Reversible Bromination. I. Isomerization and Disproportionation of *p*-Bromophenols

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The unusually facile hydrogen bromide catalyzed isomerization and disproportionation of *p*-bromophenols was studied at 25° in solution. Equilibration occurs at a rate which is greatly affected by the position and number of bromo and alkyl groups on the substrate. The resultant mixtures are rich in *o*-bromophenols and disproportionation products, but no *m*-bromophenols were detected. The degree of disproportionation and specificity of catalysis suggest that this reaction is a reversible bromination. The mechanism probably involves slow debromination and concurrent rapid rebromination *via* the same type of intermediate benzenonium ion. No isomerization or disproportionation of *p*-chlorophenols was observed under similar conditions. This novel reaction represents a useful method of preparing certain *o*-bromophenols which are otherwise difficult to obtain.

Although iodination of aromatic compounds is known to be reversible,[2] bromination and most other electrophilic aromatic substitutions have been assumed to be irreversible under normal conditions and the products formed are kinetically controlled.[3,4] Rearrangement, isomerization, and disproportionation of bromoaromatic compounds have been noted,[5-8] but only in the presence of strong Lewis acids or at elevated temperatures. Under these conditions, *meta* isomers generally predominate in the thermodynamically controlled equilibrium mixtures of products. The mechanism of these reactions is said to involve both intermolecular transbromination and intramolecular rearrangement.[8] In a few cases, very reactive substrates have been reported to disproportionate[5] and rearrange to mixtures rich in *ortho* isomers[7] under relatively severe conditions.

We have discovered that bromination of phenols is reversible under very mild conditions. For example, monobromination of *m*-cresol in nonpolar solvents at 25° gives 4-bromo-*m*-cresol as the major product and lesser amounts of 2-bromo- and 6-bromo-*m*-cresols. However, if the reaction mixture is allowed to reach equilibrium (with respect to monobromo isomers) without removing the hydrogen bromide present, the two *o*-bromo isomers and disproportionation products predominate. We have also observed that other *p*-bromophenols undergo this unusually facile hydrogen bromide catalyzed isomerization and disproportionation. This paper describes our initial efforts to determine the scope, mechanism, and utility of this novel reaction.

Results

Bromination of *m*-cresol was carried out in chloroform at 25°. Vapor phase chromatographic analysis of the reaction mixture immediately following the bromine addition indicated a molar composition of 59% 4-bromo-, 19% 6-bromo-, and 3% 2-bromo-*m*-cresol, and 19% dibromo-*m*-cresols. After this stood in the presence of hydrogen bromide generated during the reaction, however, a mixture which consisted of *ca.* 20% each of 2-, 4-, and 6-bromo-*m*-cresol, 11% *m*-cresol, and 29% dibromo-*m*-cresols was obtained. No 5-bromo-*m*-cresol or tribromo-*m*-cresols were detected. The course of the reaction is outlined in Table I.

TABLE I
REVERSIBLE BROMINATION OF *m*-CRESOL[a]

Component	Composition, mol %: 0 hr[b]	8 hr[b]	140 hr[b]	266 hr[b]
m-Cresol	0	7	11	11
4-Bromo-*m*-cresol	59	28	18	19
6-Bromo-*m*-cresol	19	30	20	21
2-Bromo-*m*-cresol	3	12	20	20
4,6-Dibromo-*m*-cresol	14	17	23	23
2,4-Dibromo-*m*-cresol	5	6	8	6
2,6-Dibromo-*m*-cresol	0	0	0	0

[a] Slow addition (2 hr) of bromine (0.229 mol) in 80 ml of chloroform to *m*-cresol (0.185 mol) in 80 ml of chloroform at 25°. [b] Reaction time; the time refers to the interval between the end of bromine addition and neutralization of hydrogen bromide in each sample.

Proof that a true equilibrium with respect to the monobromo isomers had been established was obtained by treatment of pure samples of 2-, 4-, and 6-bromo-*m*-cresol separately with chloroform saturated with hydrogen bromide at 25°. In each case, essentially the same mixture was obtained, which contained *ca.* 22% each of 2-, 4-, and 6-bromo-*m*-cresol, *ca.* 17% each of *m*-cresol, and a mixture of dibromo-*m*-cresols. The results are summarized in Table II.

The equilibration half-life (time required to reach a substrate concentration half-way between the initial concentration and the concentration at equilibrium) for each monobromo-*m*-cresol was estimated by plotting the substrate concentration against reaction time using data from Table II. Values of 3, 9, and 57 hr were obtained for 4-, 6-, and 2-bromo-*m*-cresol, respectively, and these values represent a rough approximation of the relative rates of debromination.

It is apparent from the data in Table II that equilibrium with respect to the dibromo isomers had not been attained after 337 hr in the case of 2-bromo-*m*-cresol. Reaction of an equimolar mixture of *m*-cresol and dibromo-*m*-cresols with hydrogen bromide at 25° in chloroform gave essentially the same distribution of products as that obtained with monobromo isomers.

Similar results were obtained when reversible bromination or equilibration of bromination products was

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(3) R. O. C. Norman, "Principles of Organic Synthesis," Methuen & Co. Ltd., London, 1968, p 347.
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(7) For a recent review, see H. J. Shine, "Aromatic Rearrangements," Elsevier Publishing Co., New York, N. Y., 1967.
(8) A novel method of obtaining largely *ortho*-substituted products from bromination of phenols has recently been reported by D. E. Pearson, R. D. Wysong, and C. V. Breder, *J. Org. Chem.*, **32**, 2358 (1967).

TABLE II
REACTION OF MONOBROMO m-CRESOLS WITH HYDROGEN BROMIDE[a]

A. 4-Bromo-m-cresol

Component	Composition, mol % 3 hr	24 hr	192 hr	531 hr
m-Cresol	5	9	16	16
4-Bromo-m-cresol	60	30	22	21
6-Bromo-m-cresol	23	37	22	22
2-Bromo-m-cresol	5	13	23	23
4,6-Dibromo-m-cresol	5	9	14	15
2,4-Dibromo-m-cresol	1	2	3	2
2,6-Dibromo-m-cresol	0	0	0	1

B. 6-Bromo-m-cresol

Component	Composition, mol % 6 hr	24 hr	144 hr	264 hr
m-Cresol	5	10	16	16
4-Bromo-m-cresol	20	31	22	21
6-Bromo-m-cresol	69	39	23	23
2-Bromo-m-cresol	3	11	23	23
4,6-Dibromo-m-cresol	3	8	14	14
2,4-Dibromo-m-cresol	0	1	2	2
2,6-Dibromo-m-cresol	0	0	0	1

C. 2-Bromo-m-cresol

Component	Composition, mol % 6 hr	24 hr	168 hr	337 hr
m-Cresol	0	6	11	13
4-Bromo-m-cresol	3	8	18	22
6-Bromo-m-cresol	2	7	22	22
2-Bromo-m-cresol	94	75	38	28
4,6-Dibromo-m-cresol	0	1	2	6
2,4-Dibromo-m-cresol	1	3	8	8
2,6-Dibromo-m-cresol	0	0	1	1

[a] The initial substrate concentration in each case was 1.16 M in chloroform saturated with hydrogen bromide at 25°.

carried out in other solvents, although the rates of debromination differed significantly. In the absence of a solvent, reaction with hydrogen bromide proceeded very slowly at 25°. The equilibration half-lives were in the following order: chloroform < chlorobenzene < carbon tetrachloride < no solvent.

To determine the effect of m-alkyl groups on the rate of debromination, the reaction was studied using p-bromophenol and 4-bromo-3,5-xylenol as substrates.

The isomerization and disproportionation of p-bromophenol was found to be very slow at 25° in chloroform saturated with hydrogen bromide. Equilibration was not complete after 942 hr, but the half-life was estimated to be *ca.* 115 hr. The o-bromophenol concentration had exceeded that of p-bromophenol, and a considerable amount of disproportionation had occurred. No m-bromophenols or tribromophenols were detected. The results are summarized in Table III.

TABLE III
REACTION OF p-BROMOPHENOL[a] WITH HYDROGEN BROMIDE

Component	Composition, mol % 6 hr	24 hr	144 hr	942 hr
Phenol	2	4	7	9
p-Bromophenol	95	89	67	41
o-Bromophenol	2	5	21	43
Dibromophenols	1	2	6	7

[a] The initial concentration of p-bromophenol was 1.16 M in chloroform saturated with hydrogen bromide at 25°.

As expected, the isomerization and disproportionation of 4-bromo-3,5-xylenol was very rapid at 25° in chloroform saturated with hydrogen bromide. At equilibrium with respect to the monobromo isomers, 2-bromo-3,5-xylenol was the major component of the mixture of products. A very slow isomerization of the dibromo-3,5-xylenols was observed, but no tribromo-3,5-xylenol was detected. The results are summarized in Table IV.

TABLE IV
REACTION OF 4-BROMO-3,5-XYLENOL[a] WITH HYDROGEN BROMIDE

Component	Composition, mol % 0.1 hr	1 hr	24 hr	410 hr
3,5-Xylenol	3	9	10	14
4-Bromo-3,5-xylenol	34	16	15	11
2-Bromo-3,5-xylenol	53	66	64	63
2,4-Dibromo-3,5-xylenol	10	10	9	6
2,6-Dibromo-3,5-xylenol	0	0	2	5

[a] The initial concentration of 4-bromo-3,5-xylenol (98% pure) was 0.27 M in chloroform saturated with hydrogen bromide (0.3 M) at 25°.

The equilibration half-life was estimated to be about 3 min under these conditions. In striking contrast with the rapid reaction of 4-bromo-3,5-xylenol, no isomerization or disproportionation of 4-chloro-3,5-xylenol was observed in chloroform saturated with hydrogen chloride or hydrogen bromide.

It was of particular interest to determine whether other acids would effect isomerization and disproportionation of p-bromophenols, and the very reactive 4-bromo-3,5-xylenol seemed a suitable substrate for such a study. No reaction was observed when p-toluenesulfonic acid or trifluoroacetic acid was used. Isomerization and disproportionation were effected very slowly by hydrogen chloride, but equilibration was not complete after 400 hr.

The rate of debromination was also affected by changes in hydrogen bromide concentration, temperature, and substrate concentration. As expected, a decrease in the concentration of hydrogen bromide or the substrate caused a corresponding decrease in rate as approximated by the equilibration half-life. The reaction was observed to be faster at 25° than at 0 or 65° when the substrate and hydrogen bromide concentrations were held constant. The results are summarized in Table V.

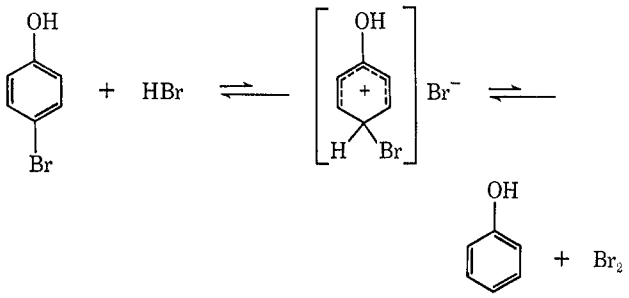
TABLE V
EFFECT OF TEMPERATURE AND CONCENTRATION ON REACTION OF 4-BROMO-3,5-XYLENOL WITH HYDROGEN BROMIDE IN CHLOROFORM

Temp, °C	Substrate concn, M	Hydrogen bromide concn, M	$t_{1/2}$, min
0	0.27	0.12	160
25	0.27	0.12	23
25	0.27	0.30	3
25	0.027	0.12	640
65	0.27	0.12	90

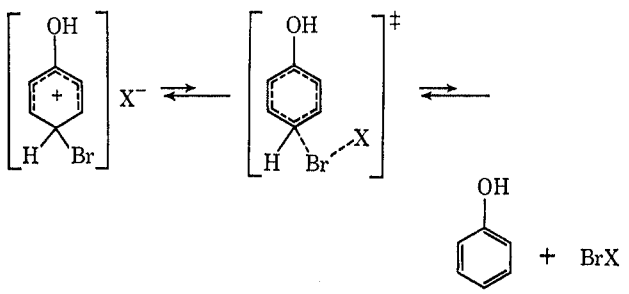
Discussion

Certain tentative conclusions concerning the mechanism of this unusual reaction seem appropriate at this point. It is clear, for example, that intramolecular rearrangement, which represents a major reaction path

in the presence of excess aluminum halides,[6,8] is not operative here in view of the high degree of disproportionation and the absence of *m*-bromo isomers. Moreover, intermolecular transbromination does not seem likely because of the observed specificity of catalysis. General acid catalysis would be expected if the mechanism involved direct transbromination by an intermediate benzenonium ion. It seems probable, therefore, that this reaction is an example of reversible bromination, as illustrated below.



Reaction of the phenol with bromine to form an intermediate σ complex is thought to be the rate-determining step during bromination.[4] Therefore, breaking of the carbon–bromine bond and formation of molecular bromine must be the rate-determining step during debromination, according to the principle of microscopic reversibility.[9] Since it is reasonable to assume that this step is facilitated by bromide ion, the rate of debromination should decrease when less nucleophilic anions are used.



The fact that hydrogen chloride effects debromination much more slowly than hydrogen bromide is in accord with this interpretation. Likewise, the poor nucleophilicity of trifluoroacetate and *p*-toluenesulfonate ions accounts for the failure of the corresponding acids to effect debromination.

Although a similar mechanism might be expected for dechlorination, the failure of *p*-chlorophenols to isomerize or disproportionate in the presence of hydrogen chloride or hydrogen bromide suggests that the greater strength of the carbon–chlorine bond results in a higher activation energy for this step.

The observed effect of *m*-alkyl groups on the rates of debromination (*p*-bromophenol < 4-bromo-*m*-cresol < 4-bromo-3,5-xylenol) represents additional evidence in support of the proposed mechanism. The stability of the intermediate benzenonium ion should be enhanced through additional delocalization of the positive charge by *m*-alkyl groups.

In the case of *o*-bromophenols, the rate of debromination is also affected by intramolecular hydrogen bonding, evidence for which has been obtained from infrared spectra (*o*-bromophenols exhibit a characteristic OH absorption band at about 3520 cm^{-1} in dilute solution).[10] The additional energy required to break the hydrogen bond would be expected to result in a reduced rate of debromination. The predominance of *o*-bromo isomers in the thermodynamically controlled mixture of products at equilibrium thus results from their greater stability toward debromination.

The steric effect of an alkyl group adjacent to the bromine atom would also be expected to destabilize the transition state for debromination of 2- and 4-bromo-*m*-alkylphenols and reduce the rate accordingly. The observed relative order (1:18:6) for debromination of 2-, 4-, and 6-bromo-*m*-cresol, respectively, seems to indicate that intramolecular hydrogen bonding has the greater effect, but that steric factors also contribute.

The same relative order was observed for the individual rates of formation of these isomers (as measured by relative concentrations immediately after addition of bromine was complete—see Table I) during bromination of *m*-cresol. At equilibrium during reversible bromination, the concentration of each isomer is dependent on the rate of formation and the rate of debromination of that isomer. Since 4-bromo-*m*-cresol debrominates most rapidly and is formed most rapidly, and 2-bromo-*m*-cresol debrominates most slowly and is formed most slowly, it is not unreasonable that the concentrations of all three isomers at equilibrium are approximately the same.

A possible explanation for the fact that 4-bromo-3,5-xylenol debrominates more rapidly at 25° than at 0 or 65° is provided by consideration of the stability of the intermediate π complex between hydrogen bromide and the substrate. At or below 25°, this complex is relatively stable and a normal temperature effect is observed. At 65°, however, dissociation of this complex seems to be considerable enough that the rate is affected. A similar phenomenon in a kinetic study of bromination of phenol has been reported.[11]

The solvent effects observed during the reversible bromination of *m*-cresol are more difficult to interpret because they do not relate to the order of reactivity expected from values for the dielectric constants,[12] and this might be the subject of further investigation. Other classes of reactive compounds will also be studied as potential substrates for reversible bromination.[13]

The utility of this reaction for the preparation of certain *o*-bromophenols (especially 2-bromo-*m*-alkylphenols) which are otherwise difficult to obtain is readily apparent. It also represents a potential method of debromination under relatively mild conditions if a suitable bromine scavenger is found.[14] Further studies of the utility and scope of reversible bromination will be reported in subsequent papers in this series.

(9) A. Liberles, "Introduction to Theoretical Organic Chemistry," The Macmillan Co., New York, N. Y., 1968, p 27.

(10) *Advan. Org. Chem.*, **5**, 151 (1965).

(11) L. M. Yeddanapalli and N. S. Gnanapragasam, *J. Chem. Soc.*, 4934 (1956).

(12) N. A. Lange, "Handbook of Chemistry," 10th ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1966, p 1234.

(13) No isomerization or disproportionation of *p*-bromothiophenol or bromomesitylene was observed, but rapid disproportionation of 4-bromoresorcinol was detected. Other potential substrates include 3,5-dimethylanisole, 3,5-xylidine, and the naphthols.

(14) When acetone was used as the solvent for the reaction of 4-bromo-*m*-cresol with hydrogen bromide, large amounts of *m*-cresol and no dibromo *m*-cresols were detected.

Experimental Section[15]

Materials.—4-Bromo-*m*-cresol was prepared by addition of a solution of bromine in chloroform to a solution of *m*-cresol in chloroform, and immediate isolation by extraction with aqueous sodium hydroxide and neutralization. Recrystallization from heptane or cyclohexane afforded 99% pure material (vpc analysis): mp 60–61° (lit.[16] mp 56–57°).

6-Bromo-*m*-cresol was prepared by bromination of *m*-cresol in chloroform and equilibration of the resultant mixture (saturated with hydrogen bromide) for *ca.* 6 hr at 25°. The crude product obtained by isolation and fractional distillation at 1 mm was treated with benzenesulfonyl chloride and pyridine. Recrystallization from methanol gave 99.8% pure 6-bromo-*m*-cresol benzenesulfonate (vpc analysis): mp 99–102° (lit.[17] mp 92–93°). Pure 6-bromo-*m*-cresol was obtained by hydrolysis and distillation: mp 38–39°; bp 56–57° (3 mm) [lit.[17] bp 81–82° (4 mm)].

2-Bromo-*m*-cresol was prepared by bromination of *m*-cresol in chloroform and equilibration of the resultant mixture (saturated with hydrogen bromide) for about 24 hr at 25°. The crude product obtained by isolation and fractional distillation at 1 mm was treated with *p*-toluenesulfonyl chloride and pyridine. Recrystallization from methanol gave pure 2-bromo-*m*-cresol *p*-toluenesulfonate: mp 86–87° (lit.[17] mp 85–85.5°). Pure 2-bromo-*m*-cresol was obtained by hydrolysis and vacuum sublimation: mp 59–61° (lit.[17] mp 58.5–59°).

4-Bromo-3,5-xylenol purchased from Aldrich Chemical Co. (mp 114–115°) was found to be 98.5% pure (vpc analysis) and was used without further purification.

p-Bromophenol purchased from Eastman Kodak Co. (mp 66–68°) was also used without purification.

Chloroform (Merck reagent grade), chlorobenzene (Matheson Coleman and Bell), and carbon tetrachloride (Matheson Coleman and Bell) were used without purification for most runs. In one case, chloroform was treated with sulfuric acid, washed with water, dried, and distilled to remove traces (0.75%) of ethanol. Equilibration of 4-bromo-*m*-cresol proceeded more slowly in this material than in untreated chloroform, but more rapidly than in chlorobenzene.

General Method of Equilibration.—The substrate was dissolved in the appropriate solvent and the solution was saturated with anhydrous hydrogen bromide (Matheson Coleman and Bell) at room temperature.[18] The resultant solution was allowed to stand at room temperature (25°) in a tightly stoppered flask. Samples were removed periodically, neutralized with anhydrous sodium carbonate, and analyzed by vapor phase chromatography.

Vapor Phase Chromatography.—All vpc analyses were obtained using an F & M Model 500 or Model 5750 chromatograph with a thermal conductivity detector. The column conditions and retention times for the compounds studied are provided in Table VI.

TABLE VI

VAPOR PHASE CHROMATOGRAPHIC RETENTION TIMES

Compd	Retention time, min				
	A[a]	B[b]	C[c]	D[d]	E[e]
Phenol	1.1				
o-Bromophenol	1.9				
p-Bromophenol	5.2				
2,6-Dibromophenol	6.6				
2,4-Dibromophenol	6.6				
m-Cresol		2.0		64	10
2-Bromo-*m*-cresol		3.4		48	8
6-Bromo-*m*-cresol		3.4		52	8
4-Bromo-*m*-cresol		5.4			32
2,6-Dibromo-*m*-cresol		7.6			22
2,4-Dibromo-*m*-cresol		7.6			24
4,6-Dibromo-*m*-cresol		7.6			26
3,5-Xylenol			1.4		
2-Bromo-3,5-xylenol			2.6		
4-Bromo-3,5-xylenol			4.8		
4-Chloro-3,5-xylenol			6.0		
2,4-Dibromo-3,5-xylenol			8.0		
2,6-Dibromo-3,5-xylenol			8.8		

[a] 6-ft 10% UC-W98 column (1/8-in. i.d.) at 140° with a helium flow rate of 45 ml/min. [b] Column A at 150–200° (6°/min). [c] Column A at 170°. [d] 6-ft 20% Carbowax 20M column (1/4-in. i.d.) at 135° with a helium flow rate of 200 ml/min. [e] Column D at 175° for 12 min, increase to 200° for 20 min.

Registry No.—*m*-Cresol, 108-39-4; 4-bromo-*m*-cresol, 14472-14-1; 6-bromo-*m*-cresol, 14847-51-9; 2-bromo-*m*-cresol, 22061-78-5; *p*-bromophenol, 106-41-2; 4-bromo-3,5-xylenol, 7463-51-6.

Acknowledgment.—Assistance was provided during the experimental portion of this work by Mr. Anthony Mujsce and Mr. Richard Narburgh. The authors also wish to thank Professor Fausto Ramirez for suggestions.

(15) All melting points and boiling points are uncorrected.

(16) R. C. Huston and J. A. Hutchinson, *J. Amer. Chem. Soc.*, **54**, 1504 (1932).

(17) R. C. Huston and W. J. Peterson, *ibid.*, **55**, 3880 (1933).

(18) In several cases, the hydrogen bromide was passed through a carbon tetrachloride solution of phenol to remove traces of bromine, but no significant effect on the rate of equilibration was observed. Exclusion of light also had no observable effect.