K_{Br} = [CH_3OBr]\,[H^+]\,[Br^-]/[Br_2]$$

is less than 1.7×10^{-8}. A rough estimate of the strength of methyl hypobromite as a base can be obtained by the following consideration. Substitution of bromine for the hydrogen of the hydroxyl ion lowers the basic strength of this ion by a factor of about 10^6. If we make the assumption that the effect of this substitution for the hydroxyl hydrogen of methyl alcohol will be about the same, we shall have the relation

$$\frac{[CH_3OBr]\,[CH_3OH_2^+]}{[CH_3OBrH^+]\,[CH_3OH]} = 10^6$$

or roughly

$$\frac{[CH_3OBr]\,[H^+]}{[CH_3OBrH^+]} = K_a = 2.5 \times 10^7$$

The dissociation constant $[Br^+]\,[Br^-]/[Br_2]$ is therefore equal to K_{Br}/K_a, and is less than 7×10^{-15}. In the light of this figure it will be found that some of the reactions which have been attributed to the positive bromine ion call for a specific reaction rate in excess of the possible collision frequency of this ion with the substance undergoing reaction.

(10) Jones and Hartmann, *Trans. Am. Electrochem. Soc.*, **30**, 295–326 (1916).

(11) Jones and Kaplan, THIS JOURNAL, **50**, 1600 (1928).

(12) There is also to be considered the possibility of a reversed order of events, yielding a negatively charged intermediate, as postulated by Ogg [THIS JOURNAL, **57**, 2727 (1935)] for the formation of dibromides. In this case we might have for the methoxybromide

$$C_6H_5CH{=}CHC_6H_5 + CH_3OH \overset{\text{(fast)}}{\rightleftarrows} \underset{\text{(A)}}{C_6H_5CH^-{-}CH(OCH_3)C_6H_5} + H^+$$
$$\Big\downarrow Br_2\ \text{(slow)}$$
$$C_6H_5CHBr{-}CH(OCH_3)C_6H_5 + H^+ + Br^-$$

the negative intermediate here competing with the stilbene-bromide ion intermediate for reaction with bromine. If this were the mechanism, acids should strongly diminish the rate by cutting down the concentration of the reactive form A, which is not observed. Therefore only the Robinson mechanism is capable of explaining both the dibromide and methoxybromide formation.

alcohol at 0°; k_1 and k_2 are the rates of reaction of the tribromide ion and of bromine, respectively, with stilbene.

x = $[Br_2] + [Br_3^-]$
c = $[\text{stilbene}] - x$
x_0 = initial value of x
b_0 = initial concentration of bromide ion
a = $x_0 + b_0 + K$
R = k_2/k_1

The total rate of reaction is

$$-dx/dt = [\text{stilbene}]\,(k_1\,[Br_3^-] + k_2\,[Br_2])$$
$$= k_1\,(x + c)\,([Br_3^-] + R\,[Br_2])$$
$$x = [Br_2] + [Br_3^-] = [Br_2]\cdot\left(1 + \frac{[Br^-]}{K}\right) \quad (1)$$
$$\text{Now } [Br^-] + [Br_3^-] = b_0 + x_0 - x$$
$$\text{so that } [Br^-] = b_0 + x_0 - x - [Br_2]([Br^-]/K)$$
$$\text{or } [Br^-] = \frac{b_0 + x_0 - x}{1 + ([Br_2]/K)}$$
$$\text{Substituting, } x = [Br_2]\left(1 + \frac{b_0 + x_0 - x}{K + [Br_2]}\right)$$

Solving this for $[Br_2]$ and simplifying by the introduction of a, we get

$$[Br_2] = {}^1/_2(2x - a + \sqrt{(2x - a)^2 + 4Kx})$$

Since the runs to which this formulation is to be applied are all very rapid, we may neglect the small contribution to the rate made by $[Br_3^-]$ and write

$$-dx/dt = {}^1/_2k_2(x + c)\,(2x - a + \sqrt{(2x - a)^2 + 4Kx}) \quad (2)$$

or

$$\frac{-dx}{(x + c)\,(2x - a + \sqrt{(2x - a)^2 + 4Kx})} = {}^1/_2k_2\,dt$$

The quantities in this expression are all of such magnitude as to make approximations by expansion of the radical unreliable toward the beginning of the reaction. The complete integration of this differential equation leads to the result

$$(a + 2c - A)\ln(x + c) + A\ln[AU + 2(x_0 + 2c)x - (a^2 + 2x_0c)] - a\ln[aU + 2x_0x - a^2] - 2c\ln[U + 2x - x_0] = 2Kck_2t + \text{constant} \quad (3)$$

Here $A = \sqrt{(a + 2c)^2 - 4Kc}$ and $U = \sqrt{(2x - a)^2 + 4Kx}$

When the concentration of bromide ion initially present greatly exceeds that which is formed in the course of the reaction, the kinetics will of course be second order.

$$\text{From Eq. (1), } [Br_2] = \frac{x}{1 + ([Br^-]/K)} \text{ and}$$
$$[Br_3^-] = \frac{x\,([Br^-]/K)}{1 + ([Br^-]/K)}$$
$$\text{since } [Br_2] + [Br_3^-] = x$$
$$\text{then } -\frac{dx}{dt} = kx(x + c) =$$
$$\left\{k_1\frac{[Br^-]}{K + [Br^-]} + k_2\frac{K}{K + [Br^-]}\right\}x(x + c)$$
$$\text{So } k = k_1\frac{RK + [Br^-]}{K + [Br^-]} \quad (4)$$

From the bimolecular velocity constants at four different concentrations of bromide ion, and the experimentally determined value of K, 0.0024, Eq. (4) can be utilized to determine the constants k_1 and R, and therefore k_2 also since $k_2 = k_1 \times R$. These constants have the values $k_1 = 2.02$, $R = 99$, and $k_2 = 200$. Table I shows the agreement between the calculated and observed bimolecular constants using these values.

TABLE I

BIMOLECULAR VELOCITY CONSTANT AND BROMIDE-ION CONCENTRATION AT 0°

$[Br^-]$	k calcd.	k obsd.	Deviation	% deviation
0.500	2.96	3.00	0.04	1.3
.205	4.26	4.15	.11	2.6
.205	4.26	4.28	.02	0.5
.114	6.11	6.45	.34	5.3
.0186	24.7	23.7	1.0	4.2

(Average deviation, 2.8)

Figure 1 shows these results graphically.

We may now compare this formulation with one based upon the assumption that the active agent is something whose concentration is proportional to the concentrations of methyl hypobromite and of hydrogen ion. Any such active molecular species, whose concentration may be denoted by y, would be subject to the following equilibria

$$K_{Br} = \frac{y[Br^-]}{[Br_2]} \text{ or } y = K_{Br}\frac{[Br_2]}{[Br^-]}$$

Then instead of Eq. (4) we should have

$$k = k_1\left\{\frac{RK_{Br}}{[Br^-] + ([Br^-]^2/K)} + \frac{[Br^-]}{K + [Br^-]}\right\}$$

We have endeavored to fit this equation to the data, using normal equations in exactly the same manner as was done to get the data of Table I. The best fit obtainable using this formulation gives $k_1 = 4.63$ and $RK_{Br} = 0.704$. The constants calculated for these values appear in Table Ia, the average deviation being 24.9%.

TABLE Ia

ATTEMPTED FIT OF FORMULATION ASCRIBING ACTIVITY TO CH_3OBrH^+

$[Br^-]$	k calcd.	k obsd.	Deviation	% deviation
0.500	4.63	3.00	+1.63	54.3
.205	4.76	4.15	+0.61	14.7
.205	4.76	4.28	+0.48	11.2
.114	5.12	6.45	−1.33	20.6
.0186	29.26	23.7	+5.56	23.5

(Average deviation, 24.9)

The inability of this formulation to account at all for the data is sufficient to eliminate any mechanism which ascribes the bulk of the activity either to the conjugate acid of methyl hypobromite or to an acid-catalyzed addition of methyl hypobromite.

Turning back to the results obtained from Eq. (4), we now have a value of k_1 from the bimolecular runs, so that the applicability of Eq. (3) can be tested not only by obtaining a linear plot of the integral against time, but also by comparing the numerical value of the constant so obtained with that from the other types of run. Figure 2 shows this integral plotted against time, for a run in which there was no bromide ion initially present, the ionic strength being maintained by 0.2 M lithium benzenesulfonate. The points lie on a fairly straight line except for the point corresponding to zero time, which is below the line for all the runs of this type. In deriving Eq. (3) we ignored the pentabromide ion, which might well exist during the early part of one of these experiments in a concentration sufficient to diminish the concentration of free bromine more rapidly for a time than our equation demands.

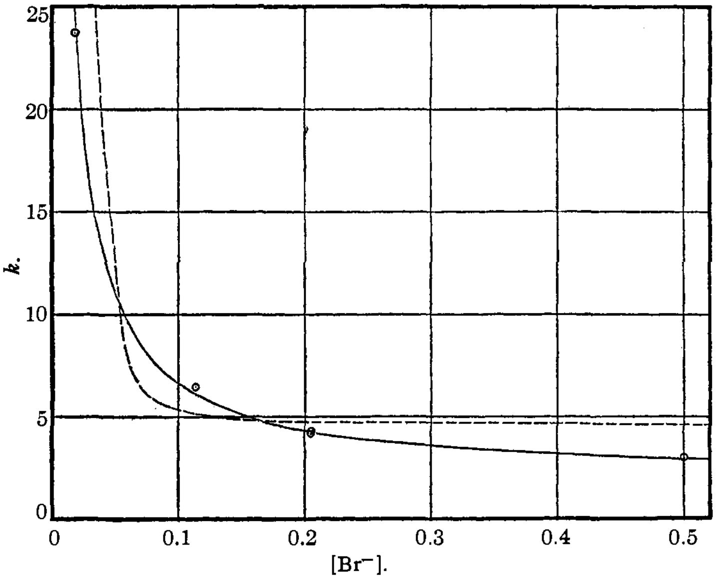

Fig. 1.—Bimolecular velocity constant as a function of bromide ion concentration: solid curve, theoretical relation ascribing activity to Br_2; broken curve, best fit for the data ascribing activity to CH_3OBrH^+ or to CH_3OBr catalyzed by hydrogen ions.

In Table II are tabulated the values of k_1 obtained from five runs containing no initial bromide ion.

The average value of k_1 for the two runs in the presence of 0.2 M lithium benzenesulfonate is 2.84 against 2.02 from the bimolecular runs. This is rather poor agreement, but seems to us not poor enough to cast doubt on the mechanism assumed.

TABLE II

REACTION RATES WITH NO ADDED BROMIDE ION AT 0°

Added substance	Concentration, M	k_1
Lithium benzenesulfonate	0.20	2.62
Lithium benzenesulfonate	.20	3.05
Sulfuric acid	.059	1.86
Hydrogen chloride	.20	6.56

Sulfuric acid appears to have a slight retarding effect and hydrogen chloride an accelerating effect upon the reaction. These effects are both too small to be surely distinguished from specific ion effects, but it is interesting in this connection to note that in non-polar solvents hydrogen bromide has been observed to be an important catalyst for the addition of bromine to double bonds.[13]

Ratio of Products

If the addition of methyl hypobromite is initiated by molecular bromine, then the ratio of dibromide and methoxy bromide found in the product must measure the relative extents to which the bromide ion and the solvent molecule participate in the second step of the reaction. If k_s is the rate at which the intermediate reacts with the solvent, and $k_b[Br^-]$ is the rate at which the intermediate reacts with the bromide ion, then the fraction of the product which is methoxybromide is equal to

$$\frac{k_s}{k_s + k_b[Br^-]} = \frac{1}{1 + Q[Br^-]}$$

where $Q = k_b/k_s$. The ratio of products was determined for various runs at ionic strength 0.20, but with initial bromide ion concentration between 0 and 0.20 the percentage of methoxy bromide in the product varies only between 80 and 99%, and the determinations are accurate only within two or three per cent. Within these limits, Table III shows the observed ratios and those calculated on the basis of $Q = 1.21$, the average value determined from the experimental points included.

TABLE III

PERCENTAGE STILBENE METHOXYBROMIDE AND BROMIDE-ION CONCENTRATION AT 0°

$[Br^-]$	% calcd.	% obsd.	
0.200	81.2	82.1	83.8
.193	81.6	81.3	
.100	89.7	87.0	90.7

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[13] Williams, *J. Chem. Soc.*, 2911 (1932); for other references see Anantakrishnan and Ingold, *ibid.*, 984 (1935).

In the presence of 0.50 *M* sodium bromide 75% of the product was methoxy bromide. This is not included in the table because of the great difference in ionic strength. To be sure, these figures on the ratio of products are too rough to prove anything about the mechanism one way or the other, but it is of interest that they are thoroughly consistent with the conclusions drawn from other parts of the work.

A Donor Theory of Halogenation

Halogen-containing compounds which have been proved to be capable of direct attack upon an ethylenic linkage now include the molecular halogens, the hypohalous acids, alkyl hypohalites, acetyl hypohalites,[14] interhalogen compounds and trihalide ions, beside halogen atoms. Our kinetic evidence now shows that, at least in the present instance, the addition is a reaction in steps and the initiator of the reaction is not the compound which, from the formula of the product, appears to have been added. We believe this to be typical of many halogenation processes occurring *in polar solvents.* For such reactions the criterion for potential activity of a reagent appears to be that the halogen is in combination with some atom or radical which readily assumes the condition of a negative ion. Thus the molecular species which we have been forced to reject as controlling the reaction rate under our experimental conditions—methyl hypobromite and its conjugate acid—are potentially very active agents for this type of process, but happen not to be present in sufficient amount to be important contributors to the reaction under the conditions which we have used. In each case a choice among the possible halogen donors must be made by a separate study.

Despite the lack of generality of our results in this regard, they establish a close parallel, in the first place, between "addition" reactions in polar solvents and "substitution" reactions in the sense in which this term is used by Olson.[15] Here in the general equation, $X^- + AY \longrightarrow AX + Y^-$, the charge type is different, but the stilbene molecule performs the function of X^- in the first step, and both *A* and *Y* are bromine atoms. Robinson[4] represents chlorohydrin formation as a process essentially involving ternary collisions of hydrocarbon, halogen molecule and solvent. His theory thus does not demand the existence for any time of a free positively charged organic intermediate. If such an ion does exist in the solution, it must exist for too short a time to allow a change of configuration, since stilbene and isostilbene yield different methoxybromides as well as dibromides.

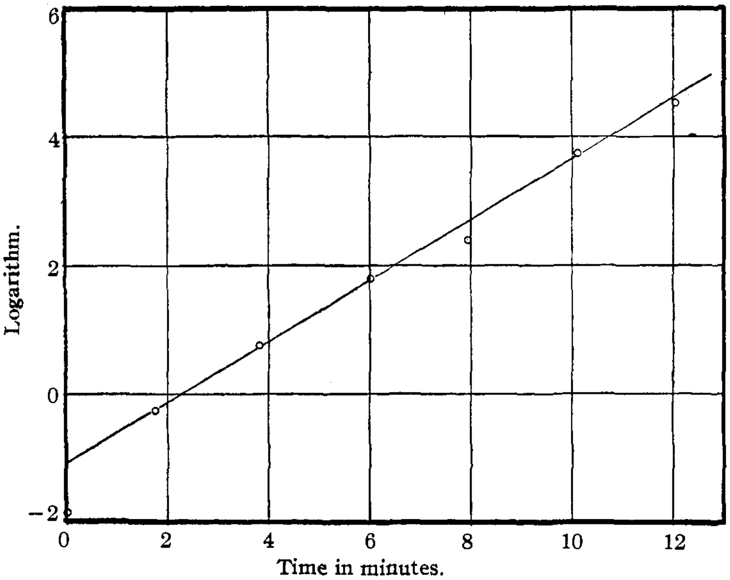

Fig. 2.—Application of equation (3) to a bromination of stilbene in the presence of 0.2 *M* lithium benzenesulfonate. The left-hand member of equation (3) is plotted against time in minutes (the scale is in common logarithms).

It should be pointed out that although the stilbene molecule is pictured as acquiring a positive charge at the same time that the carbon–bromine bond is formed, this does not imply the existence of positive halogen ions any more than positive secondary butyl ions are implied in the racemization of secondary butyl iodide by iodide ion according to Bergmann, Polanyi and Szabo.[16]

In the second place, halogenation in polar solvents now assumes a formal resemblance to general acid catalysis initiated by proton donors, which latter can be arranged in a series of decreasing efficacy which parallels their decreasing acid strength. Although we regard positive halogen

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(14) Hoffmann and Bockemüller, *Ann.*, **519**, 165 (1935).

(15) Olson, *J. Chem. Phys.*, 1, 418 (1933); Olson and Long, THIS JOURNAL, **56**, 1294 (1934). Ogg[12] also calls attention to such a parallelism.

(16) Bergmann, Polanyi and Szabo, *Z. physik. Chem.*, **20B**, 161 (1933).

ions as a fiction, it is not to be ignored that free hydrogen ions in solution are also a fiction,[17] and it may develop that for purposes of classification, positive halogen ions may be just as useful a fiction as free protons.

Experimental

Synthetic methyl alcohol was purified by the method of Lund and Bjerrum.[18]

Stilbene was prepared by the reduction of benzoin.[19] After six recrystallizations from ethyl alcohol, it melted at 124°.

Lithium benzenesulfonate was prepared by treating lithium carbonate with an aqueous solution of benzenesulfonic acid, evaporating the solutions, recrystallizing the salt from absolute methyl alcohol and drying it in an oven at 110°.

Stilbene methoxy bromide, for the trial runs testing the reversibility of the reaction, was prepared by the reaction of bromine on 4 g. of stilbene in 200 cc. of methyl alcohol. The product melted at 115–116°[20] after repeated recrystallization from benzene and methyl alcohol. The much less soluble stilbene dibromide, m. p. with dec. 235–238°, was also obtained in this reaction.

Measurement of Reaction Rates.—The reaction of bromine with stilbene was followed kinetically by pipetting samples from the reaction flask into about five times their volume of water containing excess potassium iodide, acidulating with acetic acid, and titrating the liberated iodine with standard 0.0200 *M* or 0.0235 *M* thiosulfate solution. The stilbene and reaction products were precipitated by the large amount of water which interfered but slightly with the iodine-starch end-point. In the runs containing much mineral acid, sodium acetate was added before the titration to prevent too rapid oxidation of the hydriodic acid. The runs were all carried out in blackened flasks immersed in an ice-bath.

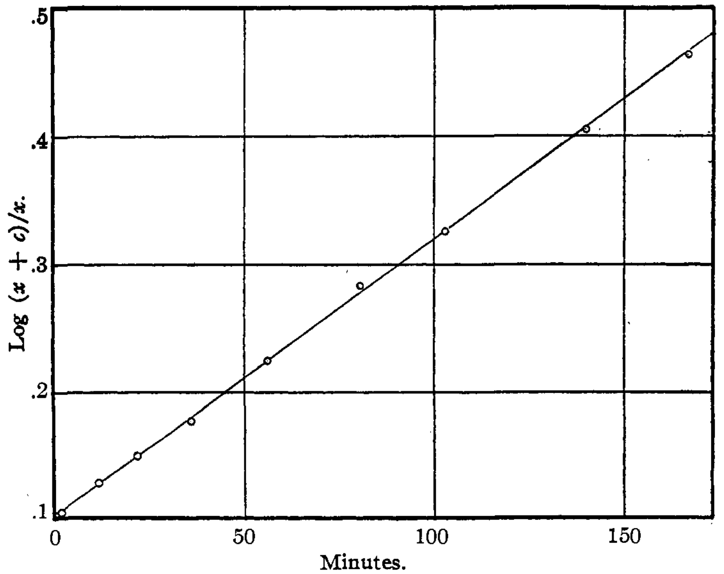

Fig. 3.—Showing the bimolecular character of the reaction in the presence of 0.1 *M* sodium bromide and 0.1 *M* lithium benzenesulfonate.

A typical set of data for a run containing 0.113 *M* sodium bromide and 0.094 *M* lithium benzenesulfonate is as follows.

x_0 = 0.00299. $x_0 + c$ = 0.00377

Time	Titer	x	$\log_{10} (x + c)/x$
0	7.45	0.00299	0.1004
1.7	7.20	.00288	.1038
11.66	5.70	.00228	.1277
21.63	4.75	.00190	.1492
35.29	3.84	.00154	.1775
56.1	2.87	.00115	.2248
80.4	2.12	.00085	.2833
102.8	1.74	.000697	.3263
139.8	1.26	.000505	.4055
166.5	1.02	.000410	.4634

These results are shown graphically in Fig. 3, where the linear variation of log $(x + c)/x$ with time shows the bimolecular character of the reaction. Most of the reactions measured were rapid, and the velocity constants were determined by drawing a straight line through the points and estimating its slope. On account of the instability of methyl alcoholic solutions of bromine, such solutions were made up immediately before use and the titration at zero time was obtained by pipetting duplicate samples of the bromine solution into the reaction mixture and into a blank solution whose bromine strength was then determined as soon as possible. Determinate stock solutions of stilbene, sodium bromide and lithium benzenesulfonate, all in anhydrous methyl alcohol, were used.

Test of Effect of Oxygen.—In separate bulbs in a closed apparatus were put the requisite amounts of material to make 100 cc. of solution 0.2 *M* in sodium bromide, 0.00928 *M* in stilbene, and 0.00552 *M* in bromine. Fifty cubic

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[17] Kolthoff, *Rec. trav. chim.*, **49**, 407 (1930).

[18] Lund and Bjerrum, *Ber.*, **64**, 210 (1931).

[19] Ballard and Dehn, THIS JOURNAL, **54**, 3969 (1932).

[20] Jackson, *ibid.*, **48**, 2171 (1926).

centimeters of methyl alcohol was added and the contents boiled under suction until the weight of the vessel was the same as before the addition of extra solvent. Dry, oxygen-free hydrogen was admitted to the vessel, the solutions brought to 0° and mixed, and the reaction followed in the usual manner, an outward current of hydrogen protecting the reaction against air at the moments of opening. The velocity constant determined for this run was 3.78, compared to 4.15 and 4.28 for the runs in which oxygen was admitted.

Colorimetric Measurements.[21]—Successive dilutions were made starting with a 0.0628 *M* solution of bromine in methyl alcohol, diluting portions of each solution with an equal volume of methyl alcohol down to a concentration of 0.00392. If the alcoholysis constant of bromine were as great as 10^{-6}, then, at a concentration between the two lowest here represented, the light absorption should be diminished to 70% of that which would be observed in the absence of alcoholysis. In a colorimeter, solution 6 was compared with solutions 3, 4 and 5, and solution 3 with solution 2. Assigning an index number of 100 to represent the percentage of bromine in solution 2 which was in colored form, we calculated the results as follows.

Solution	Concentration of all forms of bromine	% of bromine in colored form
2	0.0628	100.0
3	.0314	95.9
4	.0157	97.5
5	.00785	98.2
6	.00392	105.3

It is evident that there may be errors as great as 5% in this measurement, but the error surely cannot exceed 10%. Assuming that in solution 6 only 90% of the bromine is present as Br_2, and the rest as methyl hypobromite and hydrogen bromide, we arrive at the maximal value of K_{Br} of 1.7×10^{-8}, previously referred to. The constant may, of course, be enormously smaller than this.

For the quantitative measurement of the fraction of methyl hypobromite addition indicated in the product, the great excess of sodium bromide present in some of the runs rendered the titration for bromide ion, used by Meinel, undesirable in our case. We estimated the hydrogen bromide produced during reaction by titration with standard sodium hydroxide, using methyl red as an indicator. Samples containing an excess of stilbene were kept for about twelve to fifteen hours in an ice-bath in a large thermos jug until the bromine had completely reacted, and samples were then titrated directly. The fraction of methyl hypobromite addition reported in Table III is the quotient of the hydrogen bromide found by titration divided by the initial bromine concentration as determined from a blank. It was ascertained that the stilbene and salt solutions showed no acid content when titrated with sodium hydroxide.

For the approximate measurement of the dissociation constant of the tribromide ion in methyl alcohol at 0°, successive approximations were used, since the time required for complete attainment of equilibrium is sufficient to produce considerable deterioration of methyl alcoholic bromine solutions, with formation of some bromide ion. In compartment 1 of the equilibrator, a 0.1 *N* solution of sodium bromide in methyl alcohol was placed, containing about 0.05 *M* bromine. In compartment 2 was placed some of a 0.1 *N* solution of lithium benzenesulfonate containing less than one tenth as much bromine. These concentrations were arrived at on the basis of some preliminary rough experiments. The remainder of the lithium benzenesulfonate–bromine solution was kept in a glass-stoppered flask in an ice-bath as a control. The control was titrated and the equilibrator was started rocking in an ice-bath. After two and one-half hours the rocking was interrupted, and the control and the contents of compartment 2 were titrated for bromine.

Titration of 10 cc. of solution

Control before shaking	4.26 cc.
Control after 2.5 hrs.	4.19 cc.
Compartment 2, after 2.5 hrs.	3.90 cc., 3.86 cc.

Bromine had unmistakably migrated from compartment 2 to a greater extent than could be accounted for by decomposition of the solution. The contents of compartment 2 were then removed and diluted exactly one-to-one with 0.1 *M* lithium benzenesulfonate solution. Repetition of the experiment, with two and one-half hours more shaking, gave the following titers

Control before shaking	2.03 cc.
Control after 2.5 hrs.	2.01 cc.
Compartment 2, after 2.5 hrs.	2.05, 2.07 cc.

This time the change was in the opposite direction. Titration of the solution in compartment 1 gave 0.0514 as the concentration $[Br_2] + [Br_3^-]$. If the concentration of bromine had reached equilibrium on the two sides, $[Br_2]$ would be 0.00206 in

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[21] We are indebted to Dr. C. E. Barnes for these measurements.

the second experiment, and $[Br_3^-]$ would be 0.0494. The constant K, therefore, lies between $(0.00206 \times 0.0506)/0.0494 = 0.00211$ and the value 0.00429, obtained by a similar calculation on the first run. With equilibration so slow, it would be difficult to obtain great accuracy in these measurements. Our working value of 0.0024 was obtained by interpolation on the basis of the apparent extent of bromine migration in the two experiments.

Acknowledgment.—We thank Mr. T. P. Palmer for valuable aid in the integration of Eq. (2) and its application to the experimental data.

Summary

1. The rate of bromination of stilbene in methyl alcohol solution is sharply diminished by bromide ions, but not by hydrogen ions.

2. Therefore, although stilbene methoxy bromide is the principal product of the reaction, methyl hypobromite is not responsible for its formation.

3. The kinetics of the reaction is consistent with a mechanism of reaction in two steps, in which molecular bromine is the active agent.

4. The kinetics of the reaction is inconsistent with any mechanism attributing the principal activity to methyl hypobromite catalyzed by acids, or to a positive bromine ion.

5. A general theory of halogenation in polar solvents is briefly discussed.

CAMBRIDGE, MASS. RECEIVED JANUARY 8, 1936

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

Synthesis of Compounds with Hypnotic Properties. I. Alkoxymethylhydantoins[1]

BY NEIL E. RIGLER WITH HENRY R. HENZE

Rather striking evidences of the relationship of physiological action to chemical constitution have been demonstrated in the relation of isomerism and molecular weight of the simple alkyls to soporific power.[2] In this respect the series of alkyl disubstituted barbituric acids has been most thoroughly investigated and studies of a large number of these compounds have resulted in the synthesis of several soporifics of definite potency and usefulness. The heterocyclic compound hydantoin, which is structurally related to barbituric acid, has been chosen as an innocuous substance which might be converted into soporific derivatives by the attachment to the nucleus of suitable alkyl, alkyloxy, aryl, or aryloxyalkyl groups. The derivatives of hydantoin have been but briefly investigated and one of them, phenylethylhydantoin, Nirvanol, has been demonstrated to be of considerable value in the treatment of chorea and other nervous disorders.[3] In our research the groups attached to the hydantoin nucleus, either directly or through the methoxy grouping, were those which have been demonstrated to possess a definite narcotic effect. The combinations of alkyls chosen were such that the total number of carbon atoms (10 or 11) was that known to be most effective among the barbiturates.[4] However, an additional variation was obtained by having one of the alkyls attached, not directly to the nuclear carbon, but indirectly through the methoxyl group, so that the compounds prepared are 5,5′-alkoxymethyl alkyl (or aryl) hydantoins. It was hoped that in some one compound of this type the soporific properties might be of the same order as those of the newer barbiturates while at the same time any appreciable deleterious effects upon the system would be absent.

For obtaining the hydantoins desired, a method of preparation from ketones developed by Read,[5] and recently used by Herbst and Johnson,[6] was chosen. The alkoxy ketones required were synthesized from chloro ethers according to the method previously described.[7] The entire process may be represented as follows

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[1] From a dissertation presented by Neil E. Rigler to the Faculty of the Graduate School of the University of Texas in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June, 1935.

[2] Shonle, *Ind. Eng. Chem.*, **23**, 1104 (1931).

[3] De Rudder, *Chem. Zentr.*, **99**, I, 2628 (1926); Poynton and Schlesinger, *Lancet*, II, 267 (1929); Pilcher and Gerstenberger, *Am. J. Diseases Children*, **40**, 1239 (1930); Jones and Jacobs, *J. Am. Med. Assoc.*, **99**, 18 (1932).

[4] Carnot and Tiffeneau, *Compt. rend.*, **175**, 241 (1922); Dox, *J. Am. Pharm. Assoc.*, **12**, 602 (1923); ref. 2.

[5] Read, THIS JOURNAL, **44**, 1746 (1922).

[6] Herbst and Johnson, *ibid.*, **54**, 2463 (1932).

[7] Henze and Rigler, *ibid.*, **56**, 1350 (1934).