Aromatic Displacements. II. The Cleavage of Benzhydrols. Rates as a Function of Structure[1]

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Excellent second-order rate constants out to several half-lives are obtained for the reaction of bromine with various activated benzhydrols (and related compounds) in aqueous acetic acid. Good agreement is found between spectrophotometric rates and those obtained from iodometric titration for the disappearance of bromine. Under these conditions bromination results in competing bromodeprotonation and cleavage as described in the previous paper. In one case the rate of disappearance of bromine, when corrected by product analysis to give the rate of cleavage alone, agreed with the rate of appearance of cleavage products by direct measurement. The effect of variation of leaving group structure is examined on several phases of the bromination reaction. The effect of substitution on the ring undergoing attack is found to be very large. In contrast the influence of the leaving group is small but definite in a controlled series of 4-methoxy-4'-substituted benzhydrols. Steric effects on the cleavage reaction seem to be rather large. Competing ring bromination ortho to the methoxy group is correlated with the inductive effect of the group para to the methoxy group.

Introduction

In the preceeding paper in this series[2] we set about applying current laboratory and interpretive methods to the further study of the cleavage of arylcarbinols by electrophiles.[3] This potentially versatile reaction has

$$\underset{\substack{| \\ OH}}{ArCHAr'} + Br_2 \longrightarrow ArBr + Ar'CHO + HBr \qquad (1)$$
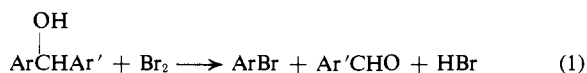
passed almost unnoticed for nearly 50 years although a careful examination of it could reveal important information about the influence of the leaving group in electrophilic substitution.

We have found, in agreement with the previous workers, that when applied to activated benzhydrols (and some cognate compounds) bromination in aqueous acetic acid results in two competing reactions, cleavage and ring bromination *ortho* to the activating group. With less reactive compounds of the series oxidation of the carbinol function to a carbonyl group may be an important or even the only reaction.

Fortunately, this stoichiometric complexity can be dealt with quite easily and a nearly complete kinetic dissection of the results is possible. As will be seen below, the over-all kinetics of the bromination is cleanly first order in each reactant (carbinol and bromine) when properly performed in 50% aqueous acetic acid. Berliner[4-7] and his colleagues have shown with great care that bromodeprotonation, the main competing reaction, is strictly first order with respect to the substrate and bromine in aqueous acetic acid from 50 to 75% acetic acid containing bromide ion, the conditions we have chosen for our kinetic work. Although the oxidation is not an important side reaction in most of the cases to be discussed, it is significant to our kinetic argument that it too is a clean second-order reaction for alcohols in water.[8] The over-all rate constant then may be dissected on the basis of product yields from the respective competing reactions as shown in eq. 2 and 3, so that the rate

$$-d(Br_2)/dt = k_{obsd}(Br_2)(\text{carbinol}) \qquad (2)$$

$$k_{obsd} = k_{cleavage} + k_{bromodeprotonation} + k_{oxidation} \qquad (3)$$

constant for each reaction of a given substrate compound under a given set of conditions may be obtained by multiplying the over-all rate constant by the fraction of the material that was converted into each type of product.

In order to perform this analysis we assume that yield data in 80% acetic acid may be applied to rates in 50% acetic acid and at lower substrate concentrations. The rates of all reactions which consume bromine will surely be affected by the medium change. However, we make the important assumption that the shift of the relative rates is so small that yields under the 80% acetic acid conditions are a good measure of partitioning under our rate conditions. A check on this is found under part C, Kinetic Methods. Although this assumption may be partially wrong in some cases, it is highly unlikely that its failure will be so general or so erratic as to invalidate the gist of our analysis.

It has been well known[9] for some time that aromatic bromination by molecular bromine in glacial acetic acid is kinetically complex since bromine enters the rate equation in a series of terms of successively higher order. However, order with respect to bromine falls as the bromine concentration is lowered and as water and sodium bromide are added to the solvent. In 75% aqueous acetic acid in the presence of 0.1 M bromide ion and reactant concentrations in the neighborhood of 10^{-3} M the reaction becomes cleanly first order in halogen.[4] There is little doubt that the halo-

(2) E. M. Arnett and G. B. Klingensmith, *J. Am. Chem. Soc.*, 87, 1023 (1965).
(3) E. P. Kohler and R. H. Patch, *ibid.*, 38, 1205 (1916).
(4) U. P. Zimmerman and E. Berliner, *ibid.*, 84, 3955 (1962).
(5) E. Blinerer and M. C. Beckett, *ibid.*, 79, 1425 (1957).
(6) E. Berliner and J. C. Powers, *ibid.*, 83, 905 (1961).
(7) E. Berliner and B. J. Landry, *J. Org. Chem.*, 27, 1083 (1962).
(8) C. G. Swain, R. A. Wiles, and R. F. W. Bader, *J. Am. Chem. Soc.*, 83, 1945 (1961).
(9) P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution," Academic Press Inc., New York, N. Y., 1959, Chapter 9.

genating species itself is molecular bromine under these conditions.

The problem of limited solubility which prohibits stoichiometric runs under exactly the same conditions as the kinetic ones also limits seriously our ability to examine the rate equation by the usual method of varying initial concentrations. However, excellent confirmation of the unit order with respect to each reactant was demonstrated by means of the differential rate method.[10] Unusually good adherence of our measurements to the simple integrated second-order rate equation was confirmed following the disappearance of bromine through two independent analytical methods and the rate of appearance of cleavage products through yet another.

On the basis of these results we will consider in this paper the effect of structural variation in the ring suffering bromination, at the carbinol carbon, and in the leaving group on the two main reactions, cleavage and bromodeprotonation.

Experimental

Materials. Information regarding the sources and purification of the acetic acid solvent, bromine, and sodium bromide has already been given.[2] The 50% aqueous acetic acid solvent was prepared by mixing equal volumes of acetic acid and freshly distilled water. The two components were thermostated before mixing them at 25° in the 1-l. volumetric flasks used for measuring. The pseudo-first-order rate constant for the reaction of bromine with this solvent under our reaction conditions was measured spectrophotometrically and found to be 2.7×10^{-7} sec.$^{-1}$ which is negligible for the cases to be discussed.

Potassium iodide, sodium thiosulfate, potassium iodate (dried for 2 hr. at 120° before use), and soluble starch were all Fisher certified reagent chemicals and were used without further purification. Mallinckrodt analytical reagent potassium dichromate was dried at 200° for 2 hr. before use. The preparation and purification of the aromatic reactants were described in the previous paper[2] as also were the details of their bromination reactions and yield data.

Kinetic Methods. One of the features of the cleavage reaction 1 which first attracted us to its study was the possibility of following the reaction rate by a variety of techniques. In addition to the traditional iodometric method,[4-7] one might suppose that the disappearance of bromine or carbinol could be followed spectrophotometrically and the appearance of cleavage product by spectrophotometry or gas chromatography. A variety of other techniques also suggests themselves. The majority of rate measurements were made by observing the change in optical density of the reacting solution at 380 mμ where the main absorbing species is tribromide ion generated by the rapidly reversible reaction of bromine with the 0.2 M sodium bromide present in our solutions. Absorption from bromine or tribromide is so intense over much of the ultraviolet spectrum where our aromatic carbinols or carbonyl compounds might absorb that it was impractical to follow their appearance or disappearance directly. Our technique was checked in three ways. Firstly, we

(10) S. W. Benson, "The Foundations of Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, pp. 82, 83.

repeated a determination of the bromination of naphthalene which had been made by Berliner and Beckett[11] using iodometric titration. The fact that our value is 1.83×10^{-2} l./mole sec. while theirs under nearly similar conditions is 1.95×10^{-2} l./mole sec. means that agreement is good between the two determinations, made as they are by different workers using different methods in different laboratories. In addition we have used the iodometric method to check some of our own data and finally have followed a product appearance rate by spectrophotometric analysis.

a. Disappearance of Bromine by Spectrophotometry. Keefer, Andrews, and their co-workers have used this procedure successfully in a number of cases.[12-16] In our study as well as theirs[12] initiation of competing radical reactions by the spectrophotometer light beam introduced no error as was shown by identical rates when the cell was held in the light path continuously or introduced only for readings.

Spectrophotometric measurements of bromine concentration in the reaction solutions were made with a Beckman Model DU spectrophotometer equipped with a photomultiplier and line operated power supply. The 1-cm. quartz cells were used in close-fitting brass cell holders contained in a brass compartment through which water from a constant temperature bath was circulated.[17] The temperature control for reactions run at 25° was ±0.03°.

Most of the rate measurements were made on solutions in 50% aqueous acetic acid containing 0.2 M sodium bromide. In this system the concentration of free bromine, $(Br_2)_f$, is quite small due to instantaneous complexing with bromide to form the tribromide ion

$$Br^- + Br_2 \rightleftharpoons Br_3^- \qquad (3)$$
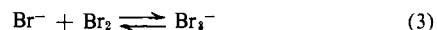
Tribromide ion absorbs strongly in the ultraviolet, λ_{max} 269 mμ (ϵ 5.5×10^4), as determined by measurements with tetra-n-butylammonium tribromide.[18] The total bromine concentrations, $(Br_2)_T = (Br_2)_f + (Br_3^-)$, of solutions in 50% aqueous acetic acid containing 0.2 M sodium bromide were obtained by optical density measurements at 380 mμ on tribromide ion with a small contribution from uncomplexed bromine. Total bromine concentrations were determined by iodometric titration (using the procedure described below for iodometric rate studies) and from the absorbance of these solutions the bromine, bromide–tribromide system was found to follow Beer's law closely between 6.4×10^{-5} and 2.36×10^{-3} M, the working kinetic range. The apparent molar absorbtivity index (ϵ) was obtained as the slope of the Beer's law plot for the system at 25.15° and used to calculate the total bromine concentrations $(Br_2)_T$ for the reactions at this temperature at zero time.

(11) E. Berliner and M. C. Beckett, J. Am. Chem. Soc., 79, 1425 (1957).
(12) R. M. Keefer, J. H. Blake, III, and L. J. Andrews, ibid., 76, 3062 (1954).
(13) L. J. Andrews and R. M. Keefer, ibid., 78, 4559 (1956).
(14) R. Josephson, R. M. Keefer, and L. J. Andrews, ibid., 83, 2128 (1961).
(15) R. M. Keefer and L. J. Andrews, ibid., 78, 3637 (1956).
(16) R. M. Keefer, A. Ottenberg, and L. J. Andrews, ibid., 78, 255 (1956).
(17) Designed by Professor Frank Westheimer and built by Mr. Norman Nicholson of M.I.T.
(18) A. I. Popov and R. F. Swensen, J. Am. Chem. Soc., 77, 3724 (1955).

Reactions which were followed spectrophotometrically were conducted in the following manner. Stock solutions of bromine and the arylmethyl derivative, of twice the desired starting concentrations, were prepared immediately before use in the particular solvent system employed at the temperature of the rate run. Since a bromine solution cannot be prepared conveniently to an exactly predetermined concentration, the actual concentration of bromine at zero time in the reaction solution was obtained from a blank as follows. With a 10-ml. pipet a sample of thermostated reaction solvent was placed in a 100-ml. glass-stoppered, wide-mouth bottle. Using the same pipet, 10 ml. of thermostated bromine stock solution was placed in a small weighing bottle. This was then dropped carefully into the larger bottle which was stoppered and inverted several times to effect mixing. A portion of the solution was then transferred to a 1-cm. Beckman cell and the absorbance was measured against a solvent blank. The concentration of bromine, $(Br_2)_T$ at zero time, was determined from the absorbance and the apparent extinction coefficient for the particular system. The actual reaction was then started as soon as possible in exactly the same manner as the bromine blank was prepared except that now the wide-mouth bottle contained 10 ml. of the stock solution of the arylmethyl derivative. A timer was started at the instant of mixing. The initial absorbance reading on the reaction solution (against a solvent blank) could be obtained within 1 min. Absorbance readings were converted to bromine concentrations using the relationship[19]

$$(b_0 - x) = \frac{b_0(A_\infty - A)}{(A_\infty - A_0)}$$

where b_0 is the total bromine concentration at zero time (from blank), x represents the amount consumed in time t, and A_0, A_∞, and A are the initial, final, and time t values of the absorbance, respectively.

b. *Iodometric Method.* Iodometric titrations were conducted with 0.01 N sodium thiosulfate solutions stabilized with sodium carbonate and standardized within two parts per thousand immediately before use with potassium iodate or potassium dichromate according to the procedures described by Kolthoff and Belcher.[20]

Iodometric rate runs were conducted in the following manner. Stock solutions of bromine and the arylmethyl derivative, of twice the desired starting concentrations, were prepared immediately before use in the particular solvent system employed at the temperature of the rate run. Using the same 50-ml. pipet, aliquots of thermostated stock solutions of bromine and organic substrate were transferred to a pair of 100-ml., ⅌ one-neck, round-bottomed flasks. These were then connected with a 105°-bend adapter. The reaction was started by tilting the apparatus back and forth several times to mix the solutions. A timer was started at the instant of mixing. The reaction solution was then transferred to a 100-ml. class A buret which was fitted with a glass jacket through which

water from a constant temperature bath was circulated. Ten-milliliter aliquots were withdrawn at intervals into 50-ml., glass-stoppered erlenmeyer flasks. These were quenched with 10-ml. portions of 5% potassium iodide and the time of quenching noted. The bromine concentration at zero time was determined from a blank. The quenched reaction solutions and blank were titrated immediately after they had all been collected. The time between quenching of the first sample and its titration was 1 hr. for the slowest reaction studied by this method and volatility loss of iodine over this period was shown to be negligible.

The precision obtained by the iodometric method was somewhat poorer than obtained with the spectrophotometric technique. This is to be expected when the speed of the reactions studied and the several additional steps involved in the iodometric procedure are considered.

c. *Rates from Appearance of Products.* A further important check on the technique and kinetic treatment was obtained in the case of 4,4'-dimethoxybenzhydrol. Negligible oxidation occurs in this case so that the 320-mμ carbonyl band of their cleavage products is not influenced by the presence of the corresponding benzophenone; it is also well removed from absorption regions of the starting benzhydrol or the bromoanisole fragment.

The details of the method are as follows. Thermostated 100-ml. volumes of benzhydrol and bromine stock solutions (bromine starting concentration was determined spectrophotometrically) of twice the desired starting concentrations were mixed by dropping a beaker containing one into a bottle containing the other. A timer was started at the instant of mixing. The bottle was stoppered, inverted several times to effect mixing, and replaced in the constant temperature bath. At intervals, 25-ml. portions were withdrawn with a fast-draining pipet, and quenched by adding them to a flask containing a few crystals of sodium bisulfite, the time of quenching being noted. A 15-ml. aliquot of the quenched solution was neutralized with sodium hydroxide, cooled under a water tap, and extracted with 25 ml. of cyclohexane. The separated cyclohexane layer was dried by filtration through Whatman No. 41 filter paper and the absorption spectrum of the solution was obtained using 5-cm. quartz cells in the Cary Model 14 spectrophotometer. The concentration of the carbonyl fragment in the cyclohexane layer was determined using a Beer's law plot obtained for the aldehyde in cyclohexane.

Rate Calculations and Errors. In all cases the experimental data were treated by means of the usual integrated second-order rate equation, the rate constant being obtained graphically from the slope in some cases or analytically from rate constants at different times in others, depending upon which method seemed to give the less error. Usually 10 to 20 points were taken for each run and when freshly prepared solutions were employed the rate constants were reproducible within 1%, although the error naturally varied from compound to compound. Usually a twofold excess of aromatic substrate was taken in order to suppress side reactions of the bromination products with bromine. When this was done it was quite common to maintain pure second-order behavior to over 5

(19) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p. 28.
(20) I. M. Kolthoff and R. Belcher, "Volumetric Analysis," Vol. III, Interscience Publishers Inc., New York, N. Y., 1957, pp. 235, 237.

half-lives. This is unusually good for aromatic bromination reactions which often cannot be dealt with directly in terms of integrated equations because of drifts. In Table I and Figure 1 are shown typical

Table I. The Spectrophotometric Determination of the Rate of Bromination of 4,4'-Dimethoxybenzhydrol in 50% Aqueous Acetic Acid[a]

Time, sec.	A, 3800 Å.	$x \times 10^3$	k_{obsd}
0	0.457	0.000	...
57	0.291	0.236	6.62
87	0.229	0.324	6.97
125	0.176	0.399	7.02
152	0.147	0.440	7.07
190	0.116	0.484	7.09
225	0.094	0.515	7.10
263	0.076	0.541	7.10
313	0.057	0.568	7.15
352	0.047	0.582	7.07
413	0.033	0.602	7.19
473	0.024	0.615	7.23
528	0.019	0.622	6.87
620	0.012	0.632	7.10
5 hr.	0.000		

[a] NaBr 0.20 M; 25.30°; a_0 = initial concn. of 4,4'-dimethoxybenzhydrol = 1.330 × 10^{-3} M, b_0 = initial concn. of bromine = 0.649 × 10^{-3} M; x = moles/l. at time t. Average k_{obsd} = 7.04 l. mole^{-1} sec.$^{-1}$ Standard deviation = ±0.16 l. mole^{-1} sec.$^{-1}$ (12 degrees of freedom); error = ±2.3%. k_{obsd} as obtained from the graph (Figure 1) = 7.06 l. mole^{-1} sec.$^{-1}$.

data for a rate measurement on 4,4'-dimethoxybenzhydrol. The rate constant obtained in this case (7.04 ± 0.16 l./mole sec.) agrees satisfactorily with the results from two similar runs made at different times on the same system (7.09 ± 0.1 and 7.00 ± 0.1 l./mole sec.; see Tables II and III).

Table II. The Iodometric Determination of the Rate of Bromination of 4-Methoxyphenylcyclohexylcarbinol in 50% Aqueous Acetic Acid[a]

Time, sec.	0.009941 N thiosulfate, ml.	$x \times 10^3$	k_{obsd}
0	2.217	0.000	
130	1.894	0.160	0.692
193	1.750	0.232	0.717
271	1.610	0.302	0.705
393	1.403	0.405	0.724
599	1.187	0.513	0.678
799	1.012	0.601	0.667
1159	1.767	0.724	0.666
1899	0.505	0.855	0.620

[a] NaBr 0.20 M; 25.15°; a_0 = initial concn. of 4-methoxyphenylcyclohexylcarbinol = 1.829 × 10^{-3} M, b_0 = initial concn. of bromine = 1.107 × 10^{-3} M; x = moles/l. at time t. Average k_{obsd} = 0.683 l. mole^{-1} sec.$^{-1}$ Standard deviation = ±0.034 l. mole^{-1} sec.$^{-1}$ (seven degrees of freedom); error = ±5.0%. k_{obsd} as obtained from the graph (Figure 1) = 0.655 l. mole^{-1}sec.$^{-1}$.

When the observed rate constant for disappearance of bromine given under Table I is corrected for the fraction of the reaction that is going by cleavage (see Table I of previous paper), the cleavage rate is found to be 5.13 l. mole^{-1} sec.$^{-1}$ (7.04 × 0.731 = 5.13) in rather good agreement with the above figure considering the difficulties of following the rate of product appearance.
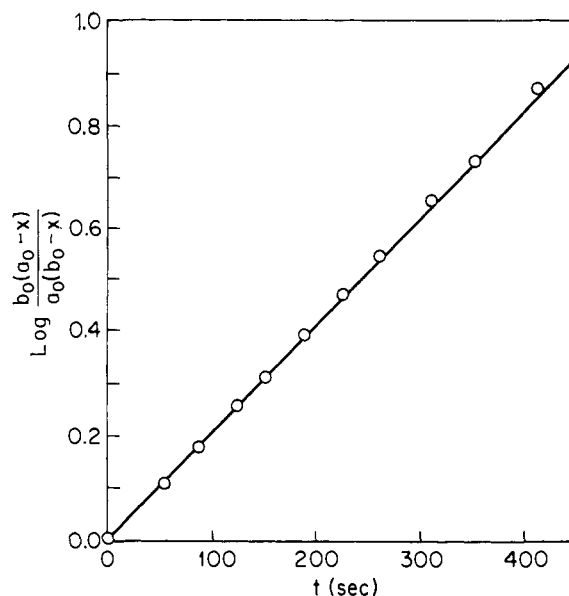

Figure 1. Second-order plot for the spectrophotometric determination of the rate of bromination of 4,4'-dimethoxybenzhydrol in 50% aqueous acetic acid containing 0.2 M sodium bromide at 25.30°.

Determination of the Order of the Reaction. The Rate Expression. Because of the speed of the carbinol brominations which give substantial cleavage yields, the van't Hoff method for determining the order of a reaction with respect to the individual participants using initial rate as a function of initial concentrations cannot be applied with reasonable accuracy. In addition, the analytical method does not allow the determination

Table III. Rate of Bromination of 4,4'-Dimethoxybenzhydrol in 50% Aqueous Acetic Acid by Determination of Anisaldehyde Formed[a]

Time, sec.	A (324 mμ)	$x \times 10^3$	$(a_0 - x)/(b_0 - x)$	log $(a_0 - x)/(b_0 - x)$
72	0.169	0.982	1.140	0.0569
107	0.189	1.078	1.157	0.0633
139	0.220	1.250	1.200	0.0792
181	0.228	1.298	1.217	0.0852
217	0.237	1.349	1.238	0.0927
251	0.249	1.412	1.270	0.1038

[a] NaBr 0.2 M; 25.15°; a_0 = initial concn. of 4,4'-dimethoxybenzhydrol = 2.00 × 10^{-3} M, b_0 = initial concn. of bromine = 1.875 × 10^{-3} M; x = concn. of anisaldehyde at time t. k_{obsd} = 4.75 l. mole^{-1} sec.$^{-1}$ as obtained from the graph (Figure 1).

of the rate with a constant excess concentration of bromine. However, the rate could be obtained at what is essentially a constant excess of the arylcarbinol reactant, thus allowing a simple differential rate treatment described by Benson.[10] This leads to an order of 0.98 for bromine and 0.94 for the carbinol.

Results and Discussion

The rate of brominative cleavage of a benzhydrol under our conditions is determined by the effect of substitution in the two aromatic rings of the system: (1) that being attacked and (2) that associated with the leaving group. We shall consider below the ob-
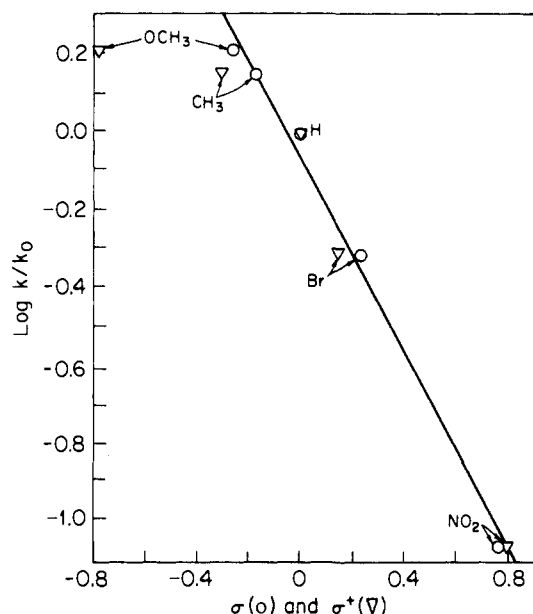
Figure 2. Correlation of rates of bromination of 4-methoxy-4'-X-benzhydrols in 50% aqueous acetic acid containing 0.2 M sodium bromide with σ and σ^+ substituent parameters (25°).

Table IV. Observed Second-Order Rate Constants for Brominations in 50% Aqueous Acetic Acid Containing 0.2 M Sodium Bromide[a]

Compd.	k_{obsd} (over-all), l. mole^{-1} sec.$^{-1}$	k_{obsd} (cleavage), l. mole^{-1} sec.$^{-1}$ [b]
4,4'-Dimethoxybenzhydrol	7.02	5.13
4-Methoxy-4'-methylbenzhydrol	3.07	2.23
4-Methoxybenzhydrol	2.43	1.58
4-Methoxy-4'-bromobenzhydrol	1.32	0.787
4-Methoxy-4'-nitrobenzhydrol	0.346	0.136
3,5-Dimethyl-4-methoxybenzhydrol	0.0958	0.0769
4-Methoxybenzyl alcohol	3.22	1.96
4-Methoxyphenylcyclohexylcarbinol	0.655	0.0190
4-Methoxytriphenylcarbinol	0.483	0.00242
4,4'-Dimethylbenzhydrol	0.00267	...
Benzhydrol	1.77 × 10^{-4}	...
4,4'-Dimethoxydiphenylmethane	5.63	0.01
Anisole	81.7	...
4-Bromoanisole	0.00408	...

[a] At 25 ± 0.2°. [b] These values were obtained by multiplying k_{obsd} (over-all) from the column to the left by the corresponding cleavage fraction from the per cent yield of bromoanisole from Table I of the previous paper.[3]

served results of substitution at these two sites on the cleavage reaction and the main reaction with which it must compete: bromodeprotonation on the ring being attacked. We have already seen that oxidation is not detectable in compounds which are sufficiently activated to undergo the cleavage.

Our original hope of doing a wide study of the cleavage reaction has been frustrated to this point mostly by its extreme sensitivity to substitution on the ring being attacked. So large is the p-value that methoxybenzhydrols are almost the only ones that can be studied conveniently by the methods described here.[21] The result of this sensitivity is that (with proper activation, and only with it) the cleavage reaction can be made to outpace competing side reactions. For example, if the oxidation rates for benzhydrol and 4,4'-dimethylbenzhydrol, which are considered to be *unactivated* in the present context, are estimated from the difference between over-all rate of bromine consumption and cleavage rate (Table II and Table I of previous paper[2]) p for this side reaction is found to be −6.9 if σ parameters are used and −3.79 for σ^+. The high degree of carbonium ion character implied by this value for the oxidation transition state is in good accord with the recent conclusions of Swain[8] that the oxidation of 2-propanol by bromine proceeds by hydride ion transfer.

Effect of the Leaving Group on Cleavage Rate. Variation of the 4'-substituent in 4-methoxy-4'-X-benzhydrols produces a significant but small electronic influence upon the rate of cleavage. As seen from Table IV only a 19-fold decrease in rate is found on going from methoxy (when corrected for symmetry) to nitro, and from Figure 2 it is clear that the electronic effects of five *para* substituents in the leaving group are correlated far better with σ-substituent parameters than with σ^+. This is the first time to our knowledge

(21) We are currently using flow systems to study more activated compounds which give cleaner reactions.[3]

that it has been possible to separate the electronic influence of the leaving group in electrophilic aromatic substitution from other contributions, and the result seems to be in keeping with the commonly accepted notion that aromatic bromination of highly activated compounds follows a mechanism involving at least two steps. We have just commented on the sensitivity of the cleavage reaction to substitution on the ring being attacked. When compared with the small p-value (−1.24) expressing the over-all influence of the leaving group, it is plain that substitution at the two sites is being mainly felt in two different phases of the reaction's progress. Actually, as will be seen in the following paper, the influence of the leaving group is a composite one on the prior equilibrium formation of an intermediate which then partitions between the leaving step and return to starting material. It is an oversimplification then to suggest that the effect of substitution in the leaving group is only on the leaving step.

Pratt and Green[22] have examined the acid-catalyzed Baeyer condensation of substituted benzaldehydes with p-dimethylaminobenzene, a reaction which is in some ways analogous to a reversal of the benzhydrol cleavage although hydrogen is displaced rather than bromine. Their results are correlated best with σ^+ to give a p-value of 1.24 (they used σ and got $p = 0.95$). Their reaction, in contrast to ours, suggests considerable carbonium ion character to the step involving the protonated aldehyde moiety. Considering the great difference in conditions, the similarity between the two reaction constants must be fortuitous.

The rates of cleavage of 4-methoxybenzyl alcohol, 4-methoxyphenylcyclohexylcarbinol, and 4-methoxytriphenylcarbinol are given in Table IV. The rate constants decrease in that order by a factor of 800. Neither the magnitude of this change nor its direction is explainable in terms of the electron release of the leaving group. However, examination of molecular models shows that the transition state for attack by bromine on the ring carbon bearing the carbinol group

(22) E. F. Pratt and L. Q. Green, *J. Am. Chem. Soc.*, **75**, 275 (1953).

should be highly sensitive to steric hindrance and this seems a reasonable explanation for the order of these rates.

Effect of Substitution on the Central Methyl Group on the Rate of Ring Bromination. For the anisyl compounds which we have studied, oxidation competes so poorly with electrophilic attack on the ring that the only side reaction to complicate the study of cleavage is bromination *ortho* to the methoxy group. Treatment of over-all rates with the fraction leading to ring bromination generates the data presented in Table V.

Table V. Second-Order Rate Constants for Bromination *ortho* to the Methoxy Group in Some 4-Methoxyphenylmethyl Derivatives in 50% Aqueous Acetic Acid[a]

Compd.	k_{obsd} (*ortho* substitution),[b] l. mole^{-} sec.$^{-1}$
4,4'-Dimethoxybenzhydrol	0.47
4-Methoxy-4'-methylbenzhydrol	0.42
4-Methoxybenzhydrol	0.42
4-Methoxy-4'-bromobenzhydrol	0.27
4-Methoxy-4'-nitrobenzhydrol	0.11
4-Methoxybenzyl alcohol	0.63
4-Methoxyphenylcyclohexylcarbinol	0.32
4-Methoxytriphenylcarbinol	0.24
4,4'-Dimethoxydiphenylmethane	1.41
Anisole	0.65[c]

[a] NaBr 0.2 M; 50°. [b] Statistically corrected for the number of equivalent positions. [c] Obtained using our value for the second-order rate constant (81.7 l. mole^{-1} sec. $^{-1}$) and the isomer distribution (1.6% *ortho* substitution, 98.4% *para* substitution) reported recently by Brown and Stock, *J. Am. Chem. Soc.*, **82**, 1942 (1960), for the bromination of anisole in glacial acetic acid.

Since the groups on the carbinyl carbon are remote from the position *ortho* to the methoxy and cannot enter into conjugative interaction with any carbonium ion formed by the attack of bromine at that position, their influence should be expressable in terms of Taft's σ^* parameters.

In this treatment the organic substrates are considered as 4-methoxyphenyl-CRR'R'' where, σ^* for –CRR'R'' equals $\sigma^*_{CH_2R} + \sigma^*_{CH_2R'} + \sigma^*_{CH_2R''}$. For –CH$_3$, $\sigma^* = 0.000$ and for 4-X-C$_6$H$_4$CH$_2$–, $\sigma^* = \sigma^*_{C_6H_5CH_2} + \sigma_p^0$.[23] The rate constant for bromination *ortho* to the methoxy group in 4-methoxybenzyl alcohol is taken as k_o. σ^* is then found to be –0.67.

It is clear from Figure 3 that a rather good correlation of the bromination rates with σ^* is obtained by this

(23) The substituent parameters, σ_p^0, are those given by Taft (R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960)) and are the inductive substituent parameters for the 4-X-C$_6$H$_4$– group taken as a whole. They are adjusted to the σ^* scale by adding to them $\sigma^* = 0.215$ for the C$_6$H$_5$CH$_2$– group (it is assumed in doing this that $\rho^* = \rho^0$; this is usually a good approximation). We are grateful to Professor Taft for suggesting this treatment to us.
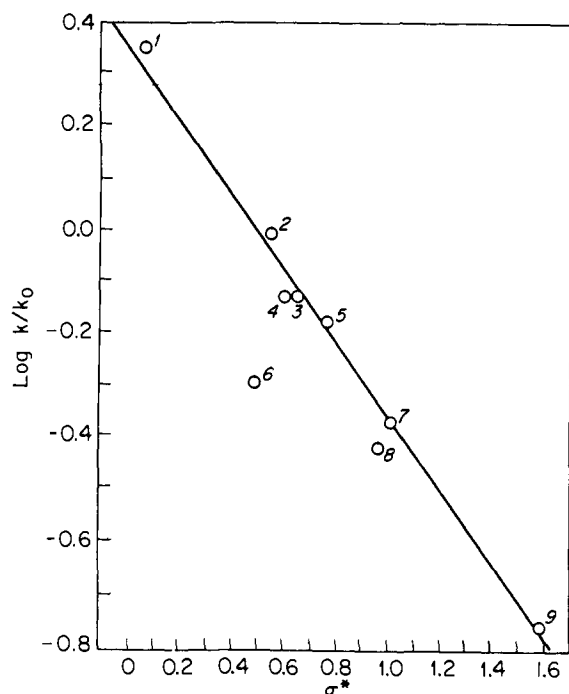

Figure 3. Correlation of rates of bromination *ortho* to the methoxy group in some 4-methoxyphenylmethyl derivatives with σ^*: 1, 4,4'-dimethoxydiphenylmethane; 2, 4-methoxybenzyl alcohol; 3, 4,4'-dimethoxybenzhydrol; 4, 4-methoxy-4'-methylbenzhydrol; 5, 4-methoxybenzhydrol; 6, 4-methoxyphenylcyclohexylcarbinol; 7, 4-methoxy-4'-bromobenzhydrol; 8, 4-methoxytriphenylcarbinol; 9, 4-methoxy-4'-nitrobenzhydrol.

treatment with the exceptions of two compounds (**6** and **8**) which we have already seen give very slow rates in the cleavage reaction. We cannot explain these anomalously slow rates in the bromination reaction where a steric interaction can obviously not be invoked.

The fact that these indirectly obtained rate constants for the most part follow a sensible correlation with Taft's substituent parameters is further evidence for the validity of our method of dissecting the over-all bromination rates. The influence of the groups is what might be expected in terms of deactivation of the ring through increasing electron attraction of the groups through the inductive effect. In connection with the *hydroxy effect* referred to in the previous paper[3] it is noteworthy that, despite the great acceleration of the cleavage reaction for all of the carbinols shown here relative to 4,4'-dimethoxydiphenylmethane, they all deactivate the same ring relative to this compound when electrophilic attack at a point away from their immediate vicinity is involved, and deactivate the ring relative to *para* hydrogen when attached to the anisyl nucleus (Table V).