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Mechanism of the Non-Aryne Hydroxydehalogenation of Unactivated Aryl Halides^{1,2}

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The hydroxydehalogenation of aryl halides upon reaction with aqueous alkali at temperatures up to 333 °C was examined to determine the nature of an ipso hydroxydehalogenation process reported in 1957 to compete with the aryne mechanism. The reactions of *p*-iodo-, *p*-bromo-, and *p*-chlorotoluene with aqueous solutions of sodium or potassium hydroxide or carbonate, carried out in Pyrex glass tubes with exclusion of traces of transition metals, led in all cases to the same product distribution. *m*-Cresol and *p*-cresol, the two main products, formed with a *para*/*meta* ratio of 0.82 ± 0.03 , consistent with the occurrence of the aryne mechanism only. Addition of traces of copper salts or conducting the reaction in a Monel bomb, as done by other investigators, caused the occurrence of a non-aryne ipso hydroxydehalogenation. This effect was not produced by nickel, iron, manganese, or cadmium. The ipso hydroxydehalogenation observed in previous studies is identified as a copper-catalyzed process.

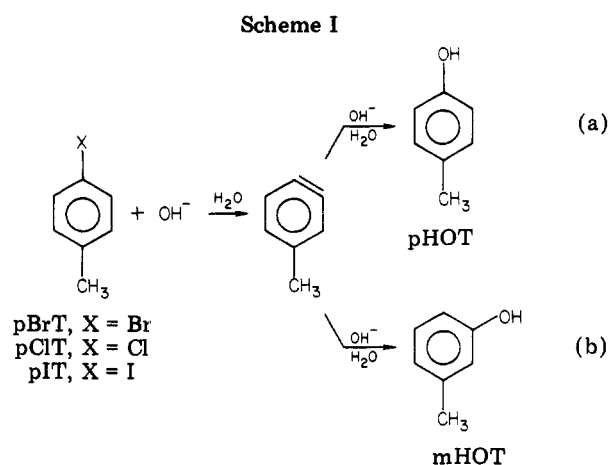
Reactions of aryl halides with aqueous alkali metal hydroxides at high temperatures to give phenols were shown by Bottini and Roberts,³ with attention also to experiments of earlier workers,^{4,5} to occur largely via the aryne mechanism. A prominent observation was that *p*-halotoluenes (pXT's) afford mixtures of *p*-cresol (pHOT) and *m*-cresol (mHOT). The mechanism was represented as in Scheme I.

Bottini and Roberts³ also observed a competing reaction of ipso hydroxydehalogenation that forms only *p*-cresol from a pXT (eq 1). This mode of reaction was more



prominent at lower temperatures and with larger halogens. From pIT reacting at 340 °C, they obtained nearly equal amounts of mHOT and pHOT, but the product from the reaction at 250 °C was almost entirely pHOT. They considered but rejected the possibility that the process of pure ipso hydroxydehalogenation was a copper-catalyzed reaction, mainly because reaction of pCIT with 4 M NaOH at 340 °C in the presence of pieces of copper wire afforded pHOT and mHOT in the same ratio as in the absence of copper wire.⁶

Bottini and Roberts³ proposed the ipso hydroxydehalogenation to occur by an S_N2-type mechanism, not further defined. A current textbook considers it to be an example of the S_NAr mechanism.⁷



Possibly closely related was the observation of reaction of pIT with 4 M aqueous NaCl at 340 °C to form pCIT.³

Our interest in further study of the ipso hydroxydehalogenation stemmed in part from the thought that it might occur by the radical chain S_{RN}1 mechanism.⁸

Results

We have conducted a study of the products of reactions of KOH, NaOH, and certain other inorganic bases with *p*-halotoluenes in sealed Pyrex glass tubes. We used glass tubes in order to control the reaction environment, with particular regard to metal ions. Care had to be taken to avoid accidental contamination by traces of transition

(1) Based in part on ref 2.

(2) Zoratti, M. Ph.D. Dissertation, University of California, Santa Cruz, CA, June 1979.

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(4) Meharg, V. E.; Allen, I., Jr. *J. Am. Chem. Soc.* 1932, 54, 2920.

(5) Shreve, R. N.; Marsel, C. *J. Ind. Eng. Chem.* 1946, 38, 254.

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(7) Morrison, R. T.; Boyd, R. N. "Study Guide to Organic Chemistry", 3rd ed.; Allyn and Bacon: Boston, MA, 1975; p 379.

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metals. Solutions were normally prepared with glass-distilled water, and the tubes were washed repeatedly with aqueous ammonia before use. The temperatures employed ranged up to about 333 °C, though in most experiments the maximum temperature attained was ca. 300–310 °C. The pressure in the reaction system was typically as high as 120 atm. To prevent explosion of the tubes, we placed them in a bomb reactor containing outside the tubes the same materials as inside. Four tubes fit in the reactor snugly, and thus four reactions could be and were run simultaneously.

Under the conditions employed, alkaline aqueous solutions undergo significant reaction with glass, causing partial consumption of the base and corrosion of the glass tubes. The tubes were heated from room temperature to the desired temperature over approximately 70–100 min, held at the maximum temperature for a period ranging from a few minutes to about 1 h, and allowed to cool. The assembly was rocked while at higher temperatures, for periods of 50–120 min, roughly centered at the time the maximum temperature was reached. Thus, each reaction was conducted over a range of temperatures, pressures, and base concentrations. Procedures and conditions are detailed in the Experimental Section.

It should be noted that our conditions were not strictly comparable to those of Bottini and Roberts.³ Besides the difference in reaction vessels employed, there are some differences in reaction temperature and in the duration of rocking of the reaction vessels.

The halotoluenes are insoluble in aqueous NaOH or KOH at room temperature but possibly form a homogeneous solution at, say, 305 °C. Shreve and Marsel⁵ felt that their systems probably were homogeneous. Bottini and Roberts³ reached the opposite conclusion. We have experimental evidence indicating homogeneity. When *p*-iodotoluene, in amounts of approximately 1, 2, 3, and 4 mmol, was allowed to react in four sealed tubes with 25 mL of 1.0 M NaOH in each case, under identical conditions of time and temperature, the *percent yield* of iodide ion was essentially constant for the 1-, 2-, and 3-mmol experiments and somewhat lower for the fourth. Had the systems been heterogeneous with the reaction occurring in the aqueous phase, a constant *absolute amount* of iodide ion should have been released. A few incidental observations concerning other experiments indicate similar behavior.

Our principal results concerning the hydroxydehalogenation of halotoluenes are summarized in Table I.

When precautions (see above) are taken to exclude metallic ions from the reaction medium, similar product distributions are obtained from reactions of all three *p*-halotoluenes with NaOH. There is a preponderance of *m*-cresol over *p*-cresol in a ratio of 1.22 ± 0.04. This behavior is approached even when pIT and solutions of relatively weak bases, such as carbonate ion, are used (see entries 1–6 in Table I). Alkali metal hydroxides react faster than carbonates, which in turn are more reactive than sodium acetate or bicarbonate.

pIT reacts with aqueous NaOH more rapidly than pBrT, which in turn reacts more rapidly than pClT. Pertinent data are shown in Table II. Under analogous conditions, *p*-fluorotoluene reacts very slowly to give only pHOT, possibly via an S_NAr reaction (entry 16, Table I).

On the other hand, if precautions to exclude metal ions are neglected or copper ions are intentionally introduced into the reaction medium, conversion and the relative amount of pHOT in the products increase. Very small

Table I.^a Product Distribution in Hydroxydehalogenation Reactions of *p*-Halotoluenes

entry	run	ArX ^b	medium ^c	t _{max} , °C	additive (amt, mol)	atm	X ⁻	PhCH ₃	PhOH	oHOT	mHOT	% yield			pHOT/ mHOT ratio	
												pHOT	mXT	pXT		ArOAr ^d
1	129-1	pIT	1.0 M NaOH ^e	309		Ar	28.7	0.08	0.1	0.06	18.8	15.9	1.6	63.6	2 ^f	0.84
2	127-1	pBrT	1.0 M NaOH ^e	~326		Ar	39		0.2	0.1	20.6	16.3	1.6	56.1	2 ^g	0.79
3	132-3	pClT ^h	1.0 M NaOH	315		Ar	4.8		tr		1.13	0.96		93.7		0.85
4	109-4	pIT	1.0 M K ₂ CO ₃	~332		air	52	1.0	4.6	<i>i</i>	31.0	23.2	1.3	19.0	7 ⁱ	0.90 ^k
5	109-2	pBrT	1.0 M K ₂ CO ₃	~332		air	52	0.7	3.7	<i>i</i>	23.9	15.6	0.6	42.0	3 ^j	0.81 ^k
6	124-2	pBrT	1.0 M NaOAc	306		Ar	1.5	tr	0.1		0.30	0.19		102.7		~1 ^k
7	129-2	pIT	1.0 M NaOH ^e	309	CuSO ₄ (8 × 10 ⁻⁷)	Ar	56.8	0.1	0.16		11.8	48.9	0.95	30.5	2 ^l	4.1
8	122-2	pBrT	1.0 M NaOH	306	CuSO ₄ (8 × 10 ⁻⁶)	air	83	tr	5.4		3.5	62.4	tr	21.1	2 ^l	19.4 ^k
9	131-2	pClT ^m	1.0 M NaOH ^e	333	CuSO ₄ (1.6 × 10 ⁻⁵)	Ar	16.6		0.08	tr	1.50	12.9		80.4	tr	8.6
10	129-b	pIT ⁿ	1.0 M NaOH ^o	309	<i>p</i>	Ar	93.6	1.8	0.1		0.7	86.8		1.9	0.4	124
11	H ₂ O/OH ⁻ no. 4	pBrT ^q	1.0 M NaOH ^o	302	<i>p</i>	Ar		0.9	0.5	tr	18.9	45.4	tr	10.3	0.2 ^s	2.4
12	107-3	pIT	1.0 M K ₂ CO ₃	~294	<i>t</i>	Ar	36.2	0.1	0.3	<i>i</i>	13.4	17.9	0.8	58.2	2	1.3
13	107-4	pIT	1.0 M K ₂ CO ₃	~294	CuSO ₄ (1.2 × 10 ⁻⁵)	Ar	40	0.1	0.4	<i>i</i>	13.6	27.8	0.6	54.1	2	2.0
14	75-2	pIT	1.0 M Na ₂ CO ₃	~275	Cu ⁰ (1.9 × 10 ⁻⁵ u)	air	62.6	6.0	3.4	<i>i</i>	1.0	44.9	<i>i</i>	34.7	1 ^j	45
15	104-4	pIT	0.8 M K ₂ CO ₃ ^e	309	Cu ⁰ (6 × 10 ⁻⁷ v)	air	48.5	8.6	0.8	<i>i</i>	10.8	23.7	<i>i</i>	49.3	tr ^j	2.2
16	122-4	pFT ^w	1.0 M NaOH	309		air	<i>i</i>	tr	0.9		1.9	1.9	<i>i</i>	98	<i>i</i>	∞

^a Yields are based on the *p*-halotoluene reactant. ^b Aryl halide, 2.3 × 10⁻³ mol unless otherwise specified. ^c Volume of 25 mL unless otherwise specified. ^d Yields are 200 mol of ArOAr^d/mol of pXT. ^e Volume 30 mL. ^f The proportions of the three isomers were 3,3'/3,4'/4,4' = 31:48:21. ^g The three isomers were in the proportion 3,3'/3,4'/4,4' = 30:50:20. ^h 2.7 × 10⁻³ mol. ⁱ Not determined. ^j Small amounts of oxidation products were also formed; see text. ^k This ratio represents (PhOH + pHOT)/(mHOT); see text. ^l The three isomers were in the proportions 3,3'/3,4'/4,4' = 14:50:36. ^m 3.5 × 10⁻³ mol. ⁿ 1.2 × 10⁻³ mol. ^o Volume 190 mL. ^p In Monel-metal bomb. ^q 4.7 × 10⁻³ mol. ^r Volume 250 mL; the solution was also 0.5 M in NaCl. ^s Chlorotoluene (6.8%) also formed. ^t Tube not washed with ammonium hydroxide before use. ^u Copper introduced as a 0.15% copper in iron (filings) alloy. ^v Copper introduced as a 0.01% copper in nickel (filings) alloy. ^w 2.72 × 10⁻³ mol.

Table II.^a Relative Reactivity of *p*-Halotoluenes with Sodium Hydroxide under Aryne-Forming Conditions

entry ^d	run	pXT ^c (amt, mmol)	medium	<i>t</i> _{max} , °C	X ⁻ (amt, mmol)	PhCH ₃	PhOH	% yield ^d					ArO- Ar' ^b	pHOT/ mHOT ratio	
								pHOT	mHOT	pCT	mBrT	pBrT			mIT
1	134-1	pIT (2.28), pBrT (2.28), pCT (3.50)	2.0 M NaOH (30 mL)	~311	I ⁻ (40.6) Br ⁻ (25.1)	0.9		10.3	8.7	0.84	71.7	2.8	54.3	3	0.84
2	127-2	pBrT (3.50), pCT (3.50)	1.0 M NaOH (30 mL)	~326	Br ⁻ (41.0) Cl ⁻ (4.2)		0.16	13.1	10.5	0.8	53.8			2	0.81

^a Yields are based on the total of both pXT reactants, except that X⁻ and each recovered pXT are based on the relevant pXT. ^b Ar and Ar' = 3- or 4-methylphenyl; yields are approximate and are 200 mol of ArOAr'/mol of pXT. ^c The atmosphere was argon in both cases. ^d Only traces of oHOT found in both cases.

amounts of copper are sufficient to make pHOT, rather than mHOT, the predominant product. Indeed, if the reaction tubes are not washed with aqueous ammonia before use, more pHOT than mHOT is often formed, especially in reactions of pIT with solutions of weak bases (see, for example, entry 12 in Table I). Formation of the ipso-substitution product predominates when reactions are conducted directly in a Monel metal bomb (see entries 10 and 11 in Table I). Inasmuch as Monel alloy contains about 28% copper, this effect may well be ascribed to it. We have verified the ability of copper-containing alloys to catalyze ipso hydroxydehalogenation, even if copper is a minor component of the alloy (see entries 14 and 15 in Table I).

A certain amount of rearrangement to the *m*-halotoluene was often observed. The proportion of meta isomer in the recovered halotoluene increased with the extent of reaction. This phenomenon was most noticeable when the reaction was run in the absence of copper and in the reactions of pBrT and pIT.

Only small amounts of diaryl ethers were generally formed, presumably because the concentrations of aryl-oxide ions in our experiments were lower than those in the commercial phenol synthesis, in which diphenyl ether was a major product unless it was recycled.⁹ The isomeric composition of the ditolyl ethers obtained was not generally determined. Some representative analyses are, however, given as footnotes to Table I. When considerable amounts of phenol are formed during the reaction, small quantities of phenyl tolyl ethers are also detectable. Hydroxybiphenyl derivatives, expected products,¹⁰ could not normally be detected, again, presumably, because of the relatively small concentrations involved. When the reaction was run in the presence of added phenoxide, methylhydroxybiphenyl(s), of unknown isomeric composition, was observed among the products.

Product composition was found to depend to some extent on the atmosphere in the tubes. When the atmosphere was air, phenol was among the products, along with small quantities of *p*-hydroxybenzaldehyde and another, unidentified, product. The latter two compounds did not appear if the reactions were run under an inert atmosphere, while phenol decreased to trace amounts, the formation of which may probably be ascribed to residual air. Control experiments showed that pHOT, but not mHOT, was converted to phenol when subjected to reaction conditions with an air atmosphere. Release of pressure was observed upon opening the sealed tubes when dealkylation had been severe. Some of our results suggest that oxidation proceeds faster in the presence of Monel metal, but in other cases there is no indication of acceleration.

Similar trends were observed for the formation of toluene, the hydrodehalogenation product. Toluene is formed only in trace amounts when air and metals are excluded, but the amount slightly increases when the reaction is run in air or in the presence of certain metals.

The effects of a few metals other than copper on product composition were investigated. Representative results are summarized in Table III. For most of these reactions (runs numbered 103 and lower), the tubes were not washed with aqueous ammonia before use. No doubt for that reason there was a general and rather irreproducible predominance of pHOT over mHOT in the products.

(9) (a) Meyer, K. H.; Bergius, F. *Ber. Dtsch. Chem. Ges.* 1914, 47, 3155. (b) Lederman, S. J.; Poffenberger, N. In "Kirk-Othmer's Encyclopedia of Chemical Technology", 2nd ed.; Wiley-Interscience: 1968; Vol. 15, pp 153-5.

(10) Hale, W. J.; Britton, E. C. *Ind. Eng. Chem.* 1928, 20, 114.

Table III.^a Effects of Metals, Benzene, and *N*-Methylmorpholine on Reactions of *p*-Iodotoluene

entry	run	<i>t</i> _{max} , °C	medium	metal and additives ^b (amt, mmol)	I	PhCH ₃	PhOH	mHOT	pHOT	Iodo- toluene ^c	ArO- Ar ^{d,e}	NTM ^d	Ph-Ar ^d	% yield	
														Ar	Ph-Ar
1	96-2	~291	0.8 M K ₂ CO ₃ (30 mL)	Fe ^o (9.7)	29.2	3.6	0.8	7.1	12.7	65.0	0.6				
2	96-1	~291	0.8 M K ₂ CO ₃ (30 mL)		32.1	0.2	0.6	6.6	20.8	72.7					
3	93-3	~311	1.0 M K ₂ CO ₃ (25 mL)	Cd ^o (38.6)	62.8	32.3	0.4	6.1	7.0	34.4	0.6				
4	93-1	~311	1.0 M K ₂ CO ₃ (25 mL)		25.4	0.3	0.3	7.8	14.3	73.0	0.6				
5	102-4	321	1.0 M K ₂ CO ₃ (25 mL)	Mn ^o (8.1)	72.5	0.9	1.0	20.5	42.9	23.2	3.8				
6	102-1	321	1.0 M K ₂ CO ₃ (25 mL)		74.7	0.2	1.9	22.7	37.7	31.1	3.9				
7	116-1	~299	1.0 M NaOH (25 mL)	Ni ^o (3.0) ^f	33.3	0.1	tr	17.2	14.5	65.9 ^f	3				3.8 ^g
8	103-2	~276	1.0 M K ₂ CO ₃ (25 mL)	Fe ^o (5.1), benzene (112)	<i>h</i>		tr	tr	tr	97.8					0.3 ^f
9	103-1	~276	1.0 M K ₂ CO ₃ (25 mL)	benzene (112)	<i>h</i>					100.2					0.5
10	91-4	~291	1.0 M K ₂ CO ₃ (25 mL)	Cu ₂ O (1.7 × 10 ⁻³), benzene (112)	90.9		0.5	tr	89.2	13.2	0.9				
11	101-3	~276	1.0 M K ₂ CO ₃ (25 mL)	Fe ^o (5.1), NMM (44.7)	19.1	5.0			8.2	74.0					6.5
12	101-1	~276	1.0 M K ₂ CO ₃ (25 mL)	NMM (44.7)	12.0	1.7			5.5	86.9					8.1
13	97-1	~296	1.0 M K ₂ CO ₃ (25 mL)	Cu ₂ O (7.7), NMM (44.7)	98.5	0.2	0.2		87.7		0.8				

^a All tubes initially contained 2.3 mmol of pIT. The atmosphere was argon containing some air unless otherwise specified. The tubes were not washed with aqueous ammonia unless otherwise specified. Product distribution is given in terms of percentages of starting pIT. ^b oHOT and mIT were not determined except where specified. ^c NMM is *N*-methylmorpholine. ^d Includes all isomers (mostly pIT). ^e NTM is *N*-tolylmorpholine. Values are approximate, not having been corrected for response factor. However, they are comparable, being in error by the same factor. ^f Ar and Ar' = 3- or 4-methylphenyl. ^g Yield is 200 mol of ArOAr'/moles of pIT. ^h Atmosphere was air-free argon; mIT, 1.45%; pIT, 64.5%. The tube had been washed with ammonium hydroxide. ⁱ Also 1.4% of biphenyl. ^j Also 0.3% of biphenyl.

Inasmuch as most of the experiments of Table III were run in tubes not rinsed with aqueous ammonia, they were somewhat affected by traces of copper from the glass. Accordingly, experiments should be considered in pairs (entry 1 vs. 2, entry 3 vs. 4, etc.) so as to discern the effect of the metal or other additive.

Manganese, nickel, iron, and cadmium were examined. None of these metals appeared to cause significant variations in the relative amounts of cresols formed.¹¹ Iron and cadmium, however, significantly stimulated hydroiodination to toluene under the conditions used. The data provide no indication of any copper-catalyzed hydrodehalogenation in these systems.

Reaction of pIT with 1 M K₂CO₃ in the presence of a massive amount of benzene (entry 9, Table III) occurred only to a slight extent, possibly owing to the system not being homogeneous. However, the same reactants in the presence of iron (entry 8, Table III) afforded 3.8% of methylbiphenyl(s) without much else. When a rather large amount of Cu₂O was present instead of iron, a large amount of reaction occurred, mainly ipso hydroxydeiodination to pHOT (entry 10, Table III).

When a substantial amount of *N*-methylmorpholine (NMM) was present, some pHOT but no detectable amount of mHOT was formed; a significant amount of *N*-tolylmorpholine(s) was also produced (entry 12, Table III). The same ingredients with Cu₂O also present afforded mainly pHOT, no mHOT, and very little of anything else (entry 13, Table III). No detectable amount of *N*-methyltoluidine(s) or *N*-methyl-*N*-(β-hydroxyethyl)-toluidine(s) was formed in the NMM experiments.

Discussion

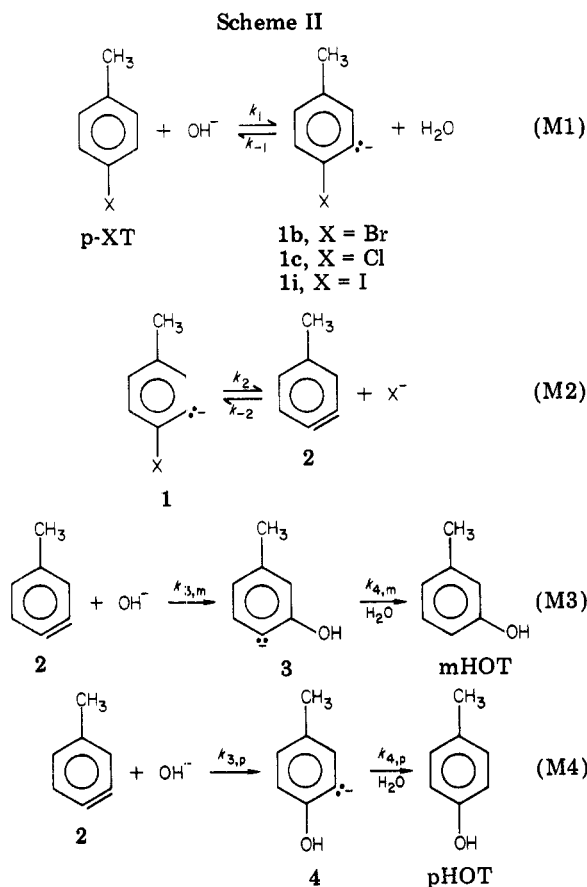
Aryne Mechanism of Hydroxydehalogenation. The fact that more *m*- than *p*-cresol is obtained on reaction of *p*-halotoluenes with aqueous hydroxide ion when traces of metal are excluded from the system strongly indicates that under these conditions the reaction occurs via the aryne mechanism³ (Scheme II). The fact that the observed pHOT/mHOT ratio, 0.82 ± 0.03, does not depend on the identity of the halogen serves to confirm that no incursion by a direct substitution mechanism took place (except for *p*-fluorotoluene). In unfavorable cases, such as reaction of pIT with carbonate ion or of pBrT with acetate ion (entries 4 and 6, Table I), the pHOT/mHOT ratio somewhat exceeded 0.82, suggesting that a small amount of direct substitution still occurred. We suppose that its occurrence is due to catalysis by traces of copper ion present despite our efforts to exclude them. In other reactions with carbonate or acetate salts, described elsewhere,² variation of this ratio from 0.82 upward is similarly indicative of catalysis by traces of copper.

The *p*-cresol/*m*-cresol ratio of 0.82 is similar to those obtained from the additions of several other nucleophiles to 4-methylbenzylene under a variety of conditions.¹² For example, reaction with KNH₂ in ammonia leads to toluidines in *p/m* ratio 0.67,¹³ and attack by iodide ion in ethanol yields iodotoluenes in a *p/m* ratio of 0.89.¹⁴

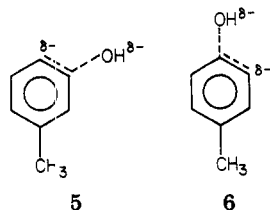
(11) The variation in pHOT/mHOT ratios, for example, between runs 96-2 and 96-1 or between runs 93-3 and 93-1 in Table III is attributed to an uneven incidence of copper catalysis. If anything, the presence of Fe or Cd metal tended to suppress the complication leading to excess pHOT, possibly by reacting with traces of copper ions to reduce them to Cu metal which was then absorbed onto the Fe or Cd surface. Large amounts of metals were used on purpose so as to ensure that they would cause dramatic changes in the product composition if endowed with even a weak catalytic ability.

(12) Hoffmann, R. W. "Dehydrobenzene and Cycloalkynes"; Academic Press, New York, 1967; pp 134-47.

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This type of selectivity is easily rationalized in terms of the inductive effect of the methyl group on the transition states leading to C-O bond formation (see 5 and 6). The



partial negative charge that has developed on a ring carbon in the transition state interacts unfavorably with the electron-releasing methyl group. The further away from the methyl group the incipient negative charge, the lower the energy level of the transition state. It follows that attack at the 2-position of 4-methylbenzynes, via a transition state with the charge partially localized at the 1-position (5), and leading ultimately to mHOT, is favored over attack at the 1-position.

The para/meta ratios tabulated by Hoffmann¹² for attack on 4-methylbenzynes range from about 0.5 to 0.9. Our observed ratio of 0.82 expresses relatively low selectivity. This is probably to be attributed to the leveling effect of high temperature.

Copper-Catalyzed Hydroxydehalogenation. Our work provides strong evidence that the direct displacement observed by Bottini and Roberts was due to catalysis by the metal composing the vessels in which their reactions had been conducted. Nearly all their reactions were performed in a Monel-metal liner in a manganese-steel bomb. The few that were performed directly in the bomb were no doubt exposed to traces of copper and nickel

transferred from the liner to the inner surface of the bomb.

In particular, copper strongly catalyzes the reaction. Copper has long been known to catalyze these hydroxydehalogenations,^{5,9a,10} but the effectiveness of even trace amounts had not been realized, perhaps owing to the fact that aryl chlorides had been used in most of the work.

Our work does not provide much insight into the form of copper that catalyzes hydroxydehalogenation. We observed catalysis variously by Cu metal, Cu₂O, CuCl, and CuSO₄, as well as by whatever form contaminates laboratory glassware but is largely washed away on rinsing with aqueous ammonia. The active species appears not to be Cu metal.

The isomer distributions of the ditolyl ethers given in the footnotes to Table I are in good agreement with those calculated for operation of the aryne mechanism only, if the ratio of attack at the 1- and 2-positions of 4-methylbenzynes is the same for the cresolate ion as for the hydroxide ion ($p/m = 0.82$). The distribution is only mildly shifted toward more para orientation when some copper is added to the system (entry 7, Table I). It appears that aryloxydehalogenation is not as sensitive to copper catalysis as is hydroxydehalogenation. Dalman and Neumann¹⁵ had concluded in 1967 that diphenyl ether is formed only via nucleophile attack on a benzyne intermediate in the reaction of radiolabeled chlorobenzene with 4 M aqueous NaOH in a steel reactor. Copper-catalyzed condensation of phenols or phenoxide ions with aryl halides is an important method for the preparation of diaryl ethers.¹⁶

Other Evidence for the Occurrence of Copper-Catalyzed Reactions. A further type of evidence for our conclusion that ipso hydroxydehalogenation is a copper-catalyzed reaction comes from observations summarized in Table IV. Bottini and Roberts reported that the proportion of hydroxydehalogenation (at 250 °C) proceeding via the nonrearranging mechanism was about 37, >67, and >94% for *o*-, *m*-, and *p*-iodotoluene, respectively.³ We find that the reactivity of the three iodotoluenes in copper-catalyzed hydroxydehalogenation is in the order ortho < meta ≥ para (see Table IV, entries 1, 2, and 3).

The mechanism of copper-catalyzed aromatic nucleophilic substitution has been much studied.^{17,18} An oxidative-addition/reductive-elimination sequence proceeding through an organocopper intermediate has been proposed for such reactions as chlorodeiodination.^{19,20} Copper-catalyzed phenol formation from diazonium salts is also thought to involve an organocopper intermediate.²¹ Conceivably, copper-catalyzed hydroxydehalogenation proceeds through a similar mechanism. If an arylcopper intermediate is involved, the retarding effect of the ortho methyl group might be attributed to steric hindrance, to unfavorable inductive interaction with the partial negative charge expected to form on the copper-bound carbon atom, or to both.

Bottini and Roberts³ reported that heating *p*-iodotoluene with an aqueous neutral NaCl solution in their bomb at 340 °C effected complete conversion to *p*-chlorotoluene (except for considerable decomposition).

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Table IV.^a Halodeiodination and Copper-Catalyzed Hydroxydeiodination of Iodotoluenes

entry	run	iodo-toluene (amt, mmol)	medium ^b	t _{max} , °C	catal and additives (amt, mmol)	atm	% products and recovered reactants								
							I	PhCH ₃	PhOH	oHOT	mHOT	pHOT	oIT	mIT	pIT
1	105-3	oIT (1.4), mIT (1.4), pIT (1.4)	0.5 M K ₂ CO ₃	~286	CuCl (5 × 10 ⁻⁴)	Ar	73.8	0.1	0.6	54.9 ^c	84.6 ^c	80.1 ^{c,d}	55.8 ^{c,e}	9.0 ^{c,e}	17.4 ^c
2	125-2	oIT (6.46), pIT (6.46)	0.25 M Na ₂ CO ₃	315	CuSO ₄ (3.2 × 10 ⁻⁴)	air	40.7	0.4	1.0	33.8 ^c	2.7	28.8 ^{c,f}	61.1 ^{c,g}	h	56.5 ^c
3	125-3	pIT (6.46) mIT (6.83) pIT (6.83)	0.25 M Na ₂ CO ₃	315	CuSO ₄ (3.2 × 10 ⁻⁴)	air	42.1	0.5	1.4	1.0	35.7 ^c	29.9 ^{c,i}	h	51.3 ^{i,j}	52.4 ^c
4	129-3	pIT (2.3)	H ₂ O ^k	309	KCl (3.53 × 10 ⁻²)	Ar	tr	0.03							100.0
5	129-4	pIT (2.3)	H ₂ O ^k	309	KCl (3.55 × 10 ⁻³), CuSO ₄ (1.6 × 10 ⁻⁶)	Ar	15.6	0.11				0.6 ^l			84.4
6	111-3	pIT (2.3)	1.0 M KOH	~306	KCl (29.9 × 10 ⁻³)	air	25.5	0.4	0.9	0.1	1.5	0.5 ^m	h	0.4	69.2
7	114-3	pIT (2.3)	1.0 M KOH	~313	KI (6.64 × 10 ⁻³)	air	h	h	2.2	0.17	4.93	1.74	h	12.6 ⁿ	62.3

^a Yields are based on total iodotoluene(s) supplied, unless otherwise specified. ^b Volume 25 mL unless otherwise specified. ^c As percentage of the corresponding isomer of iodotoluene. ^d Traces of oxidation products were also formed (see text). ^e Relative amounts of oIT and mIT determined by NMR. Considerable error possible. ^f Also some oxidation products (ca. 0.2% of total iodotoluenes). ^g Includes any mIT formed. ^h Not determined. ⁱ Also some oxidation products (approximately 0.6% of total iodotoluenes). ^j Includes any oIT formed. ^k Volume 30 mL. A drop of 1.0 M NaOH was added to prevent decomposition problems. ^l pCIT (15.4%) also formed, but no mCIT. ^m CIT (8.2%) and pCIT (6.6%) also formed.

Entries 4 and 5 in Table IV show that no such reaction occurs at 309 °C when metallic ions are excluded, whereas chlorodeiodination does occur when copper is added. Halodehalogenation is well-known to be copper-catalyzed.^{17,19}

Finally, the reactivity order observed for the nonrearranging mechanism is consistent with a copper-catalyzed reaction.²²

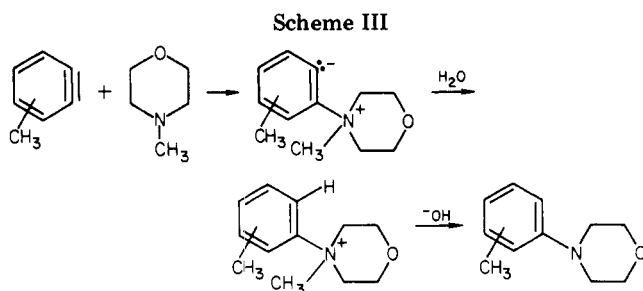
Relative Reactivities in Hydroxydehalogenation via Arynes. The reactivity order, pIT > pBrT > pCIT, observed for the *p*-halotoluenes in the aryne-forming reaction (Table II) can be rationalized by assuming that step M2 in Scheme II is the rate-limiting step under our conditions (i.e., $k_{-1} \gg k_2$) and that, as shown for other systems,^{23,24} k_2 decreases with halogen in the order I > Br > Cl. The differences are large enough to compensate for the opposite trend expected for the equilibrium constant, k_1/k_{-1} . A conceivable alternative possibility, that step M1 is rate-limiting for pIT but not for pBrT or pCIT, is rendered unlikely by the fact that the *o*-iodophenyl anion is substantially protonated to form iodobenzene even in the much less acidic solvent ammonia.²⁵ If our reaction solutions were not homogeneous, the observed reactivity order might reflect solubility differences.

Side Reactions. Readdition of halide ions to arynes (e.g., the reverse of step M2, Scheme II) and ensuing protonation may generate a rearranged aryl halide. No doubt this is how *m*-halotoluenes are formed from the para isomers in our system. Evidence for readdition of chloride ion to benzyne generated from the action of hydroxide ion on radiolabeled chlorobenzene was earlier found by Dalman and Neumann¹⁵ in the distribution of radiolabel in the phenol produced by hydrolysis of the diphenyl ether product. Addition of halide ions to benzyne in ethanol solution is well-known,²⁶ the reactivity order is I⁻ > Br⁻ > Cl⁻. Our observation of aryl halide isomerization by aryne formation and halide ion readdition is of special interest because this mechanism had been considered, and found not to apply, for the base-catalyzed halogen dance in oligohalobenzenes.²⁷

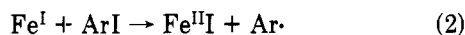
Cine-hydroxydehalogenation of the *m*-halotoluenes formed from *p*-halotoluenes accounts for the production of some *o*-cresol.

Oxidation of the methyl group of *p*-methylphenoxide ion, observed when the reaction is carried out in air, resembles certain observations of other workers. When 2,6-di-*tert*-butylphenol is treated with oxygen in dimethylformamide/*t*-BuO⁻K⁺, the methyl group is oxidized to a formyl group, presumably via the benzylic anion.²⁸ Raudsepp and Karolin²⁹ reported that when *o*-, *m*-, or *p*-cresol was heated to 300 °C with aqueous alkali in an autoclave, in air, the methyl group was oxidized to CO₂, and phenol was produced. Phenol formation presumably proceeds via oxidation to the hydroxybenzoic acid and decarboxylation. The literature contains abundant evidence for the feasibility of these steps.³⁰

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The observed enhancement of hydrodehalogenation by iron and cadmium metals might be explained in any of several ways. One postulates the formation of an organometallic complex, followed by protonolysis to toluene. In a variant of that, the organometallic intermediate decomposes to an aryl radical, leading ultimately, through reduction and protonation or by hydrogen atom abstraction, to the hydrocarbon. The literature relevant to such processes is extensive. Another possibility is that the aryl radical is generated by S_H2 attack on the halide atom, similar to what has been found to occur with alkyl halides³¹ (eq 2). Still another is one-electron reduction of the aryl



halide to its radical anion, which then splits apart to form the aryl radical, etc.

The involvement of radicals in these iron-promoted hydrodehalogenations is indicated by iron stimulation of methylbiphenyl formation in the presence of benzene (Table III). However, because of solubility considerations, these reactions should be considered more as decompositions of *p*-iodotoluene in benzene than as reactions of *p*-iodotoluene in an aqueous medium in the presence of a radical trap.

When *N*-methylmorpholine (NMM) was present as pIT reacted with aqueous K₂CO₃ (entry 12, Table III), formation of mHOT was suppressed and *N*-tolylmorpholine(s) were formed instead. We postulate that NMM, when present in much greater concentration than hydroxide ion, scavenges essentially all the 4-methylbenzyl produced, by adding to it, and that the addition is followed by further steps as in Scheme III. The generation of pHOT is ascribed to copper-catalyzed ipso hydroxydeiodination, possibly enhanced by NMM (maybe as a beneficial ligand to copper).

Experimental Section

Materials. Iodo- and bromotoluenes were purchased from Eastman Kodak Co., and they were used as received or after distillation. They were shown to be pure and isomer free by GLC. *p*-Chlorotoluene was the product of Matheson Coleman and Bell and contained a small amount of *m*-chlorotoluene. It was purified by partial crystallization until no meta isomer could be detected by GLC. Water from the Thimann Laboratories deionized water system was distilled through an all-glass apparatus shortly before use. Sodium hydroxide was the commercial "Titrisol" product of EM Laboratories. Potassium hydroxide and sodium or potassium carbonate, acetate, and bicarbonate were products of Mallinckrodt Chemical Co.

Iron was obtained as a sponge of 99.999% certified metallic purity from Research Organic/Inorganic Chemical Corp. Manganese was a powder of 99.9% certified purity from the same source. Iron filings from Matheson Coleman and Bell, containing 0.15% copper by atomic absorption (AA) flame analysis, were used in some experiments. Cadmium turnings were machined from metal sticks sold by Mallinckrodt Chemical Co. Nickel was a foil, 0.025 mm thick, of 99.998% certified metallic purity, obtained

from Ventron Corp., Alfa Division. Iron, manganese, and cadmium were found to be copper-free by flame AA analysis (estimated detection threshold was 1 ppm). The nickel foil was not analyzed.

N-Methylmorpholine was the product of Union Carbide Corp. and was fractionally distilled before use. Benzene was Mallinckrodt Spectra AR grade and was used as received. It was free of biphenyl or biphenyl derivatives by GC/MS.

General Remarks. Reaction of the aqueous basic solution with the glass tubes was extensive when hydroxide solutions were used. Thus, a 0.49 M KOH solution sealed in a Pyrex tube titrated at 0.27 M after being carried through a normal reaction cycle with a maximum temperature of 300 °C. Heavy-walled (1/8 in.) tubes were used to minimize weakening by corrosion. These tubes had to be carefully annealed before use to avoid tension and cracking due to temperature variations. Although most were recovered intact, in some cases temperature/pressure gradients inside the bomb, imperfect pressure balancing, or glass strain (especially at the sealed tip) caused ruptures.

Procedure. A typical procedure for a run under argon is given. Four annealed Pyrex heavy-walled ampules were washed repeatedly with 28% aqueous ammonia (Mallinckrodt), rinsed with glass-distilled water, inverted, and allowed to dry overnight in air. The aryl halide(s) and other reagents, if any, except the alkaline solution, were placed in the tubes, which were thenceforth handled in a purged argon-filled glovebag. The aqueous basic solution, freshly prepared by using aqueous ammonia-washed glassware, was also introduced into the glovebag, and argon was bubbled through it for several minutes. The desired amounts of solution were loaded into the tubes, which were capped with deflated, argon-purged, rubber balloons, taken out of the glovebag, and immediately sealed. The balloons acted as expansion chambers during the sealing operation. The tubes were sealed at such a length as to fit exactly inside the bomb, a Parr Instrument Co. Model 4052. This prevented ruptures due to shifting of tubes during rocking of the bomb. In the bomb, outside the tubes, were placed the same chemicals as inside the tubes, and in similar proportions. The tubes were ordinarily separated from each other by strips of stainless-steel foil, to prevent them from "gluing" together. After it had been heated to a chosen temperature for a measured period of time, the bomb was allowed to cool overnight. In a typical run, rocking was started 55 min after the commencement of the heating (at 260 °C), the maximum temperature of 309 °C was attained at 80 min, and rocking was discontinued at 130 min (when the bomb had cooled to 240 °C). After cooling, the bomb was opened, and the tubes were removed, rinsed externally with water and then with acetone, and opened by the file-scratch and hot glass rod technique. The contents were transferred with careful rinsing to an Erlenmeyer flask containing internal standards for GLC analysis. After a first ether extraction, the water layer was acidified with dilute HNO₃, HCl, or H₂SO₄ and extracted again. When HNO₃ is employed, care must be exercised not to cause nitration of the phenols. The water layer was diluted to the mark in a volumetric flask, and the halide ion released was measured by potentiometric titration with AgNO₃. The combined ether extracts, generally about 200 mL, were dried over CaCl₂ or MgSO₄ and concentrated to about 100 mL by distillation at atmospheric pressure through a Vigreux column. Extraction with ca. 4 M NaOH then allowed separation of the acidic products (phenols) from the neutral fraction. After recovery of the phenols by acidification and extraction, the two ether solutions obtained from each tube were concentrated as needed and analyzed separately by GLC.

For most of the runs summarized in Table III, loading operations were conducted in air. Argon was bubbled through the aqueous basic solution and blown into the tubes for several minutes before and after the addition of the solution. The tubes were then sealed open to the air, so that the atmosphere inside, while presumably mostly argon, contained some air as well.

Analysis. Product analysis was carried out by GLC and GC/MS. Mass balances usually fell short of 100%, as a consequence of workup losses and analytical error. Various compounds found among the products of the industrial process,^{9b} such as phenoxybiphenyls and diarylphenols, would be expected to form in small quantities in our system as well, but they were not actively sought and would have easily gone undetected because of their GLC characteristics. They might account for some of the missing

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material. Also, oxidation products, if any, were not quantitatively evaluated, and tars were observed in some runs.

Analysis was carried out by means of a Hewlett-Packard 5750 analytical gas chromatograph equipped with a flame-ionization detector. Most of the neutral product fractions and a few of the acid fractions were examined by using a Model 4000 Finnigan GC/MS system as well. Most of the analyses were carried out by using a 240-cm, 2-mm internal diameter, 0.1% SP-1000 on Carbowax C (Supelco) column, which provided satisfactory separation of the isomers of cresol, of the isomeric dimethyldiphenyl ethers mentioned in this paper, and of isomeric halotoluenes, with the exception that certain isomer pairs, namely, *o*- and *m*-bromotoluene and *o*- and *m*-iodotoluene, were not separated. Other columns used contained OV-1, OV-101, OV-17, UC-98, SE-54, and polyphenyl ether liquid phases. Assignment of peaks was done on the basis of comparison of retention times and mass spectra with those of true samples. Internal standards used were bromobenzene or *p*-bromotoluene for the halotoluenes, xylene for toluene, and *p*-chlorophenol for phenol and the cresols. *o*-Cresol was used as internal standard for the phenolic products up to run 110. In these cases, analytical error due to *o*-cresol formed in the reaction was considered negligible. Integration was carried out by cut-and-weigh techniques or by using a Spectra Physics Minigrator electronic integrator.

Analysis for metal purities was done by using a Varian Techtron AA 6 atomic absorption spectrometer and suitable standards from Varian Analytical Instruments.

Experiments To Test the Homogeneity of Reaction Mixtures. Four heavy-walled Pyrex glass reaction tubes were charged respectively with 1.00, 2.05, 2.99, and 3.98 mmol of pIT as well as with 25 mL of 1.0 M aqueous NaOH. The atmosphere within the tubes was air. The tubes were sealed and heated in the usual way to a maximum temperature of 303 °C, with the tubes being rocked for 44 min, corresponding approximately to the time the bomb interior was hotter than 260 °C. The only reaction product determined was iodide ion, by potentiometric titration. Iodide ion was formed in yields of 15.9, 14.5, 15.2 and 12.5%, respectively.

Further Data. Supplementary experiments are summarized in appendices A, B, C, and D of chapter I of the dissertation of M.Z.²

Acknowledgment. We thank the National Science Foundation for financial support and Professor A. T. Bottini for discussions and for making available to us unpublished notes and reports from his earlier work on this topic.

Registry No. pIT, 624-31-7; pBrT, 106-38-7; pCIT, 106-43-4; CuSO₄, 18939-61-2; Fe, 7439-89-6; Cd, 7440-43-9; Mn, 7439-96-5; Ni, 7440-02-0; benzene, 71-43-2; Cu₂O, 1317-39-1; NMM, 109-02-4; oIT, 615-37-2; mIT, 625-95-6; CuCl, 7758-89-6; KCl, 7447-40-7; KI, 7681-11-0; 4-methylbenzynes, 5849-21-8; NaOH, 1310-73-2; K₂CO₃, 584-08-7; NaOAc, 127-09-3; Na₂CO₃, 497-19-8; KOH, 1310-58-3; H₂O, 7732-18-5.

Reactivities of Several Nucleophiles toward 4-Methylbenzynes in Very Hot Water¹

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By means of competition experiments, the relative rates of reaction of several nucleophiles with 4-methylbenzynes in aqueous solution at temperatures up to 318 °C have been determined. The relative nucleophilicities vs. chloride ion are as follows: PhS⁻, 46; I⁻, 6.2; piperidine, 3.0; Br⁻, 1.7; aniline, 1.3; Cl⁻, (1.0); PhO⁻, 1.0; ammonia, 0.55; F⁻, 0.20. For all but PhS⁻, piperidine, and iodide, the *p/m* product ratio is 0.83 ± 0.02. In the cases of PhS⁻ and piperidine a competing mechanism of ipso substitution, probably involving catalysis by copper ions, caused the observed *p/m* ratios to be high and variable. Our experimental design precluded determination of the *p/m* ratio for iodide ion. Because of chemical complications, only rough estimates could be made of the nucleophilicities of nitrite and benzenesulfinate ions.

The addition of nucleophiles is one of the prominent modes of reaction of arynes. Assessing the relative addition reactivity of various nucleophiles is of obvious interest.

Among studies of relative nucleophilicity by means of competition experiments, an early one by Scardiglia and Roberts³ served to rank several reagents in reactivity toward benzyne in ammonia as follows: PhS⁻ > PhC≡C⁻ > PhO⁻ > RO⁻, I⁻, CN⁻, the last three giving no detectable addition. Wittig and Hoffmann⁴ determined the halide ion reactivity ratios (I⁻:Br⁻:Cl⁻ = 65:8:1) against benzyne in ethanol. Huisgen, Mack, and Möbius⁵ explored the relative reactivities of the lithium salts PhSLi, PhLi,

lithium piperidide, and PhOLi, as well as of piperidine, vs. 9-phenanthryne in diethyl ether, but it is unclear whether they took into account effects of aggregation of the lithium salts in ether. These and other studies are summarized by Hoffmann.⁶

We mention also determination of the relative reactivities of CH₃O⁻ vs. CH₃OH in methanol⁷ and of NH₂⁻ vs. NH₃ in ammonia⁸ in addition to 4-chlorobenzyne. These determinations were made by the method of ad eosdem competition.

We are unaware of any previous determination of nucleophilicities toward any aryne in water.

In the present work, we generated 4-methylbenzynes (1) by the action of aqueous NaOH or KOH on *p*-bromo-

(1) Based in part on ref 2.

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